Marko Jukić, Mladen Carev, Nenad Karanović &Mihajlo Lojpur

Anesthesiology and intensive medicine for students

For internal use (*Scripta ad usum privatum*)

Department of Anesthesiology and Intensive Care Medicine

Split, 2015.

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Note: It is not proof-read because it is not the final version of the script.

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Literature

1. Miller's Anesthesia, seventh edition
2. Morgan and Mikhail's Clinical Anesthesiology, fifth edition
3. Barash Clinical Anesthesia, sixth edition
4. Jukić i sur. Klinička anesteziologija, second edition
5. *Nolan JP, Hazinski MF, Billi JE i sur.* 2010 International Consensus on Cardiopulmonary Resuscitati-on and Emergency Cardiovascular Care Science with Treatment Recommendations. Resuscitation. 2010.
6. American College of Surgeons Committee on Trauma. Advanced Trauma Life Support for Doctors, Student Course Manual, 8th ed, American College of Surgeons, Chicago 2008.
7. Newgard CD, Schmicker RH, Hedges JR, et al. Emergency medical services intervals and survival in trauma: assessment of the »golden hour« in a North American prospective cohort. Ann Emerg Med 2010; 55:235.

CONTENTS

1. ANESTHESIA, MEDICAL, LEGAL AND ETHICAL ISSUES

Ana Šarić**, Marko Jukić*

1.1. Introduction

Anesthesia is a procedure of inducing insensitivity. Anesthesiology is a clinical medicine branch which studies procedures employed to cause insensitivity.

There are: general, regional, conductive and local anesthesia. In general anesthesia we achieve the state of complete insensitivity to external stimuli, which is caused by reversible depression of neural cells. This includes loss of consciousness and of all painfull sensations, turning off all defensive reflexes and often sceletal muscles' relaxation. These effects can be achieved by using single anesthetic agent, but are usually achieved using several different agents: anesthetic, analgesic and muscle relaxant. Inhaled anesthetic enters bloodstream through lungs, intravenous anesthetic is applied through veins. Moreover, it is possible to cause anethesia by intramuscular or rectal application of drugs.

Regional anesthesia is divided into central regional anesthesia (subdural anesthesia, epidural anesthesia, caudal block), periferal regional anesthesia (regional intravenous anesthesia, periferal blocks of upper and lower limbs, retrobulbar block), and local infiltrating anesthesia. By giving anesthetic/analgesic, one part of the body becomes insensitive to external stimuli. Patient is conscious, with preserved reflexes, and breathes normally.

We can combine general and regional anesthesia (general+ epidural anesthesia; general+ retrobulbar block). Peridural catether is sometimes inserted during general anesthesia and is used for intraoperative and postoperative analgesia.

In local anesthesia, insensitivity is achieved by infiltration, dropping, rubbing or spraying anesthetic into tissue.

1.2. Choosing type of anesthesia

Choice of type of anesthesia depends on planned operation. For example, operations on head, neck, thorax and upper abdomen are most frequently performed in general endotracheal anesthesia; it depends on the type of surgical procedure, patient's safety and operating surgeon. Operations on lower limbs and lower abdomen could be performed in subdural or epidural regional anesthesia. Operations on upper and lower limbs could be performed using peripheral block anesthesia. The choice of anesthesia is decision of anesthesiologist in accordance with surgeon and patient. Patient's health status, surgeon's demands, patient's safety and consent are the factors that determine choice of anesthesia.

In order to perform anesthesia, it is necessary to ensure: qualified staff (anesthesiologist and anestehesiology technician), device for performing aneshesia, intubation set, devices for monitoring patient's vital functions (oxygenation, ECG, ventilation, circulation, temperature), defibrillator, aspirator, gases (oxygen, nitrous oxide, compressed air, vacuum) and drugs for performing anesthesia (inhaling and intravenous anesthetics, muscle relaxatnts, opiats, antidots, infusion solutions, anti-shock drugs etc.).

Planning of anesthesiological care is based on:
a) data evaluation, patient's medical history
b) interview with a patient (or an accompaining person, parent) and physical examination
c) evaluation of laboratory data and ordering additional laboratory and/or funcional test in order to assess patient's health status; consulting other specialists if necessary
d) prescribing premedication, choice of type of anesthesia
e) deciding on postoperative therapy and laboratory and/or other tests, if necessary

1.3. Legal aspect of anesthesia

Anesthesia can be performed in persons who have given their consent to it after previous information about anesthesia, it`s risks and possible complications. In case of emergency and life saving situations, anesthesia can be performed without consent of a patient, guardian or legal representative, and a consent needs to be asked retrospectively. Performing anesthesia is reserved for qualified persons (physicians with completed adequate specialization in anesthesiology and health professionals educated in the field of anesthesiology). Physician must act on patient's behalf and apply the best procedure available. Anesthesiological devices must be standardized, with valid licence for use.

All procedures performed by anesthesiologist must be noted in patient's medical history. During anesthesia, list of anesthesia is kept, and after operation, postoperative list is kept.

Location, technical and personnel requirements for an operating room are regulated by law. Anesthesiologist must act in accordance with Hippocrates' oath, Geneve and Helsinki rules, International code of physician's ethics and Medical chamber ethical code.

1.4. Informed consent

Informed consent is a process in which doctor informs the patient about his (patient's) health status and at the same time about patient taking part in decision making. It consists of two components: information and consent. The patient is being acquainted with his health situation, intended diagnostic and therapeutic procedures, techinques, possible complications, therapeutical risks and alternative therapeutical options, if there are any.

Patient confirms with his signature that he is informed about his health status and that he approves suggested diagnostic and/or therapeutical procedures. The result is a written consent which confirms that the patient has received the information about his health and treatment and that he agrees with suggested therapeutical procedure.

Consent can be verbal if there are standard, small procedures involved (getting blood sample for laboratory tests, x-rays in contusions etc.).

If patient doesn't agree with certain procedures, it has to be precisely specified which procedures patient allows and which one doesn't.

Informed consent is mandatory for following procedures:
- surgery of any kind,
- anesthesia (general, regional and local)
- invasive procedures (contrast application, catether insertions, bronchoscopy, gastroscopy, colonoscopy etc.),
- chemotherapy, radiotherapy and other procedures.

When giving information, there is an important ethical principle of respecting a patient as a person who makes a decissions about his own health independently. It is necessary to establish a good relationship between patient and physician. Patient's confidence in doctor must not be played out; doctor must not lie to patient.

Legally speaking, these are elements of information:
- information about health status; diagnosis if it is known
- intended diagnostic and/or therapeutical procedures
- anticipated result of treatment (length of treatment, length of reconvalescence, daily activities restrictions, possible scars etc.)
- alternative procedures and their anticipated advantages and disadvantages
- possible complications during treatment, treatment risks, consequences if treatment is not undertaken. Patient must be informed about the consequences of his decission and about alternative treatment procedures (conservative treatment). Patient's decission must be respected.

Patient's duty is to inform the doctor about his own habits, diseases, health status, inherited characteristics. Patient must know which drugs he takes; how much; since when; for what; and what is he allergic to etc. He is also obliged to keep his own medical documentation.

Competence and capacity for deciding

When deciding wheather patient's consent is valid, it is necessary to assess if he is competent to decide, if his capacity for deciding is sufficient, and if his consent is voluntarily.

Competent patient, who has sufficient capacity for deciding, has the right to refuse treatment, even if it could save his life. Patients have their own reasons for not accepting treatment (other people's bad experiences, family reasons, benefit of the treatment etc.).

It is assumed, legally speaking, that there is insufficient capacity for deciding in following situations:
- premedicated patients (hospitalized or in surgical daily care)
- women in a state of labour (excessive pains)
- patients under stress
- patients under influence of alcohol or halucinogens

- patients with known mental disease
- immature patients (which have insufficient mental capacity- mentally hendicapped)
- patients with structural brain disease
- patients in urgent conditions etc.

Patients who recieve sedative and/or analgesic as premedication can have decreased capacity for deciding because that drug can influence the hearing, realizing of situation and decision making.

Decisison and authorization

When a patient makes a decision, he signs (authorizes) the statement and thereby confirms that he is informed about the diagnosis, inteded procedures, possible complications, treatment risks and prognosis. If a patient hasn't understood the situation, then he doesn't have adequate deciding capacity.

Consensus surrogate

Children can not give approval for medical procedures. Instead, it is given by children's parents or guardian approved by law. We must mention that some children are declared emancipated by law and they can make decisions concerning certain issues (reproduction, minor's marriage), but they are generally not competent to make other decisions. Older minors can be included in decision making, but decision in the end has to be signed by parent or guardian. Doctor should allways act on behalf of a child or a minor. Laws differ among countries and doctor must be familiar with the law of country he is practicing medicine in.

Patient is not able to give consent

When certain medical procedure is a neccessity, and patient is not able to decide about the procedures, it is necessary to find a person who will decide on patient's behalf. For adults, decisions are made by: legally appointed representative, members of close family, lawyer, person appointed by court or hospital doctors when there is no time to wait for the decision.

Law

Consent is mandatory according to the law in Croatia. Procedures on patient without the consent are usually treated as a negligence.

Refusal of consent for treatment

Patient has a right to refuse offered way of treatment, part of the tretment (blood transfusion or radical surgery) or complete treatment. It must be documented, and patient must sign the Statement of refusal of certain procedure, treatment.

Treatment without consent

In situations of urgent surgical treatment (anesthesia), consent is not necessary because there is a life threatening situation (bleeding, head injury with brain damage). Necessary treatment can be conducted without consent, but consent has to be obtained later from the patient or his close relatives if patient is not able to give it. Electroconvulsive therapy requires patient's consent, and if he is not competent, it can be obtained from a competent physician (he signs that he agrees with the other physician's procedure).

If a patient posseses legally valid document (a will) in which he requires that he is not reanimated in the case of respiratory or cardiac arrest, it has to be respected.

Patient must be informed about a planned clinical trial, about the purpose and possible consequences of the trial and he has to give (sign) his consent. Patient voluntarily agrees to participate, and if he doesn't give his consent, the trial must not be conducted. If a person is minor or incompetent, consent must be asked from a guardian or close relatives.

Students must not conduct clinical procedures without patient's consent.

Informed consent in Jehova's witnesses

Jehowa's witnesses refuse transfusion treatment due to religious reasons. Patient (Jehowa's witness) has the right to choose not to receive transfusion of blood or blood derivates. If patient has valid identification document (in countries where such document is used it has to be certified by notary public), patient's wish is respected even if in state of unconsciousness or in state of decreased deciding capacity. It's important to pay attention to the date on the document or statement, because patient could have changed his mind in the meantime. In some of these patients, attitude toward this issue is not very hard, and it is allways usefull to ask if they stick to the statement.

2. HISTORY OF ANESTHESIOLOGY

Ana Šarić**, Marko Jukić*

2.1 Discovery of anesthetics, analgesics and other drugs used in anesthesia

Ether was first used in January of 1842. by William E. Clark, then in march of 1842. By Crawford Williamson Long. First successful public demonstration of using ether was made by William Thomas Morton Green on October 16th 1846. in Boston. Discoveries of anesthetics and their impementation:

- nitrous oxide, January 1845. Horace Wells (unsuccessful presentation)
- chloroform in 1848., James Young Simpson
- cyclopropane in 1934.
- xenon in 1950.
- halothane in 1956.
- methoxyflurane in 1960.
- enflurane in 1970.
- isoflurane in 1970.
- desflurane in 1992.
- sevoflurane in 1994.
- first barbiturate (barbital) in 1903.
- hexobarbital (Evipan) in 1932.
- thiopental in 1934. (John Lundy)
- imidazole (etomidate) described in 1964., first used in 1974.
- phenol derivates (propofol, tested in 1977.). Propofol was introduced in practice in 1986.
- phencyclidine (ketamine in 1962.), in 1960.
- benzodiazepines (diazepam, midazolam), in 1963., 1970.
- steroids (althesin), in 1955.
- codeine in 1832., 1860.
- benzocaine, in 1900.
- procaine, in 1904-5.
- cocaine, in 1860., 1884.
- tetracaine, in 1930.
- lidocaine, in 1943-4.
- prilocaine, in 1959.
- mepivacaine, in 1956.
- bupivacaine, in 1957., 1965.
- ropivacaine, in 1996.
- etidocaine, in 1972.
- meperidine, in 1939.
- fentanyl in 1960.
- remifentanil introduced in 1996.
- curare, used in two patients with tetanus in 1858., used in surgery in 1912.
- physostigmine isolated in 1864.
- succynilcholine isolated in 1949.
- neostigmin synthesized in 1931.
- tubocurarine, January 1942., Griffith and Enid Johnson (first public use)
- pancuronium used in 1964.
- vecuronium introduced in 1979.
- mivacurium prepared for clinical use in 1993.
- rocuronium introduced in clinical practice in 1994.
- first subarachnoidal anesthesia in1885.

2.2. History of anesthesiology in Croatia

Five months after public demonstration of ether narcosis in Boston (October 16th, 1846.), first narcosis in our region, in Zadar, was performed on March 13th 1847. There, surgeons Cazar Pellegrini-Danieli, Jerolim Definis and Toma Fumegallo, with assistance of Ivan Bettini (1816.-1818.) performed the first operation in ether narcosis on an eighty-year woman with incarcerated hernia. Johannes Baptista Garmanus Bettini performed anesthesia and wrote a report for local newspaper. Also, narcoses in Dubrovnik on April 14th 1847., in Split on June 17th 1847. and in Sisak on August 29th 1847. were mentioned. Early narcoses were performed by surgeons. They performed both anesthesia and surgical intervention or their assistants (nurses, instrumentalists) performed anesthesia under surgeon's supervision. Dr. Mirosav Čačković in his article in the year of 1896. states that skilled assistant is required for performing anesthesia, and that different types of local anesthesia are unavailible or dangeorus if overdosed.

For achieving local anesthesia, cocaine was used (1-5% solution). There was a well-known Schleich solution, which was used by surgeons in Zagreb, dr. Dragutin Mašek and dr. Teodor Wickerhauser. In the beginning of the 20th century, medular anesthesia was performed and tropacaine was used. For achieving general anesthesia, ether and chloroform were used.

During World war II, most of operation (in our region) were performed without anesthesia. Towards the end of the war, the army was supplied with certain amount of anesthetics (from British military mission).

Chlorethyl was often used by spraying it on the skin, which actually meant that operation was performed without anesthesia. Chlorethyl was also used for *rausch*-anesthesia and novocaine, tropocaine and percaine were used for local or lumbal anesthesia. Amputations were performed by freezing of the limb.

Ether, chloroform and chlorethyl were used for inhalation anesthesia, and for intravenous anesthesia, pentothal and evipan.

Dr. Risto Ivanovski performed the first endotracheal anesthesia in this region, in Zagreb military hospital, on January 7th, 1948. The army organized courses for nurses (anesthetists) and those helped to surgeons in conducting anesthesia.

During World war II and immediately after it began fast development of anesthesiology in Europe ant the importance of doctor-anesthesiologist for patient's safety and for for optimal surgeon's performance had been noticed. In Croatia, then in Federative People's Republic of Yugoslavia, the need for physicians who would conduct anesthesia had also been noted, and the law was passed (in 1948.) which defines a new specialization-anesthesiology. It was prescribed that duration of specialization would be two years; therefore, legal frame has been set for development of anesthesiology in our country. Post-graduate anesthesiology course in Denmark in 1950. and later post-graduate courses in Zagreb have also created real prerequisites for anesthesiology development in Croatia.

When the first post-graduate anesthesiology course was held, president of the World Health Organization (WHO) was prof. dr. Andrija Štampar (professor at the University of Zagreb medical school for subject: hygiene and social medicine and director of People's Health School in Zagreb). He noted the importance of anesthesiology for modern medicine and provided one scholarship by WHO for post-graduate course in Copenhagen (in 1950./1951.).

Dr. Andrija Longhino, with the help from dr. Andrija Štampar, organized three courses of anesthesiology for doctors at the School of people's health, each of six months duration. The course was attended by 37 doctors officially, and 13 more were there unofficially. Fifteen of these attending doctor have later completed specialization in anesthesiology and have chosen anesthesiology as their activity field.

Dr. Đurđa Klaić has (as the first in Croatia) passed a specialization exam in anesthesiology in 1955. After her, exam has been passed by: Ljubomir Ribarić, Jagoda Bolčić, Višnja Svoboda, Ivana Perić, Metka Betriani, Neda Butigan, Nikola Radoš, Nikola Franičević, Maša Formanek, Vlasta Strižić etc.

In 1959., specialization in anesthesiology had a three-year duration and in 1974. a four-year. Today, specialization has a five-year duration.

Surgery clinic has been established in hospital in Drašković street, Zagreb, in 1920. However, there were no significant advances considering anesthesia: it was performed by dropping of chlorphorm and ether. It was conducted by doctors- surgeons to be or young surgeons, as well as educated technicians. Subarachnoidal (spinal), intravenous or local anesthesia were performed by doctors who, after performing anesthesia, performed surgery on the same patient. Surgery clinic, was temporarily located in Drašković street, Zagreb, after 26 years, moved to Rebro. Anesthesia was performed in similar way and by the

same means. The only difference was that operation room had electric instead of gas lighting, so chloroform was completely substituted with ether. Ether was dropped by open method through Schimmelbusch mask or by Ombredan device.

For anesthesia, ether, nitrous oxide, cyclopropane, trylene and chlorethyl were used. When it comes to relaxants, there was only d-tubocurare, and considering intravenous agents, barbutrates with ultra-short, short and prolonged activity time. For ambulatory surgical procedures, skin- cooling with ethyl spraying was used. After many years, neuroleptanesthesia, ketamine, new curariform and depolarizing relaxants have been introduced. There were also all types of regional anesthesia in use. Dr. J. Bolčić-Wickerhauser has introduced halothane on September 1st, 1960., and further enhanced performing of hypontensive and hypothermic anesthesia. At that time, there was complete program of thoracic and abdominal surgery, traumatology, neurosurgery and urology at Surgery clinic.

Technical devices were inadequate, there was no device for mechanical ventilation and patients had to be ventilated manually as long as it was necessary. Ventilators Harlow BOC type were acquired later, oxygen was supplied in steel containers.

Head of anesthesiology ward, assist. prof. dr. Jagoda Bolčić-Wickerhauser, was conducting, after prof. dr. Andrija Longhino had left in Rijeka, anesthesiology education at the Department of surgery. She had also initiated the foundation of Department of anesthesiology, which was founded in 1992. The first head of the department was prof. dr. Ivan Janjić.

In clinical and general hospitals, wards and departments of anesthesiology have been founded.

The first specialist- anesthesiologist in Children hospital was dr. Ljiljana Audy-Kolarić who founded the first department of children's intensive care in Croatia, in 1971. Besides that, she proposed organization of children's intesive care departments throughout Croatia and transportation of life-threatened child. Dr. Lj. Audy-Kolarić has written the first textbook on anesthesiology and intesive treatment in Croatia, „Anesthesia and intesive treatment of newborns".

The first department of anesthesiology at the surgery department was formed in 1952. (Zagreb), and the first independent department was formed in 1962. (Rijeka).

Anesthesiologists adopted techniques of endotracheal intubation and mechanical ventilation, and thus treated patients with acute, and sometimes chronic, respiratory insufficiency, unconscious patients, those who needed complete parenteral nutrition, etc. In the first intensive care units, anesthesiologists were leading physicians and most of these units were situated within anesthesiology departments. These units were usually multi-purpose ones, except in large hospitals where more intesive care units existed (neurosurgical, cardiosurgical, pediatric, coronary, etc.).

Founding assembly of Section of anesthesiology of Croatian Medical Association was held in the association's large hall at Šubić street 9, Zagreb, on April 25th in1962.

The first Congress of anesthesiologists of Croatia was held in Split (1994.).

Surgery should be thankfull to anesthesiology for its rapid development and success, because anesthesiology has contributed to patient's sensitivness, easiness and persuasion that surgical treatment is the right choice. At the time duration of operation was a limiting factor (one of money). Today, however, that is not the main problem and a surgeon can calmly operate. Anesthesiology development in our country, as well as worldwide, has enabled unbelievable surgical procedures and has widened treatment possibilities.

Pioneers of anesthesiology in Croatia

Prof. dr. Andrija Štampar (1888.-1958.) is responsible for the beginning of anesthesiology development in Croatia. As an influential member of WHO, he provided that our physicians attend one-year anesthesiology postgraduate course in Copenhagen and that similar courses could be held at the School of people's health in Zagreb, under his directorship. For these courses, all held in Zagreb, he had provided international support, when it comes to drugs, anesthetics, anesthesiology devices and guest lecturers.

Courses in Copenhagen and Zagreb were solid foundation for the development of Croatian anesthesiology and for realizing the importance of anesthesiology and it`s part in modern medicine in our country.

Pioneers of anesthesiology in Croatia were: prof. dr. Andrija Lonhgino (surgeon-anesthesiologist), prof. dr. Jagoda Bolčić-Wickerhauser, prof. dr. Vera Arko, prof. dr. Ljubomir Ribarić, prof. dr. Ivan Janjić.

3. PREANESTHESIA EVALUATION

Ana Šarić**, Marko Jukić*

3.1. Introduction

Preparing patients for surgery consists of several fragments: a) taking history and physical examination in order to deretmine physical condition and mental state, ordering and interpreting laboratory tests and other examinations, b) choosing adequate type of anesthesia and anestetics, c) assessment of the risks of anesthesia and surgery. While interviewing patients, doctors pay respect to patients and decrease their anxiety. In that way, a trust in doctors is created.

Phisical medication and diagnostic procedures before surgery are determined in accordance with patient`s health status, type of surgery and degree of urgency. Surgery can be, when it comes to urgency, vital, urgent and programmed. In this section we are addressing preanesthesia examination and evaluation of patients undergoing elective procedures. Preanesthesia evaluation and anesthetic care for patients undergoing elective procedures can be done in hospital or outside of hospital. The range of procedures needed depends on patient`s health condition (physical and psychological), type of surgery that is planned and on hospital`s policy.

The basic standard of preoperative anesthetic care

The plan is based on:

- Insight in patient`s medical records, medical history,
- Interview, talking to a patient,
- Physical examination of a patient,
- Ordering additional laboratory and other tests (when necessary),
- Talking about types of anesthesia and getting patient`s consent,
- Deciding on the type of anesthesia and prescribing preanesthesia pharmacological agents.

Anesthetist is responsible for deciding on patient`s medical status (ASA classification), immediate anesthesiological preparation of patients (examination, medical tests and evaluations, premedication), performing anesthesia and postoperative surveillance. Anesthetist plans anesthesiological care and informs patient or a custodian on planned and alternative procedures and asks them for their consent.

Anesthetist needs information on:

Family history: family members` experiences with anesthesia, presence of malignant hyperthermia, cholinesterase abnormalities, porphyria, hemoglobinopatias, muscle disorders etc. This is especially important for patients who haven`t been anesthetized before.

Information on previous anesthesia, e.g. reaction on premedication, experience with preoxygenation and breathing into mask, soor, hoarseness, headache, problems with inserting cannulas in veins, postoperative nausea, vomiting, difficult airway, liver damage, postoperative icterus etc.

3.2. Data on medications taken (drug, dosage, for how long, drug reactions).

Drugs that can affect anesthesia and postoperative treatment:

Aspirin – bleeding disorder, it is recommended that patients stop using it a week before planned surgery.

Aminoglycoside **antibacterial therapeutic agents** – can provoke muscle weakness and increase the action of nondepolarizing muscle relaxants.

Anticoagulants

Coumarin – occult bleeding can provoke anemia, one must check coagulation tests.

Lithium – can cause loss of sodium and weakness of sceletal muscles.

Monoamine oxidase inhibitors – they increase production of catecholamines, that is why they can provoke hypertension when given together with catecholamines, as well as prolonged depressive effect and slowing metabolism.

Tricyclic antidepressants –response to sympathomimetic agents can be increased in acute treatment, and chronic administration of tricyclic antidepressants can decrease the response.

Insulin – possible hypoglicemia, the dose usually needs to be decreased.

Oral hypoglycemic agents – there is a risk of hypoglycemias, hence these drugs are avoided prior to surgery or are substituted with insulin.

Antihypertenzives – damage of normal compensatory circulatory response is possible, that is why they should be used continuously, until and after the surgery.

Chemotherapeutic agents – anemia, thrombocytopenia, pulmonary, cardiac, renal and liver damage.

Benzodiazepines – tolerance between benzodiazepines and anesthetics.

Beta agonists – bradycardia and myocardial depression, hence the therapy should be continuous, without interruption.

Calcium channel blockers – hypotension.

Cardiac glycosides – there is a risk of digitalis toxicity and cardiac arrhythmias, especially if the serum potassium level is low. Hence the therapy should not be interrupted, especially if they are given to control cardiac rhythm.

Diuretics that decrease potassium – hypokalemia and hypochloremic metabolic alkalosis, administration of potassium can be ordered.

Aldosterone antagonists – hyperkalemia.

Corticosteroids – supression of pituitary-adrenal axis is possible, hence perioperative supplementation must be ordered.

Data on allergies to drugs, food, medical plastics (latex) etc.

Habits: smoking, alcohol consumption, other addictions and habits.

It is recommended that patients stop smoking two or more (6-8) weeks prior to surgery or at least 12 hours prior to anesthesia. Acute alcohol poisoning decreases the need for anesthetic and can lead to hypothermia and hypoglycemia. Withdrawal syndrome is possible while staying in hospital and serious complications can be expected (hypertension, tremor, delirium, excessive sweating, dehidration, electrolyte disorder, muscle cramps). Abuse of stimulans can provoke palpitations, chest pani, loss of body weight and can lower the threshold for the occurence of arrhythmias and convulsions. Routine usage of barbiturates, narcotics and benzodiazepines can be responsible for increased doses of anesthetics for induction and maintenance of anesthesia.

3.3. Preoperative interview and physical examination

General impression: consciousness, psychological condition, nutritional status, fluid status, appearance of skin and mucous membranes (anemia, peripheral circulation, icterus etc.), body temperature.

Medical history is taken and physical examination is performed with every system included: cardiovascular, respiratory, nervous, hepatal, renal, gastrointestinal, endocrinological (diabetes mellitus, diseases of the thyroid and parathyroid glands, feocromocitoma, disorders of adrenal cortex), haematological, musculoskeletal and reproductory system.

Special attention is given to **the evaluation of the upper airway.**

Inspection of regional anesthesia puncture sites is done and data on anticoagulant therapy are taken.

Routine laboratory investigations

It is recommended that:

a) Urine sample is taken from all patients (diabetes mellitus, urinary infection).

b) Complete blood count and hemoglobine measurement. Complete blood count is a routine test for women (despite age), men older than 40 years and all patients undergoing major surgery. Some patients can have family or ethnic hemoglobinopathies and they should findings of hemoglobin concentration and electrophoresis.

c) Electrolytes are not necessary before elective procedures in asymptomatic patients. In patients older than 60 years of age findings of creatinine in plasma and glucosis might be necessary. When indicated (chronic diseases, use of diuretics, alcoholism), liver functional tests should be done. Glucosis should be done when patients have diabetes, are on corticosteroid therapy or have vascular diseases.

d) Coagulation tests in selected patients: prothrombin time, partial prothrombin time and international normalized ratio (**INR**) etc.

e) Chest radiography findings are indicated in patients that have pulmonary disease in their medical history (acute, chronic) or if they have an evident indication. One should ask for chest radiography when patients have acute or chronic cardiac disease, chest disease, if tuberculosis or malignancy are suspected. It can be done as a routine test if patients are older than 60 years old. If this test was done one month before elective surgical procedure, as a part of follow up, it is not necessary to repeat imaging, unless the patient`s condition has changed.

f) Cardiovascular evaluation: ECG in not necessary (most often) in patients undergoing outpatient surgery. Recommendations vary but always include the need for preoperative ECG if there are systemic cardiovascular diseases (hypertension, periferal vascular diseases, myocardial ischemia), chronic lungs disease and age older than 40 years in men and higher than 50 years in women.

g) Noninvasive cardiovascular tests are done in accordance with cardiologist`s and anesthetist`s opinion.

h) Pulmonary function tests are to determine forced vital capacity (FVC) and forced expiratory volume in the first minute (FEV_1). Those test should be undertaken in patients with evident dyspnea during moderate effort. Blood gases findings are needed in patients with dyspnea and all patients undergoing thoracotomy. They need spirometry as well. If the patient`s condition deteriorates, those findings can be used for comparison.

i) Determination of hormone levels is done only when necessary: TSH, T_3, T_4, cortisol etc.

j) Depending on the nature of surgical illness and other comorbidities a patient might have, additional functional tests and laboratory findings might be necessary.

How many tests and findings are needed is a matter of hospital`s policy and one should act in accordance with that policy. Moreover, one should pay attention to the purpose of tests and should have in mind the reason for repeating the tests, due to medical, ethical and economic reasons.

3.4. ASA classification

ASA 1. normal, healthy patient (without organic, physiological, biochemical or psychological illnesses) without systemic diseases, with a localized process.

ASA 2. Patient with mild systemic disease (well-controlled diabetes mellitus or arterial hypertension, anemia, chronic bronchitis and obesity) that can be a reason for surgical treatment.

ASA 3. Patients with severe systemic disease that are the reason for substantive functional limitations (pectoral angina, obstructive lung disease, severe cardiac disease, former myocardial infarction, severe diabetes with vascular complications) that can be related to surgical procedure.

ASA 4. Decompensated patients with severe systemic disease that is a constant threat to life (congestive heart failure, renal failure, severe lung disease, liver insufficiency, endocrine insufficiency). The illness that is treated can be associated with surgical procedure.

ASA 5. A moribund patient who is not expected to survive more than 24 hours without being operated (ruptured abdominal aneurysm, massive pulmonary embolism, head injury with intracranial bleeding). Patient`s chances for survival are poor unless surgical procedure is performed. That is his last chance.

ASA 6. A declared brain-dead patient whose organs are being removed for donor purposes

E If a procedure is emergent, letter „E" is added, it denotes emergency surgery.

ASA (*American Society of Anesthesiologists*)

3.5. Use of pharmacologic agents prior anesthesia

Introduction

Preparation for surgery is about psychological preparation of patients and pharmacological premedication. Preoperative interview with a patient is of great importance because it gives sufficinet information about anesthesia and surgery to the patient. When talking to the patient is properly done, patient`s anxiety and level of stress are minimized. While interviewing a patient, an anesthetist gets insight into patient`s psychological status and decides or recommends that drugs should be taken. Other than psychological premedication, giving information and calming patient down, there is also pharmacological premedication. Pharmacologically benzodiazepines are the best way to remove patient`s anxiety.

Pharmacological premedication

Goals of pharmacological premedication are: stress release, sedation, amnesia, analgesia, decresing secretions in oral cavity and upper airway, preventing reflex response of autonomic nervous system,

decreasing gastric volume and increasing pH value, antiemetic effect, decreased use of anesthetics, easy induction, prophylaxis of allergic reactions, continuation of chronic therapy and prevention of postoperative infections (in some cases).

Prescribing drugs while premedicating needs to be selective and drug`s adverse effects have to be avoided. It is important that anesthetist decides whether a patient needs a drug or not (older patients), when to miss out a drug (decreased consciousness, intracranial hypertension, severe lung disease, severe hypovolemia etc.)

Choosing drugs and doses for preoperative use of pharmacological agents (Table 3-1.)

Table 3-1. Drugs used for pharmacological premedication:

Drug	Route of administration	Doses for adults (mg)
diazepam	orally (per os= po.)	5-20
lorazepam	po., im.	1-4
midazolam	im.	2 - 10
	po.	0,2 – 0,5 mg/kg
pentobarbital	po., im.	50-200
morphine	im. or sc.	5-15
meperidine	im.	50-100
promethazine	im.	25 – 50
cimetidine	po., im., iv.	150-300
ranitidine	po., iv. or im.	150–300 50 40 (infusion more than 30 min)
sodium citrate (0,3 M)	po.	30 mL
atropine	im., iv.	0,3-0,6
glycopyrolate	im., iv.	0,1-0,3
antacids	po.	10-30 mL
paracetamol	po. or rectally	1 000 (1 g)
diclofenac	po. or rectally	50 – 100

Goals when prescribing premedication:
- removing concerns - benzodiazepines
- reducing secretions – anticholinergics
- sedation – barbiturates, opioids
- removing postoperative nausea - antiemetics
- amnesia – benzodiazepines (lorazepam, diazepam)
- reducing gastric volume and decreasing acidity of gastric contents – metoclopramide, sodium citrate
- decreasing vagal reflex - anticolinergics
- decreasing sympatico-adrenal response – β blockers or clonidine
- prophylaxis of venous thrombosis.

Preoperative anesthetic agens are often prescribed in combinations, but a single drug can be prescribed as well. However, usually a combination of two drugs is used. Sedative, tranquilizer, phenothiazine, narcotic and alcaloide belladonna are used in combinations. They can be administered orally, intramusculary or intravenously on operating table immediately before induction.

Preventing complications after anesthesia

Prophylaxis (preventing complications after anesthesia/ operation):
a) deep vein thrombosis and pulmonary embolism,
b) aspiration of gastric content;
c) infections,
d) adrenal cortex suppresion.

Prophylaxis of venous thrombosis (prevention using anticoagulants)

Pulmonary embolism is responsible for 10% of all hospital deaths. Without prophylactic actions, 40 to 80% of high-risk patients develop evident deep vein thrombosis and 10% of them die from pulmonary embolism. Most pulmonary embolisms are a result of deep vein thrombosis beginning in veins of lower legs and extending proximally into femoral and iliac veins. Deep vein thrombosis is detectable in more than 10% of high-risk patients, it rarely spreads into proximal veins and can lead to chronic leg oedema, changes on skin and mucous membranes (postphlebitic syndrome).

While operating on intestines, the risk of thrombophlebitis is increased due to: hypercoagulability caused by operation or other factors (carcinoma, blood stasis in veins of legs caused by anesthesia and by not moving after the surgery, damage on veins during surgery, poor venous return due to pregnancy, surgery in pelvic area, pneumoperitoneum during laparoscopic surgery, dehidration, decreased cardiac output).

Every patient limited to staying in bed is at risk of developing venous thrombosis, even if he has not been operated, and especially if other risk factors are present. Older patients are especially prone to this and need prophylaxis as soon as they are admitted to hospital.

Risk factors for developing thromboembolism:

Patients are divided into three categories when it comes to risk: low, medium and high-risk patients, depending on the type of surgery, patient`s condition and comorbidities they might have. Low-risk patients have 0.4% chance of developing superficial venous thrombosis and 0.2% chance of developing fatal pulmonary embolism. Medium-risk patients have 2-4% chance for developing superficial venous thrombosis and fatal pulmonary embolism less then 0.5%. Superficial venous thrombosis develops in 10-20% cases in high-risk patients, and fatal pulmonary embolism in 1-5% cases.

Duration and type of surgery
- operations up to 30 minutes – low risk
- operations that last more than 30 minutes – high risk
- especially high risk – surgical procedures including major joints (hip, knee), abdominal and pelvic surgery.

Patient related factors:
- previous history of deep venous thrombosis or pulmonary embolism
- thrombophilia
- pregnancy, puerperium, estrogen therapy (contraceptives), hormonal replacement therapy
- more than 40 years of age (risk increases with age)
- obesity and immobility
- varicose veins (in abdominal and pelvic surgery, however, the risk in not increased while performing surgery on varicose veins).

Associated diseases:
- malignancy (especially metastatic tumors in pelvis or abdomen)
- trauma (injuries of spinal cord and pelvis, lower limbs fractures)
- heart failure, recent myocardial infarction
- systemic infections
- lower limbs paralysis, hematological disorders (polycythemia, leukemia, paraproteinemia)
- Other diseases, including nephrotic syndrome and inflamatory bowel diseases.

Minor surgical procedures in healthy men older than 40 years carry a small risk.

Major surgical procedures in abdomen of relatively healthy patients older than 40 years old carry medium risk.

Older patients with carcinoma undergoing pelvic surgery carry a large risk of thromboembolism.

Thromboprophylaxis

Prophylaxis of venous thrombosis is necessary in:
- patients older than 40 years old and undergoing surgery
- immobile neurosurgical patients with signs of heart failure, pneumonia, sepsis, nephrotic syndrome, intestinal inflammation and hemostasis disorder.

- immobile patients or those with trouble moving due to neurological disorders (ischemic cerebro-vascular insult)
- pregnant women older than 35 years, obese patients or those with varicose syndrome

Prophylaxis is carried out by:

a) non-pharmacological procedures

b) pharmacological therapy.

Non-pharmacological procedures

- a patient needs to get out of bed as soon as possible
- a patient needs to work out while in bed (passive excercises)
- patient`s limbs need to be elevated at 30° (when possible due to patient`s condition)
- Elastic stockings and pneumatic cuffs are used to improve circulation. They should be avoided when there are arterial diseases of lower extremities present. Air compression increases the pressure to 35 - 40 mmHg for 10 seconds every minute and is effective.

These procedures decrease frequency of venous thromboembolism, but don`t remove the risk. This is done when additional pharmacological therapy is used.

Pharmacological therapy

- unfractionated heparine
- low molecular weight heparine
- low molecular weight dextrane

Unfractionated heparine

Heparine is given 2 hours prior to surgery or even before, 5 000 units are administered subcutaneously. It is given as a prevention in immobile patients (neurosurgical, polytraumatized, patients with neurological – ischemic or cardiovascular insult), as soon as these entities have been diagnosed. Postoperative therapy: 5 000 units are given subcutaneously 2-3 times a day.

Low molecular weight heparine is administered 12 hours prior to surgical procedure.

Type of anesthesia

Regional anesthesia is preferable to general because of the protective effects (especially for hip and knee surgery) and the fact that a patient is able to move earlier.

Use of oral contraceptives

Women using oral contraceptives have an increased risk for developing venous thrombosis, especially women using pills of the 3rd generation containing desogestrel or gestodene (estrogenes). Their risk is 3-4 times higher. Progesterone doesn`t increase the risk for developing deep vein thrombosis and pulmonary embolism.

It is recommended that oral contraceptives are not taken 4 weeks prior to surgery (major surgical procedure). Two weeks after the surgery, once patients are mobile or after the menstrual bleeding is over, the use of oral contraceptives can be continued. If patients are using progesterone, they don`t need to stop using them prior to surgeries. If a patient is scheduled for some minor surgery, the use of oral contraceptives does not need to be stopped. When an emergent surgical procedure is needed, it is not possible to stop using oral contraceptives according to the above mentioned recommendationes and one should act according to clinical signs and laboratory findings. The approach is always individualised.

Gastric pH and volume of gastric content

Pulmonary aspiration of gastric content significantly increases morbidity and mortality of patients.

Following factors lead to regurgitation and pulmonary aspiration:

- inadequate anesthesia
- pregnancy
- obesity
- difficult intubation
- emergency
- full stomach
- gastrointestinal motility disorders.

Aspiration of 30-40 mL of gastric content can cause serious lung damage. Fasting is done in order to decrease volume of gastric content. Gastric emptying time depends on the type of food, amount of food, stress and patient`s gastrointestinal function. Liquids are evacuated from stomach in 20 to 40 minutes

and complete passage is done in 2 hours from the intake. Clear liquids include water, fruit juices without pulp, clear tee, carbonated beverages and black coffee. These liquids don`t include alcohol.

Gastric emptying is much slower when solid foods are ingested and varies on the type of food ingested. The food containing lots of fat and meat needs 8 hours or more in order to leave stomach. Light meal, a toast, is emptied from the stomach in 4 hours. Nonhuman milk is considered as a solid meal. However, small amount of milk (10mL) added to coffee or tea does not increase gastric volume, nor acidity. Cow`s milk is evacuated from the stomach in 5 hours. Human milk has less fat and proteins and evacuates more quickly.

Gastric evacuation is slower if following metabolic factors are present:
- poorly regulated diabetes
- renal failure
- decreased gastric motility (head injury) or pylorus obstruction (pylorus stenosis) sometimes effects evacuation of solids, especially if the food ingested has lots of celulosis like carrots and cereals
- gastroesophageal reflux is related to postponed gastric evacuation of solids, but the evacuation of liquids is not affected.
- increased intraabdominal pressure (pregnancy, obesity) lead to passive regurgitation of gastric content
- opioids have significant effect on postponing gastric evacuation
- Trauma delays gastric emptying. The time interval between the last oral intake and the injury is considered as the fasting period and a rapid sequence induction should be used if this interval is horot anesthesia is needed. The time taken to return to normal gastric emptying after trauma is not easy to establish because it depends upon degree of trauma and the level of pain. The best indicators are probably signs of normal gastric motility and patient`s hunger. .
- Anxiety, due to increased simpatic activity, is associated with delayed gastric emptying. Simpaticus relaxes gastric smooth muscles and increases sphincter tone.
- Oral premedication given 1 hour before surgery is without adverse effects on gastric volume and induction of anesthesia. Studies have shown that premedication with oral midazolam 30 minutes preoperatively have not reported any link with gastric regurgitation or aspiration.

Chemical control of gastric acidity and volume

Antacides can be used to neutralise acid in the stomach, thereby reducing the risk of damage if aspiration occurs. Particulate antacides are not recommended.

The danger from gastric content aspiration is decreased if a patient is starving and has not eaten 6-8 hours before elective procedure requiring anesthesia. For infants and small children the fasting period is 4 hours. If an emergent intubation is needed and the patient has full stomach, rapid sequence induction is used and the patient is extubated when fully conscious, with swallowing reflex present. It is also recommended that nasogastric sonde is set, gastric content is aspirated and gastric acidity decreased.

Recommendations for decreasing the risk of pulmonary aspiration:

Liquids and solids are not to be taken before induction. Time from the last oral intake should not be lower then following (according to ASA guidelines, 1999.):

Clear liquid	2 hours
Breast milk	4 hours
Milk formula	4–6 hours
Other milk	6 hours
Light meal	6 hours

Antiemetics

They decrease the feeling of disgust and vomiting. Disgust and vomiting can start before induction in anesthesia, but are more often after anesthesia. Frequency varies from 10 do 55%. When performing strabismus surgery in children, frequency of disgust and vomiting is up to 47%. They are more often when terminating pregnancy and performing ear and laparoscopic surgery.

Vomiting, increased venous bleeding, increased intraocular and intracranial pressure can happen after surgical procedure and can therefore jeopardize surgical success. Hence, they should be prevented in a timely manner.

Administration of antiemetics can be usefull as a prophylactic treatment in patients undergoing eye surgery, gynecologic surgery (pregnancy), in obese patients, patients that have a history of vomiting,

patients that are expected to have a difficult airway, when emergent surgery is necessary and a patient has a full stomach and when there are gastrointestinal motility disorders.

Prophylactic use of antibiotics

Prophylactic use of antibiotics should prevent infections in patients without clinical signs of infection. It is performed:

a) against an infectious agent using one drug,

b) in especially vulnerable patients against a specific infection,

c) Perioperative prophylaxis is used against more infectious agents over a short period of time. Antibiotic is administered before surgery, early enough to ensure maximum concentration of antibiotic at the incision site, during incision. One or two doses of antibiotics are used. Prophylaxis is not used unless a surgeon enters a space where there are bacteria (stomach, intestines, oral cavity etc.)

Example of premedicating an adult:

• Preoperative visit and interview,

• Night before surgical procedure benzodiazepines are administered orally. If the patient takes chronic therapy, he is free to use it.

• Benzodiazepines are administered orally 1-2 hours before surgery. Gastric emptying can be stimulated with 150mL water. If necessary, analgetic and opioid can be given intramusculary.

• Scopolamine is administered intramusculary 1-2 hours before surgery if sedation and amnesia are necessary.

• If antisialogenic effect is necessary, glycopyrrolate (or atropine) can be given intramusculary before leaving room or intravenously before induction,

• Oral administration of H_2 antagonists and/or metoclopramide is administered. If emergent procedure is needed, they can be given intravenously.

Preoperative medication of out of hospital patients

Premedication of those patients is controversal no matter if intravenous, oral or intramuscular routes are used. Intravenously adminisered meperidine, orally given midazolam or intravenously administered fentanyl, droperidol or metoclopramide can reduce frequency of postoperative nausea and vomiting. However, routine use of antacids and gastrocinetic drugs is questionable.

It is important to choose the right drug and adequate dose and, if those conditions are fulfilled, recovery won`t be prolonged.

Children. Psychological preparation is of great importance because separation from parents (custodians) equals stress. Preparation is related to the child`s age and skills are needed in order to release them form anxiety. Children show interest and often want to participate in induction (by holding mask on their own). Sometimes (when hospital`s condition allow) parents can be present during induction in anesthesia. In that way the entire process is less stressful for a child. Oral route of administering drugs is more often used in children and anticolinergics are often received for reducing vagal activity.

It is important to stress out that patients with chronic disorders must continue with their chronic therapy (drugs affecting heart and vessels, antihypertensives, antidiabetic agents, anticonvulsives, hormonal therapy etc.)

Patients using acetylsalicylic acid should stop using it 7 to 30 days prior to surgery, and minimum 3 days before surgery.

Patients using warfarin or other vitamin K antagonists need to stop using them 2-3 days before surgery. They need to start using low molecular weight heparins or heparin intravenously immediately before surgery, during surgery and postoperaively. Prothrombin time (PT), activated partial thromboplastin time (APTT) and INR values need to be carefully monitored.

4. LOCAL ANESTHETICS

Ines Bilokapić**, Marko Jukić*

4.1. Local anesthetics

Local anesthetics (LA) affect all organ systems with strong effect on central nervous system. They block the transmission of the action potential by inhibition of voltage-gated sodium ion channels in neurons. This process is reversible.

The typical structure of a LA consists of lipophilic group (usually an aromatic benzene ring) separated from a hydrophilic group (usually a tertiary amine).

Local anesthetics are synthesized (except cocaine), nitrogen-containing, alkaline agents and have a bitter taste. They are prepared as a salt of hydrochloric or sulfuric acid. Such salts are in the form of strong acid solutions, but irritation of tissue is minimal due to the high neutralization capacity of the organism. They have a vasodilating effect (with the exception of cocaine). Infiltration into the inflamed area can not make a satisfactory anesthetic effect because increased acidity of inflamed tissue reduces the activity of LA. The pH of inflammatory tissue is 5.

Absorption

Skin: LA do not penetrate the skin

Subcutaneous tissue: Absorption through the subcutaneous tissue is related to the vascularity of the site of injection. Addition of epinephrine causes vasoconstriction and decreased absorption

Ophtalmic area: absorption is significant through the conjunctival membrane (example: subconjunctival injections)

Mucous membranes of the nose, pharynx, trachea, bronchi and alveoli: very rapid absorption (like intravenous absorption)

Intramuscular injection: the absorption of intramuscular injections is slower than intravenous injection or superficial application on the mucosal membranes of the tracheobronchial tree

Vasoconstrictors: don't postpone absorption when applied on mucous membranes

Oesophagus: there is no significant absorption through the mucous membrane of the oesophagus

Stomach and urethra: very fast

Subarachnoidal space: absorption in the blood is slow; the level of drug in the blood is rarely seen after doses for subarachnoid anesthesia. Vasoconstrictors (epinephrine, phenylephrine) delaying absorption and prolong the anesthetic effect time by 60%

Epidural space: Local anesthetics diffuse along the nerves through the intervertebral canal. Vasoconstrictors delayed absorption.

Hyaluronidase

Hyaluronic acid is found in the interstitial tissue. It holds cells together and delays diffusion. Hyaluronidase is an enzyme which hydrolyzed hyaluronic acid, and so allows a faster passage of the solutions into the tissues. It is added to a local anesthetic and facilitates its diffusion. It reduces the duration of the block and is not recommended for conductive and block anesthesia. Also, it can increase the incidence of systemic toxic reactions caused by LA.

Vasoconstrictors

LA (except cocaine) dilatate blood vessels which leads to increase rate of absorption and reduces time of duration of anesthetic block. Addition of vasoconstrictors reduces the peak LA concetration in blood, prolongs the duration of action, and limits toxic side effects.

Epinephrine (adrenaline) is the most commonly used vasoconstrictor. It prevents depress effects LA on cardiovascular system. Recommended concentrations are 1:100 000 (1 mg/100 mL) or 1:200 000 (1 mg/200 mL). A stronger solution of adrenaline can cause tissue damage due to induced ischemia. The total quantity of a given epinephrine to the local anesthetic should not exceed 1 mg. When administered in the subarachnoid space, adrenaline 0.2-0.3 mg provides a large increase in the duration of the block.

Giving adrenaline for surface anesthesia is not effective. Adrenaline will be omitted as the addition to the local anesthetic solution under the following conditions: in patients who have a history of hypertension, thyrotoxicosis, diabetes or cardiac disease. Also, when performing a surgical procedures of the fingers or toes, adrenaline should be omitted because it can arise serious vasospasm and limb ischemia.

Other vasoconstrictor that we can add to the local anesthetic solution is phenylephrine, but it is used in concentrations of 2 to 10 times higher than epinephrine.

Detoxication

The rate of excretion of LA varies on the type of agent and its pharmacokinetics. The kidney eliminates decomposition products or part of unchanged anesthetic.

4.2. Types of local anesthetics

Aminoesters LA: 2-Chloroprocaine, Tetracaine, Procaine, Cocaine, Benzocaine

Aminoamides LA: Lidocaine, Mepivacaine, Bupivacaine, Etidocaine, Ropivacaine, Levobupivacaine, Prilocaine, Dibucaine, Trimecain,

Tetracaine (Pontocaine)

Tetracaine is ester of para-aminobenzoic acid (PABA). It is used in superficial, infiltration, block, caudal and subarachnoid anesthesia. Tetracaine is more powerful and more toxic then procaine (for 10 times). It is not aloud to use it with sulfonamides. Onset of action is for 5 to 10 minutes and duration is 2 hours.

Dosage: For conductive and block anesthesia, 0.1 to 0.25% solution with or without addition of epinephrine 1: 200,000. The maximum dose is 100 mg.

Lidocaine (Xylocaine)

Lidocaine is the prototype of the amide class of LAs which is commonly used for superficial, infiltration, block, subarachnoid, epidural and caudal anesthesia. It is also used intravenously for the treatment of chemical or mechanical induced arrhythmias during general anesthesia, cardiac surgery or induced hypothermia. Compared with procaine: onset of action is faster, stronger, more intense, lasts longer. It is more poweful and more toxic then procaine (for 2 times). By increasing concetration, toxicity also increased because the drug is absorbed rapidly. Lidocaine has the effect of 1-1.5 hours. With addition of epinephrine duration is 2 hours. The initial effect of overdose is depression. Nap and amnesia can occur, especially when you use lidocaine without adrenaline. Hypotension, sweating, nausea, vomiting, muscle twitching and convulsions may also occur. Hypersensitivity to lidocaine is extremely rare.

Dosage: for infiltration and block anesthesia, 2-60 mL 0.5 -2 % solution with or without addition of epinephrine 1: 100,000 or 1: 200,000. The maximum dose is 300 mg without adrenaline and 500 mg with adrenaline. For epidural anesthesia, 1-2 % solution with or without addition of epinephrine 1: 200,000. For subarachnoid anesthesia, 5 % solution with 7,5 % dextrose. In a normal delivery, 50 mg (1 mL) provides perianal anesthesia for two hours. For superficial anesthesia, 2-4% solution can be used for the pharynx, larynx and tracheobronchial tree. The maximum dose is 250 mg. Jelly 2% is used in endoscopy of the urethra. For the treatment of ventricular arrhythmias, doses of 50 to 100 mg or 1-2 mg / min (1 mg / 1 mL) in a slow intravenous infusion.

Mepivacaine (Carbocaine)

Mepivacaine is amino amide LA which is used for superficial, infiltration, block, subarachnoid, epidural and caudal anesthesia. Its pharmacologic properties are similar to those of lidocaine (onset of action, duration, toxicity, potency). Mepivacaine causes vasodilatation less than lidocaine and it can be used without adrenaline, which, if given, does not increase duration. Mepivacaine is indicated in patients with a history of hypertension, cardiovascular disease, diabetes, or thyrotoxicosis. Also, it is used for nerve block of ear, fingers, toe, penis, and during childbirth. In such cases, the vasoconstrictor is undesirable.

Dosage: The maximal dose must not exceed 1000 mg in 24 hours or more than 8 mg per kilogram of body weight in single dose. For infiltration and block anesthesia, 5-40 mL of 1-2% solution. Caudal anesthesia for 15-30 mL of 1-2% solution.

Bupivacaine (Marcaine)

Its structure is similar to that of lidocaine and mepivacaine. Like tetracaine, it is more cardiotoxic than lidocaine.

Dosage: For infiltration anesthesia and peripheral nerve block, 0.25-0.75% solution is used. The maximum dose is 200 mg and duration is 3-8 hours. Adrenalin (1: 200,000) can also be added. For an epidural or caudal anesthesia, 15-30 mL of 0.25-0.75% solution.

Etidocaine (Duranest)

The latest LA. Long-acting amino amide Etidocaine is structurally similar to lidocaine, with alkyl substitution on the aliphatic connecting group between the hydrophilic amine and the amide linkage. It is 4 times stronger than lidocaine while only 2 times more toxic.

Dosage: For infiltration, peripheral nerve block, epidural and caudal anesthesia (excluding subarachnoid), solution of 0.5-1.5% with epinephrine (1: 200,000) is used. The maximum dose is 300 mg, and the duration of effect is 4-6 hours.

5. REGIONAL AND LOCAL ANESTHESIA

Ines Bilokapić**, Marko Jukić*

5.1. Introduction

Regional anesthesia is specific type of anesthesia in which only part of the body is anesthetized so the surgery can be performed. Injection of a local anesthetic near a nerve or plexus causes insensitivity. Regional anesthesia involves subarachnoid, epidural, peripheral nerve blocks, intravenous regional anesthesia, infiltration and surface (topical) anesthesia. At patients with subarachnoid and epidural anesthesia, anesthetized areas are lower abdomen and lower limbs. In block anesthesia, anesthetized area is part of body which is innervated by the nerve or plexus. In intravenous regional anesthesia, anesthetized area is part of the limb which is distally from the cuffs; a surgical procedure is available on the forearm or lower leg. Anesthetic infiltration is anesthesia by layers of certain area. Dripping or spraying the solution of local anesthetic, anesthetizes certain mucous membranes and thus provides brief intervention or diagnostic procedure (eg, gastroscopy, bronchoscopy).

History

Local anesthesia was used for the first time in the second half of the 19th century after the discovery of cocaine and at the same time the syringe was invented. Although the neurologist Corning first applied cocaine in the subarachnoid space in 1885, the usage of cocaine in subarachnoid space was attributed to Augustus Biera in 1899.

In 1901 Fernand Cathelin performed caudal anesthesia.

In the first half of the 20th, few more local anesthetics were discovered and all momentarily known techniques of regional anesthesia (epidural, subarachnoid, intravenous regional, block anesthesia, etc.) were introduced. In 1921, Spaniard Fidel Pagés, invented special needle for lumbar epidural anesthesia. In 1931, Italian Dagliotti described the technique of „*loss of resistance*" for the detection of epidural space. In 1940, Edward Touhy developed a new needle and Martinez Curbelo first performed continuous epidural anesthesia.

Today, about 70% of the operations are performed in regional and local anesthesia.

5.2. Local anesthetics

The usage of local anesthetic is conditioned by many factors. One of them is type of a local anesthetic (previous adverse reactions, allergy to local anesthetics). Another one is concentration (for infiltration of the skin and subcutaneous tissue lower concentration is used (0.5 to 1 or 2% lidocaine), the surface anesthesia of mucous membranes higher concentration is used (2% to 10%), for peripheral block and regional anesthesia medium and higher concentration of local anesthetic is used (0.5% to 5%, bupivacaine, tetracaine, lidocaine). The next one is specific weight of the local anesthetic (due the cerebrospinal fluid: isobaric, hypobaric and hyperbaric, which is very important for subarachnoid anesthesia). Amount of local anesthetic is one of the factors (for subarachnoid anesthesia using a small amount of local anesthetic, and for epidural anesthesia are used greater amounts of local anesthetic). Drugs added to the local anesthetic (adrenaline) are the last fator.

5.3. Regional and local anesthesia

Indications for regional and local anesthesia

Subarachnoid and epidural anesthesia are performed for surgical procedures below the navel (umbilicus). Also is used in urological, gynecological and surgeries performed during the deliveries. When the level is above Th 10, or when there are long term operations, it is better to perform a combination of subarachnoid or epidural anesthesia with general anesthesia (abdominal, gynecological surgery). For post – surgery analgesia and treatment of chronic pain, epidural catheter can be set. The catheter can be set subarachnoidally, but serious complications are possible.

In limbs surgeries, peripheral nerve blockade can be performed. Also, surgical procedures on the lower leg or forearm, regional intravenous anesthesia can be performed.

Surface anesthesia is performed on the conjunctiva, the mucous membrane of the nose, throat, esophagus and tracheobronchial tree.

Contraindications to regional and local anesthesia
- disorders of coagulation and anticoagulant therapy
- hypovolemia
- sepsis and infection at the site of the puncture
- severe stenosis heart valve, the patient is not able to compensate vasodilation, because cardiac output is fixed
- preeclampsia, toxemia, low platelet count (100 × 109 L-1) - subarachnoid and epidural anesthesia is not performed
- acute neurologic disease; increased intracranial pressure
- when the patient does not agree to this type of anesthesia
- existing neurological damage in the region that needs to be anesthetized

Advantages of local, regional anesthesia

Advantages over general anesthesia are: technique is simple, requires minimal equipment to perform it, drugs are not flammable, bleeding is reduced, nausea and vomiting also, less damage to body functions, can be used when general anesthesia is contraindicated, no pollution equipment, less need for postoperative surveillance and care and lower incidence of pulmonary complications. The patient is awake and breathing spontaneously. In patients with subarachnoid anesthesia, there is a good muscle relaxation of lower abdomen and lower limbs. When local anesthesia is used, it is possible to recognize early signs of hypoglycemia. Patients can start with feeding. Postoperative venous thrombosis are less frequent. The price is much lower than that of general anesthesia.

Regional anesthesia causes a complete sensory block, which prevents bad stimuli in the area of the surgical field. This is not the case with general anesthesia.

Regional anesthesia is used in identification of fractured hand tendons.

Equipment

Anesthesia machine and equipment for CPR must be prepared. Monitoring of patients during anesthesia is standard (EKG, RR, SPO_2 etc...). Because of possibility for toxic reactions and complications, laryngoscope and endotracheal tube, equipment for administration of oxygen and mechanical ventilation with high pressure, must be available immediately. Diazepam, ultra - short barbiturates (to treat spasms), skeletal muscle relaxants, fluid infusions, vasopressors, antiarrhythmics, and other drugs are also used.

Equipment for regional anesthesia:
- a local anesthetic (lidocaine, bupivacaine, ropivacaine, tetracaine, and / or other)
- proper needle (for puncture): spinal needle of 24 G or more Gauge (Charrier); epidural puncture needle 14 G, 16 G, 18 G and 20 G; needles to perform peripheral nerve block - 22 G, 25 G needle
- detergents for puncture sites and surrounding areas, sterile compresses, sterile gloves, gauze, adhesive tape

The use of peripheral neurostimulators in regional anesthesia

Identification of nerve and plexus is not simple, and the individual variations makes it even more difficult.

Causing mechanical paresthesia while putting a needle, may be reliable clinical sign, but it can cause mechanical injury to the nervous tissue and harmful application of intraneural anesthetic. In order to prevent complications and to facilitate the identification of nerves, neurostimulator is being used. Peripheral neurostimulators are easy to handle, small and portable. These are small battery-powered devices that can receive constant direct current pulses. Their usage prevent occurrence of paresthesia. Motor fibers have a lower threshold then sensory fibers. So if you gradually increase amplitude, then you avoid unpleasant paresthetics sensations.

The use of ultrasound

For the identification of nerves and blood vessels, ultrasound machine is used. Under control of ultrasound, puncture is performed.

5.4. Surface anesthesia

It is the oldest method of anesthesia, that was found in South America when the numbness of tongue and mouth at domicile people was noticed when they chewed leaves of *Erythroxylon coca.* From that plant

the cocaine was isolated and after that the other anesthetics also. Some of the other local anesthetics, with appropriate concentration, are efficiently used on skin and mucosa. Indications for surface anesthesia areinterventions on mucosa, biopsies, punctures, then placement of tubes, catheters and endoscopic procedures. The nasal mucosa is anesthetized by coating or tamping of gauze soaked in a 2 to 4% solution of lidocaine. If suspecting on problematic intubation, surface anesthesia of upper respiratory tract by spraying 10% solution of lidocaine is performed. With light sedation, the endotracheal tube is placed. By mixing two local anesthetics (cream EMLA – lidocaine, procaine), better surface anesthesia can be performed. Also, local anesthesia of skin and mucose can be done by dripping (0.5 % tetracaine), coating (EMLA) and by spraying.

Size of anesthetized field depends on place of LA injection, total volume, concetration and anesthetic's ability of penetration in to the tissue.

Injection of local anesthetic into inflamed tissue can not effectly anesthetize that part because augmented acidity of inflamed tissue reduces local anesthetic activity. In inflamed tissue, pH value is around 5. Use of local anesthetic on surface is safe except if using high concentration that can be reabsorbed through mucoses. In table 5-1. local anesthetics for surface anesthesia and their clinical usage are shown.

Table 5-1. Local anesthetic's products and their clinical usage

Local anesthetic	Concentration (%)	Pharmaceutical product	Clinical usage
benzocaine	1-5	cream, unguent, aerosol	skin and mucose membranes
cocaine	4	solution	mucose of ear, nose and throat
lidocaine	2-4	solution	aerosol oropharinx, tracheobronhial tree, nose
	2	gel, unguent	urethra
	2.5-5	suppository	skin, mucose membrane, rectum
	10		gums
tetracaine	0.5-1; 0.25-1	unguent, cream, solution	skin, rectum, mucose membrane, nose, tracheobronhial tree

Surface anesthesia is a result of using certain amount of local anesthetic on traumatized skin or mucose membrane. Table 5-2. shows doses of local anesthetics for surface anesthesia.

Tablica 5-2. Doses of local anesthetics for surface anesthesia

Medication	Concentration	Duration	Maximal dose
Cocaine	4%	30 min	200 mg
Lidocaine	2 – 4%	15 min	200 mg
Tetracaine	0.5%	45 min	50 mg

Cocaine, dibucaine, lidocaine, piperocaine and tetracaine are used for surface anesthesia of conjunctiva, cornea, mouth, nose, throat, oesophagus, larynx, trachea, urethra and anus.

5.5. Infiltration anesthesia

Infiltration, injection of anesthetics in tissue allows performing simple surgeries. It must be done by injecting local anesthetics in every layer. Infiltration anesthesia is performed by injecting local anesthetics in subcutaneous tissue, submucosal, or in the area close to peripheral nerve. This technique is being used from the end of 19th. Infiltration techiniqe by Vishnjevschi consists of transversal injection of local anesthetic and it is use for surgeries of upper and lower limbs and soft tissue of chest and abdomen. Infiltration anesthesia is appropriate for surgeries of head due to anatomic location of nerves. Lower concentration of anesthetics are used with or without addition of adrenaline 1:200 000. While infiltrating, it is very important to aspirate carefully so there is not direct injection into blood vessel and therefore toxic reaction. Maximal infiltration doses are shown in table 5-3.

5.6. Intercostal block

Intercostal block is used for surgeries of thorax, front wall of abdomen, and post surgery pain control in the same area. Also, it is a therapy for pain control due to fractured ribs.

Intercostal nerves consist of anterior motor fibres, back sensory roots of spinal nerves and branches of simpatic chain. After leaving paravertebral space, nerves are on the inner side of the lower edges of ribs, together with artery and vein (from cranial to caudal: vein, artery, nerve – VAN). They innervate intercostal muscles. Sensory fibers innervate skin of thorax and front wall of abdomen.

Tablica 5-3. Local anesthetics for infiltration anesthesia and their maximal doses

Local anesthetics	Commercial product	Maximal dose (mg)	Maximal dose with adrenaline (mg)
Procaine	10 and 20 mg/mL solution		1 000 (12 mg/kg)
Lidocaine	5 and 10 mg/mL solution	300 (4.5 mg/kg)	7 mg/kg
Chloroprocaine	10 mg/mL solution	1 000 (12 mg/kg)	
Mepivacaine	10 mg/mL solution	400 (4.5 mg/kg)	7 mg/kg
Prilocaine	10 and 20 mg/mL solution		600 (8 mg/kg)
Bupivacaine	2.5 mg/mL solution	200 (3 mg/kg)	
Etidocaine	2.5 and 5 mg/mL solution	300	

Tablica 5-4. Relation of lidocaine concentration in plasma and clinical signs

Lidocaine concentration in plasma (μg/mL)	Clinical signs
1-5	analgesia
5-10	ear noise, numbness of tongue
10-15	convulsions, disturbances of consciousness
15-25	coma, respiration arrest
>25	depression of myocard

Intercostal block can be performed on any part of their way, but mostly it is done in the back area of ribs or in rear axillary line. The patient can be set in lateral, prone or sitting position. The shoulders must be relaxed, arms moved away from the body so the scapulas move apart and allow access to the fourth and fifth rib.

Distances between each costal arch and medial line are different. In upper parts distance is about 5 cm and in lower parts distance is about 10 cm. That line is in the same place as imaginary line between spine scapula and crista illiaca. In the spot where that imaginary line cross lower part of rib, needle is placed.

Tehnique

Block is performed under sterile conditions which include skin disinfection, sterile gloves and equipment for performing the block. For or five centimeters long needle is used. It is placed under the right angle toward the lower edge of the rib to the periosteum. Then the needle is directed obliquely and up, under the ribs to a depth of 2-3 mm. After passing intercostal muscle, loss of resistance can be felt. After negative aspiration, 3-5 mL of local anesthetic is injected (bupivacaine 0.25-0.5%). The same procedure can be repeated for each intercostal nerve.

Complications of intercostal blocks are: pneumothorax, intravascular injection, and general toxic reactions due to systemic absorption of large amounts of local anesthetic. Local anesthetics are rapidly absorbed from the well blooded intercostal space, so it is preferable to use lower concentration of local anesthetic with the addition of adrenaline 1: 200, 000.

5.7. Regional anesthesia

The patient should be prepared for regional anesthesia as for general anesthesia. He should be informed about sideffects and complications of regional anesthesia.

Benzodiazepines are usually used for premedications.

Types of regional anesthesia: conductive and block anesthesia, epidural, subarachnoid, caudal anesthesia and intravenous regional anesthesia.

Conductive-block anesthesia

Conductive block anesthesia is injection of local anesthetics solution around nerve tissue that is further from the area that needs to be anesthetized.

This procedure is named after the area that needs to be anesthetized (for example paravertebral block, brachial plexus block). In table 5-5. there are doses of local anesthetics for conductive-block anesthesia.

We have:
- block of brachial plexus (supraclavicular approach, interscalene approach, infraclavicular approach, axillary brachial plexus block)
- block of plexus cervicalis

- block of the nerves of the upper limb (block of radial nerve, ulnar block, block of nerve medianus, digital nerve block)
- block of intercostal nerves
- block of lumbosacral plexus: the psoas, lumbosacral block (combined) and schiatic nerve block
- block of nerves of lower limbs: femoral nerve block, block of medial cutaneous femoris lateralis, nerve block of obturatorius, schiatic nerve block, block of posterior tibialis, block of nerve peroneus.

Table 5-5. Doses of local anesthetics for conductive and block anesthesia

Local anesthetic	Concentration	Duration	Maximal dose
Procaine	2-4 %	1/2 h	1000 mg
Lidocaine	1-2 %	1-2 h	500 mg
Mepivacaine	1-2 %	1-2 h	500 mg
Tetracaine	0.1-0.25 %	2-3 h	75 mg
Bupivacaine	0.5 %	5-7 h	200 mg
Etidocaine	0.5-1 %	4-6 h	300 mg

5.8. Intravenous regional anesthesia (Bier's block)

Intravenous regional anesthesia is used for minor surgeries on forearm and lower leg. Local anesthetics, 0.5% lidocaine is injected into the vein of a limb on which surgery will be performed. Previously set cuff prevents local anesthetic to enter into systemic circulation. Instead, it stays binded to a particular part of the body. Solution of local anesthetic without vasoconstrictor is injected into vein of bloodless limb. The most used are lidocaine (0.5%), prilocaine (0.5%) and mepivacaine (0.5%).

Indications: surgeries and manipulations with duration of 1 hour or less on upper and lower limbs from cuff. This technique is recommended especially for soft tissue surgeries like ganglion removal and Dupuyetron contracture's surgery.

Contraindications: bifascicular and trifascicular block in EKG. Pacients who have syncopes and limb infections in their histories of illness.

Pacient need to be prepared as for general anesthesia. Also what needs to be set is: i.v. catether, intubation equipment, oxygen connection, atropine, sedatives, succinylcholine, vasopressors and catecholamines.

Equipment: Esmarch bandage, two cuffs or one double cuff, plastic vein cannula 20 G., 20 mL injections, rubber cuff.

Pacient's position is prone with abducted leg or arm.

5.9. Subarachnoid, epidural and caudal anesthesia

When imaginary line connects cristae iliaca superior posterior, level of processus spinosus L4 or intervertebral space L4 – L5 is determined. Counting to up or down, other spaces are identified. Subarachnoid anesthesia can be done by injecting small doses of local anesthetic (1.5-3mL) into subarachnoidal space. Anesthetic is then mixed with cerebrospinal fluid. Dural puncture is done under L2 at adults and under L3 at children. Also, subarachnoid anesthesia is adequate for surgeries under navel.

At epidural and caudal anesthesia, anesthesia is performed with greater amount of anesthetic for surgeries of lower abdomen and lower limbs. Anesthetic is injected into epidural space. Also, it is used for post surgery analgesia and chronic pain treatment.

Term used for epidural, subarachnoid and caudal anesthesia is neuraxial anesthesia.

Subarachnoid anesthesia

Local anesthetics used for subarachnoid anesthesia can be: hyperbaric, isobaric or hypobaric, depending on specific weight – greater, equal or lower than specific weight of cerebrospinal liquor. Specific weight of liquor is 1.003-1.007. Anesthetic used for that are: bupivacaine, levobupivacaine, lidocaine, tetracaine and other.

Indications:

Surgeries: of lower limbs including soft tissues, blood vessels or bone; perineum, including anus, lower rectum, vagina and urologic surgeries; lower abdomen, including both abdominal wall (hernia)

or intraperitonal surgeries (distally small intestine, apendix, rectosigmoid, bladder and lower ureter and gynecological surgeries), upper abdomen, including cholecystectomy, closed or perforated gastric ulcer and transversal colon. Subarachnoid anesthesia for upper abdomen is not indicated for all pacients because it can cause significant physiological changes: obstetrics, vaginal delivery, section: diagnostic and therapeutic treatments which are very painful.

Contraindications:

Absolute: bleeding disease (coagulation disorder). Risk of injury of great vein plexus with spinal needle which can result in compression of spinal cord; septicemia, can lead to meningitis; augmented intracranial pressure, changes in the braint can lead to loss of liquor; pacients who refuse that kind of treatmend. Subarachnoidal anesthesia without approval is disrespect of pacient's autonomy.

Chronical dermatitis or skin infection neat the spot of puncture, pathogenic causers can be brought in liquor. System disease with neurological sequelae, like pernicious anemia, neurosifilis or porphyria; threatening diseases of spinal cord, amyotrophic lateral sclerosis and multiple sclerosis. Also hypotension because sympathetic blockade removes main compensatory mechanisms.

Relative: hemorrhage, usage of low sitting block anesthesia only when it is necessary for surgery and if vital signs are compensated. Spinal problems cause muscule straining, facet syndrome, arthritis or disk degeneration. Returning spinal pain at pacients could be associated to lumbal puncture.

Epidural (lumbal epidural, thoracal epidural)

Epidural or caudal anesthesia is performed by injecting local anesthetic into epidural space of lumbal region or sacral canal. Continuous epidural anesthesia is performed by setting soft catheter through the needle into space between dura and ligament flava for reinjection of solution of local anesthetic. Injection is usually done under level of second lumbal vertebra. Also, it can be done on other places, but for doing that, additional research is needed.

Main advantages of epidural anesthesia compared with subarachnoid anesthesia is causing all-inclusive regional anesthesia without puncture of dura and injecting alien supstances into cerebrospinal space and elimination of post lumbal puncture headache. Choice of anesthetic for epidural and caudal anesthesia is: lidocaine, mepivacaine and bupivacaine.

Peridural space is between dura mater and periostum spinal canal; from foramen occipitale magnum to sacrococcygeal ligament. Dural space in sacral canal ends in level of S1, S2. Peridural anesthesia can be done on thoracal, lumbal or sacral level. Local anesthetic in peridural space has impact on nerves of peridural, subarachnoid and paravertebral space. In that way, anesthetized parts are: front and rear roots with ganglia, mixes spinal nerves and related branches, afferent visceral fibres and some descendent paths of spinal cord.

There are more factors that impacts on spreading of anesthetic in peridural space: physical and chemical characteristics, concentration and amount of anesthetic, general condition and age of pacient. Younger people have greater capacity of peridural space, so larger dose is needed. Speed of injection increases volume of peridural bloc.

Amount of local anesthetic is individual; at younger and healthier people around 1-1.5 mL or 0.75 mL at older per somatic dermatome. Injection of 15 mL of anesthetic into intervertebral space L2-L3 anesthetizes around five somatic dermatomes cranially and caudally. In table 5-7., thera are doses of local anesthetics for epidural anesthesia.

Table 5-7. Doses of local anesthetics for epidural anesthesia (peridural, lumbal or caudal - single technique)

Medicament	Concentration	Duration	Maximal dose
Lidocaine	1-2 %	1,5 hours	
Mepivacaine	1-2 %		500 mg
Tetracaine	0.1-0.25 %	2-3 hours	75 mg
Bupivacaine	0.5-0.75 %	3,5-5 hours	225 mg
Etidocaine	0.5-1 %	4-6 hours	300 mg

Continuous peridural anesthesia

Continuous peridural anesthesia is performed by introduction of catheter peridurally with continuous injection of anesthetic. Indications can be therapeutic or surgical. It is being used in delivery anesthesia, post surgical analgesia and vasospasm.

Complications in epidural anesthesia

During vasodilation, there can occur drop in blood pressure. Pacient then receive crystalloid solution intravenous, vasopressors and oxygen mask.

If there is unwanted subarachnoid injection of larger amount of local anesthetic, there can occur full spinal blockade with loss of blood pressure and breathing cessation. Pacient then needs to be positioned in Trendelenburg position, crystalloid solutions are injected intravenous, pacient is intubated and artificially ventilated and vasopressors are given.

After injection of local anesthetic peridurally because of resorption, there can occur system toxic reaction. Unwanted intravascular injection leads to intoxication with local anesthetic. That can be solved according to symptomes and health condition of pacient. Generation of peridural hematomas at pacients with tendency of bleeding or at pacients who receive anticoagulation therapy can cause neurologic complications because of hematoma pressure on nerves.

Inserting peridural catheter can cause lesion of dura, injection of anesthetic subdurally, break of catheter and infections. Adhesive changes in peridural space can prevent normal spreading of local anesthetic and lead to incomplete peridural block.

Contraindications for peridural anesthesia: hypovolemia, disbalance of electrolytes, state of shock, disorder of coagulation, local infection on the spot of puncture, neurologic damage of spine, deformation of spine on the spot of puncture.

Regional anesthesia in obstetrics: lumbal-epidural, caudal, regional anesthesia for Caesarean section, paracervical block, pudendal block.

5.10. Unwanted reactions

System and local unwanted reactions are similar for all local anesthetics. Many unwanted reactions are easy of moderately difficult for treatmend, but also disasters are possible. Often, reactions occur beacause of inattention (toxic dose of anesthetic, high spinal block), oversensitivity on local anesthetic and interaction of medicaments (epinephrine).

Unwanted phenomenon: hypotension, headache, urine retention, neurologic complications, inflammations (meningitis, arachnoiditis, epidural abscess, subarachnoidal or epidural hematoma).

Frequency of hematoma creation is 1:150 000 at epidural puncture, 1:220 000 at subarachnoid puncture. Bleeding inside of spinal canal can cause pressure on spinal cord. Symptome is pain which as a sign of nervous problem. It is necessary to do the MR or myelography so the position and size of hematome can be determined. After that, it has to be surgically removed. Also, coagulation factors and tests are very important in that case. It is recommended that hematoma is removed in 8 to 12 hours after creation. Maximal neurologic symptom is usually after 13 hours from hematoma creation. In case when hematoma is not so big and when symptomes are mild, conservative treatment can be performed. It has to be emphasized that it is the best to avoid neuroaxial anesthesia at pacients who have coagulation disorder, thrombocytopenia, significant thrombocyte disfunction and who have fibrinolytic/thrombolytic therapy.

Epidural abscess

Frequency is 1:140 000 punctures. Abscess, by pressing onto nerve tissue, directly causes ischemia and damages nerve tissue. It is very important that it is diagnosticaly processed and the mesures to prevent permanent damage of nerve tissue are taken. Symptomes are sharp pain in back and leg and motoris disfunction of sphincter. MR or CT has to be done and surgical treatment considered. Pacients can be recovered if abscess is surgically removed in 8 to 12 hours. Drainage of abscess has to be done and antibiotics taken. The most often causers are gold and epidermal staphylococcus.

Hypotension occurs beacause of vasodilation caused by local anesthetics (sympathicus blockade) in subarachnoid or epidural and block-anesthesia. At high subarachnoid block, hypotension and collapse of circulation (paleness, nausea, bradycardia) can occur. It is necessary to give infusion solution, oxygen, ephendrine 5-10 mg intravenous and pacient has to be positioned in Trendelenburg position. Sometimes, smaller doses of benzodiazepines (midazolam 1-2 mg) can be helpful. Hypotension occurs in case of predominance of vagus, anaphylactoid reaction and local toxic reaction of local anesthetic. For hypotension prevention, infusion solution (0.9% NaCl, Ringer's solution and other) is recommended before giving local anesthetic. In subarachnoid anesthesia, amount of infusion is 500-1500mL (crystalloid). In epidural anesthesia, amount is smaller, but it is determined based on clinical picture and other factors related to pacient's cardiovascular system.

Headache usually occurs after dura puncture with big needle and that makes liquor goes out. Dura puncture in epidural anesthesia is unplanned (thicker needle) and in subarachnoid anesthesia is planned

(thinner needle). To avoid post puncture headache, needle with small diameter (24, 25 G and more) are user because they damage dura less. Also, fluid compensation and rest reduce headaches. Intensity of headaches is bigger if pacient is sitting or standing. If pacient feels well, he can get up from bed or sit few hours after subarachnoid anesthesia.

Urine retention can be solved with one-time catheterization and bladder emptying. It occurs because of excessive flud input. Also, pulmonary edema can occur and it is important to be careful with giving larger amount of fluid and clinical picture has to be monitored.

Neurologic complications (nerve damages, subarachnoid hematoma) usually goes away in few weeks. Sympthomes like pain in the back usually disappear spontaneously. Longterm hypotension can cause syndrome of frontal spinal artery and permanent paraplegia. Also, there can occur inflammation of spinal cord tunic and hematoma that weights on spinal cord or nerve roots.

Pneumothorax can occur during supraclavicular brachial plexus block, intercostal and paravertebral block. Rare but possible complication is break of catheter during the pull of catheter through cannula.

System reaction of allergic etiology

Allergic reactions caused by local anesthetics are rare. More often, they are caused by amino esters (procaine, tetracaine) than amino amides, probably less than 0.5% of all allergic reactions. Signs of that are urticaria, itching, angioneurotic edema, asthmatic breathing, syncopa, respiratory arrest and even death. Treatment includes: epinephrine, oxygen, infusion solution, antihistamine, bronchodilators and other therapies.

Reactions caused by epinephrine added to solution of local anesthetic

It is most caused by overdose or interaction with another medicament. System signs and symptomes of epinephrine overdose are: fear, palpitation, tremor, tachycardia, tachypnea, hypertension, sweating, unrest, weakness, headache and pale skin. Hypertension can cause cerebral hemorrhage, arrhythmia and coronary blockage. With really high overdose, tachycardia can cause pulmonary edema and ventricular fibrillation. Reactions caused by epinephrine are different than system reactions caused by local anesthetics.

Treatment: oxygen, vasodilators, sedatives and symptomatic therapy.

Local reactions causes by local anesthetics

Swelling on the spot of injection, abscess, ulceration and skin peeling after nerve block by local anesthetic. Skin peeling can occur after injection of dibucaine and hexilacaine. Therapy includes antibiotics and sympathicus block.

Complications caused by local anesthetics

Intravascular injection of local anesthetic subarachnoidal instead of epidurally, cuff loose, nerve damage and spinal cord injury are serious regional anesthesia complications. System reactions are associated with high level of local anesthetic in blood, usually because of overdose, fast system absorption or uncareful intravenous use. Absorption occurs through mucouse membrane of nose, throat and respiratory system. It is fast and similar to intravenous absorption because of blood supply and fast absorption through alveolus. Absorped anesthetics circulating comes to heart and causes sudden death after application of local anesthetic to tracheobronchial tree. Other factors for toxic reaction are: overdose, large amount given subarachnoidal instead of epidurally, oversensitivity – anaphylactic reaction or shock.

Effects on heart and blood vessels are result of heart depression and vasodilatory impact of local anesthetics. Hypotension, bradycardia, weak pulse, paleness, wet skin, sweating and heart arrhythmia can lead to arrest. Medular centers can be affected; result is respiratoy despression, apnea and vascular collapse.

Reaction of central nerveous system are: nausea, vomit, euphoria, disturbance, vertigo, disorientation. This can be followed by muscle spasms, convulsions, coma, respiratory failure and heart failure.

Therapy

For convulsion: diazepam (Valium) or ultra-short barbiturate (thiopental) or machine ventilation with or without muscle relaxation.

For respiratory depression: oxygen and artificial ventilation

For cardiovascular collapse: vasopressors, fluid intravenous and outter massage of heart.

Precaution

If pacient is allergic to local anesthetics, usage of medicaments of other chemical groups is recommended. Local anesthetics with epinephrie will not be injected during inhalation anesthesia with cyclopropan, halothane or other halogen anesthetics because of possibility of ventricular arrhythmia. It is recommended to avoid nerve block anesthesia at older pacients with hypertehnsion, cardiovascular diseases, diabetes or thyrotoxicosis in history of illness.

Conductive or block anesthesia during pregnancy: epinephrine can cause vasoconstriction of blood vessels in uterus with effect of reduced blood supply of placenta, weaken uterine contractions and extend delivery duration.

Epinephrine must be avoided at solution of local anesthetics used for: nerve block anesthesia in area with end arteries because of possibility of rejection (gangrena).

Therapy of possible toxic reaction and complication

There always has to be:
- laryngoscope and endotracheal tube
- equipment for giving oxygen, artificial ventilation with high pressure and maintenance of path through pharynx
- diazepam, ultra-short barbiturate
- muscle relaxants
- intravenous fluids and vasopressors.

6. INHALATIONAL AND INTRAVENOUS ANESTHETICS

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6.1. Introduction

Anesthesia is actually the art of administering certain drugs aiming to achieve patient's:
1) unconsciousness
2) amnesia
3) analgesia
4) immobility and
5) weakening of the autonomous nerve system's response to a painful stimulation.

The goal of anesthesia is to administer an optimal dosage of drugs in order to achieve desired effect and on the other side to avoid side effects and drugs toxicity while maintaining patient's internal homeostasis. In anesthesia we use anesthetics and muscle relaxants. Anesthetics are mostly divided into two groups: inhalational and intravenous. Consequently, general anesthesia is divided into inhalational, intravenous and balanced anesthesia. A balanced anesthesia is actually an application of different agents (intravenous hypnotics, analgesics, inhalational anesthetics) in a minimum amount which is needed to achieve most desired effect. Muscle relaxants are discussed in a separate chapter.

6.2. Inhalational anesthetics

Inhalational anesthesia has a special advantage and popularity over other techniques because an anesthetic is taken up and eliminated exclusively through breathing.

The effect begins by inhalation at the point of entry into the body (lungs, alveolar-capillary membrane), followed then by distribution and redistribution in the body. Biotransformation (metabolism) is variable, e.g. for desflurane 0.02%, and for halothane is up to 20%. Excretion also happens primarily via the lungs.

Inhalational anesthetics such as di-ethyl-ether, chloroform, trichlorethylen and cyclopropane belong to the distant past. Nowadays fluorinated inhalational anesthetics are exclusively used. In the clinical practice, the first one was fluroxene, which was abandoned in 1974. Halothane, in clinical practice since 1956, is characterized as hepatotoxic and it is rarely used nowadays. Methoxyflurane was introduced in 1960, however it was abandoned due to its nephrotoxicity. Enflurane was introduced in 1963, but it was abandoned because of a cardiovascular depression and proconvulsive effect. Isoflurane was introduced in 1965, desflurane in 1992 (not in Croatia) and sevoflurane in 1994.

Inhalational anesthetics (except for nitrous oxide - N_2O) are in a form of liquids at the room temperature and atmospheric pressure; therefore they are called also volatile anesthetics. Today, isoflurane, sevoflurane and desflurane are mostly in clinical use among volatile anesthetics, while nitrous oxide is a gas (Fig. 6-1).
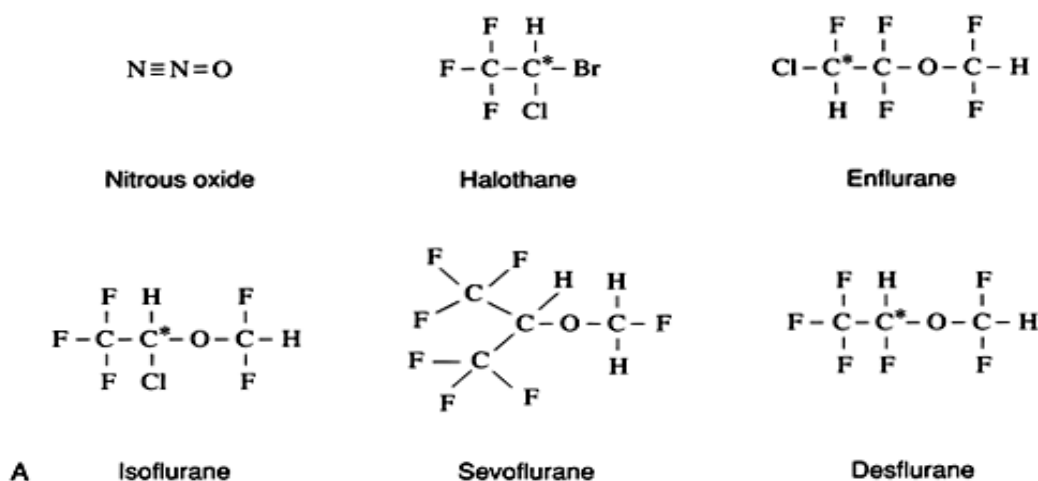
Fig. 6-1. Inhalational anesthetic chemical structure

Inhaled anesthetics are delivered to the airway by means of vaporizers. That is the most acceptable technique which converts liquid volatile anesthetic into a form that could be delivered to a patient through inhalation in a form of vapor. The vaporizer is a device that is most commonly attached to an anesthetic machine and delivers a determined concentration of a volatile anesthetic. Evaporation of an inhalational anesthetic depends on a temperature and gas flow. Modern vaporizers in every moment provide an exact concentration of inhalational anesthetic in all conditions. Each inhalational anesthetic has its specific vaporizer.

A concentration of inhalational anesthetic in the central nervous system depends on:
- Oil:gas solubility ratio (liposolubility)
- Partial pressure of an anesthetic
- Solubility of a specific anesthetic in a blood
  - if the solubility of anesthetic in a blood is increased, more anesthetic is required and induction of anesthesia is slower
- Cardiac output (CO)
  - Higher CO leads to a faster induction of anesthesia

6.2.1. MAC – The Minimal Alveolar Concentration

MAC is an abbreviation for the minimal alveolar concentration. It is the alveolar concentration of inhaled anesthetic sufficient to prevent movement in 50% patients as a response to standardized stimulus (surgical incision). If an inhalational anesthetic has a lower MAC, it is more potent (Table 6-1). MAC value is expressed as a percentage, i.e. it is the percentage of alveolar gas concentration occupied by the respective anesthetic. Caution: MAC means concentration in alveoli, but not the one set at the dial of the vaporizer, which is always higher!! MAC changes with age and also with the use of nitrous oxide along with volatile anesthetic (in that case MAC of volatile anesthetic is lower - Table 6-3). Introduction of the term MAC is very useful in clinical practice since one can compare different anesthetics, and also well define possible standards for experiments.

Table 6-1. MAC for certain inhalational anesthetics

ANESTHETIC	MAC%
N_2O	105
Halothane	0.75
Isoflurane	1.1
Desflurane	6.0
Sevoflurane	2.0

Along with standard values of MAC50, in literature other MAC values may be found, for example MACawake (MAC whereby the patient wakes up), MAC95 (concentration of inhalational anesthetic substantial to prevent movement in 95% patients as a response to standardized stimulus), MAC for blocking autonomous response - MAC BAR, MAC EI (MAC for endotracheal intubation - intubation is very invasive and painful stimulus). (Table 6-2.)

Table 6-2. Multiple MAC values for individual inhalational anesthetics

MAC %	N_2O	halothane	isoflurane	sevoflurane	desflurane
MAC 50	104	0.78	1.14	2.05	6.0
MAC awake	64	0.41	0.49	0.62	2.42
MAC 95		0.9	1.63	?	?
MAC EI		1.46	?	3.35	?
MAC BAR		1.45	1.48	2.52	7.8

6.2.2. Review of individual inhalational anesthetics

Halothane

It is a halogenated alcane, the cheapest one. It is considered that it may cause halothane hepatitis (1 in 35,000 cases). It seems that this problem occurs due to its reductive mechanism, mainly in the conditions of hypoxia. It is manifested by increase of transaminases, bilirubin and encephalopathy. It develops more

often after multiple anesthesias administered in short intervals, in middle-aged obese females and also in patients with family history of such complications.

Isoflurane

It is considered a gold standard for inhalational anesthetic. It is the most potent among volatile anesthetics in today's use, however, it has unpleasant odor and therefore it is not very suitable for induction of anesthesia but only for anesthesia maintenance.

Sevoflurane

Sevoflurane is characterized by a rapid induction of anesthesia; it has a pleasant smell and therefore is ideal for induction of anesthesia (and not only in children). For instance, a patient exposed to mixture of 6-8% sevoflurane and 50% N_2O falls asleep in about one minute. Also, awakening after sevoflurane is significantly faster than after isoflurane. However, unpleasant phenomena sometimes occur during emergence from anesthesia, especially in children (such as excitation). Those can be prevented with small doses of the synthetic opioid such as fentanyl. In contact with CO_2 absorber in the anesthesia circuit, it could be degradated into compound A (compound A = PIFE – pentafluoro-isopropyl-fluoromethyl-ether). In rats, this compound causes kidney damage. In humans, the situation is less clear. US FDA cites: "The level of compound A at which clinical nephrotoxicity could be expected has not been established yet with certainty. The clinician should still take all measures to reduce exposure to the compound A." That means, in practice it is necessary to adjust inspiratory concentration of sevoflurane and fresh gas flow (FGF) as needed. Sevoflurane should not be administered more than 2 MAC•hours with FGF of 1-2 L/min. FGFless than 1L is not recommended when using sevoflurane!!

Desflurane

It is the least soluble inhalational anesthetic, therefore characterized with rapid induction and fast awakening. It's not registered in Croatia.

Nitrous oxide

It is also called laughing gas, in German language Lachgas. It was discovered by Joseph Priestley, English priest and scientist 1773, while Humphrey Davy scientifically superbly described its metabolism and features in 1800. It is a non-flammable gas, with sweetish odor, and it is not potent anesthetic. It is mostly used as a supplement to volatile anesthetics and opioids during maintenance of general anesthesia. It is a good analgesic, however weak anesthetic. It has to be used in a mixture with oxygen.

Today, potential problems when using nitrous oxide are increasingly emphasized: postoperative nausea and vomiting, inactivation of vitamin B12 - prolonged exposure may cause bone marrow depression (pernicious anemia) and even neurological deficit (peripheral neuropathy), as well as its possible teratogenicity. These complications apply not only for patients but also for health workers, working in conditions of inadequate gas scavenging. Furthermore, the nitrous oxide is about 35 times more soluble than nitrogen (N_2), and is easily accumulated in closed spaces subsequently increasing their volume; therefore, it can be dangerous during the middle ear surgery, ileus, as well as in cases of pneumothorax, and air embolism.

Table 6-3. An overview of some physical properties of inhaled anesthetics

Property/anesthetic	SEVOFLURANE	DESFLURANE	ISOFLURANE	ENFLURANE	HALOTHANE	N_2O
Boiling point (°C)	59	24	49	57	50	-88
Vapor pressure at 20°C (mm Hg)	157	669	238	172	243	38.770
Partition coefficient oil:gas	47	19	91	97	224	1.4
Partition coefficient blood:gas	0.65	0.42	1.46	1.9	2.50	0.46
Partition coefficient brain:blood	1.7	1.3	1.6	1.4	1.9	1.1
Partition coefficient oil:blood	47.5	27.2	44.9	36	51.1	2.3
MAC with O_2 30–60 years, 37°C (%)	1.8	6.6	1.17	1.63	0.75	104
MAC with 60–70% N_2O (%)	0.66	2.38	0.56	0.57	0.29	
MAC>65 yrs old (%)	1.45	5.17	1.0	1.55	0.64	—
Metabolism (%)	2–5	0.02	0.2	2.4	20	

6.2.3. Effect of inhalational anestheticon various organ systems

Along with their anesthetic effect, inhalational anesthetics exert their effect on many other organ systems. In the central nervous system, they lead to reduction of cerebral metabolism. They cause vasodilata-

tion and consequently increase intracranial pressure. Therefore, their administration is not recommended in some neurosurgical procedures and cranial trauma.

Regarding respiratory system, inhalational anesthetics provoke dose-dependent respiratory depression. Also, they depress hypoxic ventilatory response with values as low as 0.1 MAC. This may be particularly important in awakening from anesthesia, when patients depend on the hypoxic stimulus. They are efficient bronchodilatators, therefore they are recommended for anesthesia of patients with asthma.

Regarding cardiovascular system, these anesthetics lead to a drop in arterial blood pressure: it happens primarily because of vasodilatation, but also because of reduction in CO and decrease in sympathetic tone. They affect heart rate differently (for instance, desflurane is increasing). Inhalational anesthetics are sensitive to exogenous administered catecholamine (epinephrine), when malignant arrhythmias may occur. This situation may happen in general inhalational anesthesia where a local anesthetic is injected together with epinephrine. Today, there is good evidence about cardioprotective effects of volatile anesthetics; the use of volatile anesthetics in cardiac surgery decreased myocardial injury (as reflected by lower levels of troponins) and patients' stay in intensive care unit.

Inhalational anesthetics have an effect on blood cells (nitrous oxide) and also on neuromuscular system (not only they do enhance the effect of relaxants but they can relax muscles alone). They have an effect on uterus as well, in a way that they relaxmyometrium. This can be clinically significant since it can contribute to a blood loss. Therefore they are avoided in certain gynecological-obstetric surgical procedures.

6.3. Intravenous anesthetics

6.3.1. Definition and introductory remarks

Definition of intravenous anesthetics: a drug which leads to unconsciousness in a single circulation time (hand-brain, cca 10-20 seconds), if administered in adequate dose. According to another definition, intravenous anesthetics are a group of chemical compounds of a different structure, which are entered into a venous part of circulation, transferred to the brain and subsequently cause changes in cerebral physiology of different degrees such as anxiolysis, sedation, deep sedation, hypnosis and anesthesia. Ideal intravenous anesthetic should lead to a hypnosis, amnesia, analgesia, muscle relaxation, without unacceptable cardiac and/or respiratory depression.

Intravenous anesthetic could be administered:
- One time (bolus)
- Repeatedly administration of the same or different doses
- Continuous infusion of constant or variable speed injection
    - it can be controlled manually or with computer

The current use of intravenous anesthetics inclinical practice:
- Induction of anesthesia
- Maintenance of anesthesia
- Conscious sedation
- Other (anticonvulsants, "barbiturate coma")

6.3.2. History - intravenous anesthesia

The first mention of intravenous anesthetic was in 1657. That is when Sir Christopher Wren, English scientist and architect, injected through sharp goose feather opium to a dog. He also administered intravenously so-called *crocus metallorum*, impure preparation of antimony (Sb), and noticed that the animals began to vomit violently, and soon would die. After that, there was a long period of stagnation in this field, and as late as in 1830 the lancets for administration of subcutaneous morphine were made. In 1845 Irish physician Rynd invented the hollow needle for giving morphine straight "in the nerves" and in 1855 he also invented the syringe. Early attempts of intravenous anesthesia were administration of chloral hydrate in 1872 by Pierre Oré from Lyon. In the next few years, there were 36 cases of intravenous anesthesia published, but also several postoperative deaths, so this method was not very much recommended. In 1909 in Germany surgical anesthesia with i.v. injections of chloroform and ether was attempted. In 1916 in Switzerland morphine and scopolamine were used. Both attempts did not demonstrate any progress compared to inhalational anesthesia; therefore, intravenous anesthesia did not gain much popularity mainly because of lack of adequate drugs.

New era in anesthesia started with the development of ultra-short barbiturate thiopental. It was discovered in early 1930s (Abbott Laboratories). First administration on humans was made on March 8,

1934 by Ralph M. Waters (Madison, Wisconsin, USA); the drug produced short-lived anesthesia and very weak analgesia. Three months later, John S. Lundy started a clinical trial on Mayo Clinic. Introduction of thiopental in clinical practice in 1934 marked the starting point of intravenous anesthesia. Methohexital (oxy-barbiturate) was synthesized later in UK, and it was used until recently (it was causing a pain with injection, excitation and tachycardia). In 1950s, Selye noticed that steroids produced a sleep in some animals, so hydroxidione was synthesized (abandoned for side effects), followed by althesin (Saffan; introduced in 1972, abandoned in 1984. due to frequent anaphylaxis - bronchospasm, hypotension). Anaphylaxis was likely to occur because of Cremophor EL additive.

Ketamine, derivative of fencyclidine was introduced in 1970 and is still in clinical use, however rarely. Benzodiazepines were introduced in 1955. (chlordiazepoxide-librium), however, in today's practice diazepam (1963) and midazolam (1975) are used. Etomidate is imidazolyl esther, introduced in 1974, and is in use today. Propofol is very popular today, it was introduced in 1977 and certain modifications were made in 1986. Fospropofol starts to be used in 2010 for specific procedures.

Although opioids are primarily analgesics, they need to be mentioned since they are an essential part of intravenous anesthesia. Opium is derived from poppy seeds (Papaver somniferum). In 1803 Sertürner, Prussian chemist, synthesized morphine alkaloid (in Greek Morpheus – the God of Dreams), which started to be used at the end of 19th century. The interest for opioids became significant in 1940s thanks to Lundy's concept of balanced anesthesia, which consists of:
- thiopental for introduction
- nitrous oxide for amnesia
- opioids for analgesia and
- curare for relaxation

In 1939 meperidine (Dolantin) was the first synthetic opioid to be used. In 1969 it was discovered that opioids in high doses may act as complete anesthetics. The most famous laboratory in the synthesis of opioids was Janssen's lab, especially during 1960s and 1970s; the most popular products are fentanyl, sufentanil and alfentanil, which are more than 100 times stronger than morphine. They are inevitable in modern anesthetic practice today. Remifentanil (Ultiva) is an opioid synthesized in 1996. It is characterized with ultra-short effect and along with propofol is nowadays a basic part of total intravenous anesthesia.

6.3.3. Intravenous anesthetics and their effect on cardiovascular and respiratory system

The effects of individual anesthetics on cardiovascular and respiratory systems are described further in the text.

Generally speaking, acute cardiovascular effects of specific anesthetic are summary of effects on:
- Myocardium
- Coronary flow
- Electrophysiology
- Coronary system
- Neurohormonal reflex functioning

To understand the effect of anesthetics on respiration, one needs to understand respiratory control in general. The control of breathing may be chemical/metabolic and behavioral. Chemical/metabolic control of respiration depends on the chemical compositionof arterial blood (pH, pO_2, pCO_2) and the chemical composition of the interstitial fluid in the brainstem (pH, tissue CO_2 in brain). This control happens during the non-REM sleep and anesthesia. Behavioral control adjusts respiration in special situations such as speech, physical effort, pain, stress, and awakening. Anesthetics have an effect on both mechanisms:
1) on chemical control:
   - acting on peripheral chemoreceptors
   - causing depression of respiratory centers
   - causing suppression of the motor neuron function, intercostal muscles and diaphragm
2) on behavioral control:
   - they reduce wakefulness

Therefore, it is obvious that, in term of breathing, anesthetics, either inhalational or intravenous, change:
- breathing pattern
- rhythm
- frequency

Besides, ventilatory response to CO_2 and hypoxia (hypoxic ventilatory response) is significantly decreased.

6.3.4. Review of specific intravenous anesthetics

Barbiturates

Barbiturates are derivatives of barbituric acid in which, by different substitutes on C5 atom, anticonvulsant and hypnotic properties are gained. If oxygen is replaced with sulphur on C2 atom, then the thiobarbiturates are created and those have increased liposolubility, faster onset and are generally more potent. Clinically important thiobarbiturates are thiopental (Pentothal, Nesdonal) and tiamilal (Surital) while oxybarbiturates are Methohexital (Brevital) and Phenobarbital (Luminal).

Clinical use of barbiturates for:

- Induction and maintenance of anesthesia
- Status epilepticus
- Barbiturate coma in some severe cases of cranial trauma

Thiopental

Thiopental s most commonly used barbiturate in anesthesia. Like the others, it causes dose-dependent respiratory depression. It depresses medullar respiratory center and consequently decreases responses to hypoxia and hypercapnia. Sedation with barbiturates usually leads to obstruction of upper airway. Apnea is common after an induction dose. Bronchospasm and laryngospasm are possible after anesthesia induction which is, however, mostly the result of manipulation of the airway in the "light" anesthesia (common in asthmatic patients). Possible causes of spasm may be cholinergic stimulation, release of histamine and direct relaxation of bronchial smooth muscles.

Regarding cardiovascular system, thiopental causes heart rate increase, while CO decreases or remains unchanged. After induction of anesthesia with thiopental, decrease of arterial blood pressure often occurs, mainly because of the depression of medullar vasomotor center. This leads to peripheral vasodilatation; there is an accumulation of blood on periphery and a decrease ofvenous return to the right atrium. CO is maintained principally with increase in heart rate and myocardial contractility due to compensatory baroreceptor mechanisms. Thiopental may also have a direct negative inotropic effect. In some patients (hypovolemia, congestive heart failure, beta-blockade), CO and arterial blood pressure can be dramatically reduced due to the accumulation of blood in the periphery and direct myocardial depression. In hypovolemia, CO may decrease up to 70% with significant decrease of blood pressure so patients without adequate compensatory mechanisms may have significant hemodynamic depression. Problems may also occur in patients with uncontrolled hypertension where significant oscillations in arterial blood pressure are possible. Therefore, in patients with ASA 3 and ASA 4 classification, especially in emergencies, other anesthetics are preferred, such as etomidate and ketamine. Also, increases in heart rate (10-36%) in coronary patients administered thiopental may be potentially dangerous because of a consequent increase in myocardial oxygen consumption.

Thiopental is a yellow powder that is diluted with water to 2.5 or 5% concentration (25 or 50 mg/mL). The most common dosage of thiopental is 3-5 mg/kg. When thiopental is administered quickly or in large doses, cardiovascular depression may follow. However, with adequate dosage and slow administration, hemodynamic effect is minimal.

Conclusion: administration of thiopental for induction is safe in normal patients and in patients with compensated heart disease. In patients with heart failure, hypovolemia and tamponade the use of thiopental requires a great caution or even it is better avoided. The development of tachycardia could be a problem with ischemic heart disease.

Unwanted side effects are possible with unintentional extravascular and intra-arterial thiopental administration. In extravascular administration an intense pain is possible as well as local necrosis of tissue. Unintentional arterial administration leads to a severe spasm of artery and burning pain. It is recommended that intravenous (i.e. intra-arterial) cannula remains in place (in situ) so that papaverine or local anesthetic may be administered that should counteract the spasm. Barbiturates may precipitate attacks of porphyria since they induce enzyme ALA (aminolevulinic acid) synthetase. Possible laryngospasm and bronchospasm have been already mentioned. Allergic reactions may also occur.

Propofol

Propofol (2,6 -diisopropylphenol) is used for:

- Induction and maintenance of general anesthesia

- Sedation during regional anesthesia procedures
- Sedation of patients in intensive care unit

It is especially popular for short surgical and diagnostic procedures, because of the favorable pharmacokinetic profile. It causes a very fast onset, but also very fast and pleasant awakening.

Propofol is a major part of total intravenous anesthesia (TIVA), which actually was developed with the appearance of propofol and some other drugs (opioids - alfentanil, remifentanil). All these drugs are characterized with fast elimination time which enables titration of level of anesthesia/analgesia. It is a high-quality type of general anesthesia; inhalational anesthetics are not used at all and the mixture of oxygen and air is used during anesthesia maintenance. Newer, more sophisticated form of TIVA is called TCI (target controlled infusion). It is a computer-assisted administration of propofol for induction and maintenance of general anesthesia. TCI was created because propofol has a specific pharmacokinetic profile which allows accurate calculation of certain anesthetic concentration in plasma for a particular effect.

Propofol is characteristicslightlyviscous milky-white substance. It was introduced in 1977 when it was lipid emulsion with most commonly 1% concentration. There were some problems from the very beginning: the instability of lipid solution, pain oninjection (up to 30%), lipid load, the growth of bacteria and fungi. Since propofol is not water-soluble, it was initially mixed with Cremophor EL - polyethoxylated castor oil. However, anaphylactoid reactions were common. After that (from 1986 onwards) it was prepared as an emulsion of 1% isotonic solution, 10% soybean oil, 2.25% glycerol and 1.2% lecithin derived from egg (caution with allergy to egg!). Theoretically, prolonged use may lead to hypertriglyceridemia..

Its popularity coincided with the occurrence of laryngeal mask airway (LMA), in 1980s primarily because propofol significantly suppresses pharyngeal reflexes; it is possible to insert LMA without volatile anesthetics and/or muscle relaxants.

Propofol is primarily a hypnotic. Its effect is achieved by positive modulation of the GABA inhibitory functions via $GABA_A$ receptors. It reaches its effect by binding to β-subunit of this receptor.It appears that its site of action is different from that of barbiturates and benzodiazepines. The effects of propofol on other receptors have been not determined with certainty. It has very solid antiemetic effect (possibly anti-serotonergic activity). Propofol comes in interactions with several other neurotransmitter receptors as well as ionic channels inside the peripheral and central nervous system. It probably stimulates glycine receptors and inhibits nicotinic acetylcholine receptors and glutamate NMDA and AMPA receptors.

Moreover, it increases concentration of dopamine in nucleus accumbens, which is a phenomenon seen with some addictive substances. That can explain hallucinations and sexual fantasies that are seen after administration of this anesthetic. The effects of propofol are potentially pleasant and desirable; nice dreams, sexual disinhibition, illusions, physical hugs in people who are awakening from propofol anesthesia. Patients describe their dreams as "pleasant", "euphoric", and "relaxing". Unfortunately, recreational use of propofol is seen as well as abuse and addiction, mostly in medical professionals. Most common cause of death in these situations is respiratory depression.

Propofol leads to dose-dependent respiratory depression. The dose of propofol for anesthesia maintenance leads to reduction in "tidal volume" and increase of respiratory frequency. Ventilatory response to hypoxia and CO_2 is also significantly depressedby propofol. Apnea (cessation of breathing) occurs more often after induction dose of propofol than with other anesthetics. It may last longer than 30 seconds, especially if opioid was administered simultaneously. Propofol causes bronchodilatation in patients with COPD.

Regarding cardiovascular system, propofol may provoke significant decrease in arterial blood pressure, especially in hypovolemia. Hypotension occurs mostly because of decrease of systemic vascular resistance and is usually not followed by reflex tachycardia: consequently, CO may be decreased. With usual induction (2-2.5 mg/kg) and maintenance dose (100 ug/kg/min), arterial blood pressure is reduced by 15-40%. Cardiovascular effects of propofol are considered much more pronounced than those of thiopental! Except arterial vasodilatation, it also leads to venodilatation, and that aggravates the hypotension even further. Aging leads to increased circulatory depressive response to propofol - it is necessary to decrease the dose significantly.

Among unwanted side effects of propofol, the pain during injection occurs relatively often. Pain is most common in small veins of dorsum of the hand. Therefore it is recommended to administer propofol to larger cubital veins and many physicians add 10-20 mg of lidocaine to induction dose of propofol. Sometimes, excitatory effects are seen (myoclonus, opisthotonus, convulsions). Bradycardia and hypotension have been already mentioned. Allergic reactions are also possible. Propofol infusion syndrome (PRIS) is a rare syndrome affecting patients undergoing long term exposure to propofol in higher doses

(higher than 4 mg/kg/h over the period longer than 24 hours). It may lead to cardiac arrest, rhabdomy-olysis, metabolic acidosis and kidney failure. It is believed that the cause of such disturbance is fat acids' dysfunctional metabolism on a mitochondrial level. It most frequently happens in children and patients who are simultaneously exposed to catecholamines and steroids. Treatment is supportive, i.e.early recognition and cessation of propofol infusion.

Fospropofol

Fospropofol is a pro-drug of propofol, with the chemical structure of phosphono-O-methyl-2,6-diiso-propylphenol ($C_{13}H_{19}O_5PNa_2$). Propofol is created by hydrolysis (active metabolite) plus phosphate plus formaldehyde. Methylphosphate group is added to the position C1 of propofol, which contributes to the water-solubility of this anesthetic.

Fospropofol is a clear yellowish aqueous solution. Its maximal dose is 12.5 mg/kg. In 2008 it was approved in the USA for sedation in local anesthesia. It is still in a clinical trial phase.

Allegedly, there is no pain in injection when using fospropofol although short-lived genital rash is possible as well as paresthesia. Fospropofol, unlike propofol, leads to less incidence of apnea in healthy volunteers.

Etomidate

Chemical structure of etomidate is R-(+)-ethyl-1-(-methyl-benzyl) imidazole-5-carboxylate. Administered at a dose of 0.3 mg/kg (the most common clinical dose) it causes an immediate loss of consciousness.Its margin of safety is relatively high; the amount between a therapeutic dose and a lethal dose of this anesthetic is 1:30 (for propofol and thiopental 1:4-5).

It has very little effect on the cardiovascular system; therefore it is suitable for unstable patients and in cardiac anesthesia. It does not change the myocardial contractility, oxygen consumption, or the coronary blood flow. Moreover, of all the anesthetics it has the least impact on breathing. It does not release histamine; therefore, it is good in patients with reactive airways. Cough and hiccups are possible during the introduction.

Minimum cardiorespiratory depression makes it an ideal drug even in patients with heart and lung diseases. Also, it is safe to use etomidate in patients with reactive airway, which makes etomidate the anesthetic of choice for induction of anesthesia in high-risk patients or in patients where we want to avoid fluctuations in blood pressure.

Clinical indications for the use of etomidate are conditions where the rapid induction is necessary, but without major cardiovascular and respiratory oscillations:

- Hypovolemia
- Cardiac tamponade
- Decreased CO

For "healthy" patients who undergo elective surgery, it does not provide a greater advantage over other intravenous anesthetics!!

Among the undesirable effects of etomidate there is the pain on injection (30-60% of cases); propylene glycol in the formulation is a possible factor. To some extent it can be reduced by prior administration of opioid and/or lidocaine. Thrombophlebitis is possible even in 30% of cases, and can also occur after 2-3 days. Involuntary muscle movements (myoclonus) are frequent, as well as the hypertonus, cough, and hiccups. Postoperative nausea and vomiting are encountered in 25-30% of patients. Attacks of porphyria may be triggered. Suppression of adrenocortical function by etomidate is increasingly emphasized, as etomidate inhibits the enzyme 11β-hydroxylase important for the synthesis of corticosteroids. There are indications that even a single dose can suppress adrenal function for 5-8 hours. Continuous infusion of etomidate is not recommended!

Ketamine

Ketamine is chemically related to phencyclidine (a hallucinogenic drug, "Angel dust"). It is a non-competitive antagonist of the excitatory neurotransmitter glutamate on NMDA receptors in the CNS; it seems not to react with GABA receptors (the only one). Due to this, "dissociative" anesthesia and good analgesia occur. Dissociative anesthesia means the functional dissociation between thalamocortical and limbic systems, i.e. in the cortex and the thalamus leads to depression of functions and activates the limbic system. Clinically, it is manifested by sedation, anterograde amnesia, deep analgesia and minimal effects on breathing. The patient is dissociated from the environment – he/she can swallow, and keep the eyes open, but can not process information.

Ketamine has significantly slower onset than other anesthetics: IV – more than 2 minutes, IM – more than 8 minutes. Doses for intravenous injection are 1-4 mg/kg, and 6–13 mg/kg for intramuscular injection.

It has strong cardiovascular stimulatory effects due to a direct stimulation of the sympathetic nervous system. It is the only anesthetic that increases peripheral blood resistance. Induction with ketamine causes the increase of heart rate and arterial blood pressure, as well as CO. Possible mechanism of cardiovascular stimulation is probably central, i.e. it weakens baroreceptor response by affecting NMDA receptors in nucleus tractus solitarius.

Ketamine is probably the safest and the most effective anesthetic for patients who:
- are hypovolemic
- have a cardiac tamponade.

Its use in coronary patients, especially those suffering from atrium fibrillation, is not recommended, for the very reason of tachycardia. In patients with valvular heart disease (especially those with pulmonary hypertension), it leads to significant increase of pulmonary vascular resistance in relation to systemic vascular resistance. Also, there is always accompanying tachycardia. In these patients the use of ketamine is a very bad choice. Its use is contraindicated in adult patients with poorly functioning right ventricle.

At clinically relevant doses, there is no or minimal respiratory depression. Respiratory rate may be even slightly increased. Unlike other anesthetics, the airway reflexes are largely preserved. Ketamine also has bronchodilatatory effects, which makes it suitable for inducing anesthesia during an active bronchospasm.

Awakening from ketamine anesthesia may be accompanied by:
- Delirium
- Agitation
- Disorientation
- Confusion
- Psychosis, occasionally.

Undesired tachycardia and problems during the awakening may be diminished by co-administration of lower doses of benzodiazepine.

Besides intravenously, ketamine may be administered intramuscularly and is, therefore, suitable for children anesthesia; intraoral, rectal and nasal administration is also possible. Ketamine is also frequently used in veterinary anesthesia.

In adults ketamine is used in:
- Changing of dressings in burns
- Catheterization of the heart
- High risk patients (polytrauma)
- Spinal and epidural administration, with neuropathic pain.

However, ketamine has a limited use in modern anesthesiology, mainly because of undesired effects to CNS and cardiovascular system.

Benzodiazepines

Benzodiazepines are a class of drugs which bind to distinct benzodiazepine binding sites on the GABA$_A$ receptor.

All lead to:
- Anxiolysis
- Anterograde amnesia
- Sedation
- Hypnosis
- Myorelaxation.

They are used for:
- Induction of anesthesia (rarely)
- More often as co-induction (i.e. they are administered in a small dose with thiopental or propofol)
- Most often as premedication
- Sedation during local/regional anesthesia
- Also for treatment of: convulsions, delirium, agitation

In anesthesia the following preparations are used: midazolam (Dormicum, Versed), diazepam (Apaurin, Normabel, Valium) and lorazepam (Ativan, Lorsilan), provided that the latter is not used in Croatia as a parenteral preparation. It is important that they all have their specific antagonist, which is flumazenil (Anexate).

Benzodiazepines induce dose-dependent respiratory depression, which is less significant if not administered intravenously. Combination with opioids is especially "dangerous". Benzodiazepines depress the swallowing reflex and reflexes of the upper airway. Apnea is slightly rarer than upon barbiturate induction. However, even very low doses of midazolam and diazepam can cause respiratory arrest. Ventilation, therefore, must be monitored in all patients receiving benzodiazepines IV. The equipment for resuscitation and establishment of the airway must be immediately available.

Benzodiazepines lead to decreased systemic vascular resistance and arterial blood pressure, although this decrease is usually "masked" by the stimulus of laryngoscopy and intubation. In hypovolemic patients depression by midazolam is significantly higher. Midazolam (0.15 mg/kg) and ketamine (1.5 mg/kg) are mentioned as a safe and useful combination for rapid induction of anesthesia in emergency conditions. Otherwise, it should be remembered that benzodiazepines are not analgesics and, during induction should be combined with opioids.

6.3.5. Intravenous analgesics – conclusion

Today on the market there are several preparations of intravenous anesthetic for induction and/or maintenance of anesthesia. Thiopental is cheap; awakening is little slower compared to propofol. Propofol has a favorable pharmacokinetic profile, awakening is quick, and postoperative nausea and vomiting are reduced. It is an integral part of modern methods of anesthesia - TIVA, TCI. Benzodiazepines have a slower onset and prolonged awakening, but are characterized by minimal cardiac depression, amnesia, the possibility of co-induction, and as a useful supplement to regional anesthesia. Etomidate is an ideal anesthetic for high-risk patients, due to its minimum cardiac and respiratory effects; its impact on the adrenal function is possible, especially in repeated administration. Ketamine is a unique anesthetic, not only because of its mechanism of action, but also by clinical effects. It causes analgesia, bronchodilation, stimulation of the sympathetic system, and there is a possibility of IM induction (in children). It is good in emergencies (hypovolemic shock, tamponade, acute bronchospasm). However, there is a very unpleasant response to awakening from anesthesia.

Despite the great advances of science, an ideal intravenous anesthetic has not been found yet. However, using existing suitable properties of today's anesthetic in combination with various types of analgesia (opioids, local anesthetic, etc.), very good anesthetic effects and a favorable outcome can be achieved.

7. NEUROMUSCULAR BLOCKING DRUGS - MUSCLE RELAXANTS

Božena Ivančev**, Mladen Carev*

7.1. Introduction

The muscle relaxation is often required during surgical procedures. It can be achieved using:

1) Deep inhalational anesthesia
2) Peripheral nerve blocks
3) Neuromuscular blocking drugs (muscle relaxants)

These muscle relaxants are used not only for skeletal muscle relaxation during surgery but also for facilitation of endotracheal intubation. According to their effects upon the motor end-plate they are divided into either depolarizing (practically the only representative is the succinyl-choline) or nondepolarizing (antagonists of the nicotinic acetyl-choline receptors, there are plenty available on the market: vecuronium, rocuronium, mivacurium etc).

7.2. Historical context

One of the most important events in anesthesia history is the discovery of curare. The curare is arrow poison used by South American natives. Death would have occurred due to the effects of toxins on the nicotinic acetylcholine receptors and consequent neuromuscular relaxation (cessation of breathing), and with a completely preserved consciousness. George Harley (1829–1896) showed in 1850 that curare was effective for the treatment of tetanus and strychnine poisoning. But only with introduction of d-tubocurarine (dTC) into clinical practice by Griffith in 1942, began one of the most important periods in the history of anesthesia. The use of dTC enabled skeletal muscle relaxation and allowed reduction of anesthetic depth and therefore avoidance of cardiorespiratory complications of deep inhalational anesthesia. Succinylcholine (SCh) was introduced in 1952 as a short-acting depolarizing muscle relaxant that was ideal for facilitating endotracheal intubation. Later, many nondepolarizing relaxants were introduced: pancuronium (1967), atracurium and vecuronium (1970s). In 1990, mivacurium and rocuronium were introduced. Rocuronium is the first fast-acting nondepolarizing muscle relaxant comparable to SCh. In 2001 rapacuronium was introduced, but it was abandoned because of its side-effects (Figure 7-1).

7.3. Muscle relaxants - Mechanism of action

The process of muscle contraction originates at the neuromuscular junction. There, striated muscle is innervated by myelinated axon of somatic efferent nerve fibers. Acetylcholine (ACh) is synthesized, stored, mobilized and released by a motor nerve terminal. Neuromuscular junction presents a connection of 20 nm width between muscle and nerve terminal. On postsynaptic membrane there are nicotinic cholinergic receptors. When the propagated action potential reaches a nerve ending, the ACh is released into the junctional gap near nicotinic cholinergic receptors on motor end-plate in sufficient quantities to produce an action potential in muscle and induce muscle contraction. Once released from the nerve terminal, ACh is exposed in the junctional cleft to the enzyme acetylcholinesterase (AChE), which inactivates ACh by hydrolizing it to choline and acetate. The choline is then efficiently re-uptaken within the nerve terminal for the use in synthesis of new ACh (Figure 7-2.).
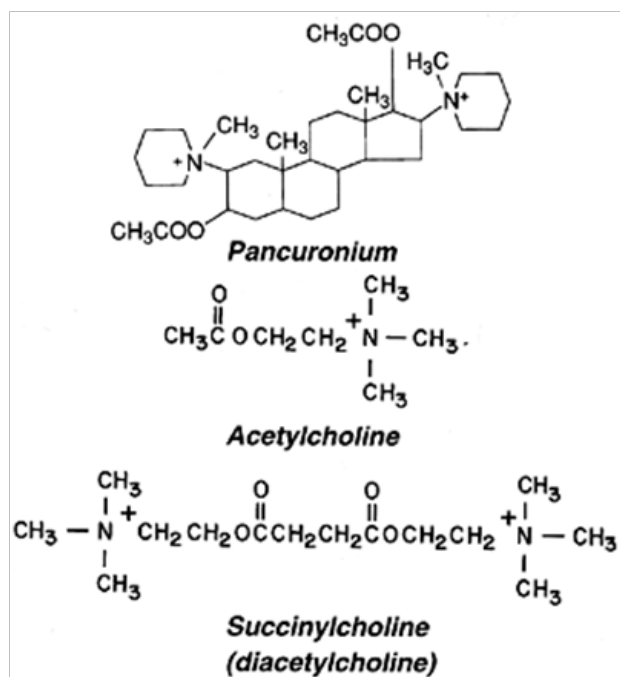
Figure 7-1. Chemical structure of acetylcholine, succinylcholine and pancuronium
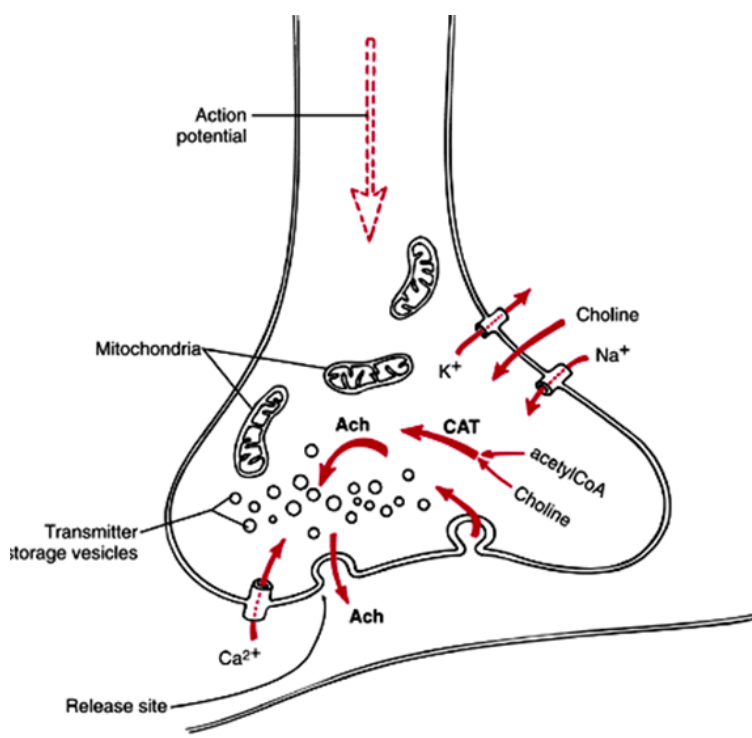
Figure 7-2. Axon of the motor nerve and neuromuscular junction

7.3.1. Depolarizing block

Succinylcholine consists of two ACh molecules joined together and it forms strong attachments to cholinergic receptors. It is obvious that Sch has a biphasic effect; through depolarizing the motor end-plate it is initially causing muscular contraction, and afterwards relaxation. The block persists because the half-life of SCh is substantially longer than that of ACh. SCh is rapidly hydrolyzed by plasma cholinesterase (pseudocholinesterase) to succinylmonocholine and choline. This is a very fast process and only about 10% of the drug comes to the neuromuscular junction. At junction there is little or nothing of the enzyme, and the activity of SCh is completed by diffusion from the nerve end in the extracellular tissues; therefore, the enzyme acts prior to arrival of SCh at the junction. It is clear that problems may occur with succinyl-choline metabolism at low values of pseudocholinesterase (pregnancy, liver disease, kidney disease, oral contraceptives, hypothermia), and in certain genetic disorders.

Pseudocholinesterase is enzyme synthesized in liver. Biosynthesis of pseudocholinesterase is controlled by 4 allelic genes at a locus E1: Eu = "usual", Ea = atypical, Ef = fluoride-resistant, Es = "silent". There is one normal (EuEu) and 9 abnormal genotypes. There are 3 combinations clinically: 1) heterozygous for the abnormal gene, e.g. EuEa - depolarizing block after 1 mg/kg of succinylcholine, with slight prolongation of the action, 2) heterozygous for two abnormal genes, e.g. EfEs usually dual-block after 1 mg/kg. However, recovery is not terribly long, about 30 minutes, 3) homozygous for the 2 abnormal genes, for example, EaEa; after 1 mg/kg there is a dual block, and clinical recovery is a very long> 2 hours, and up to 8 hours (forms EfEf and EsEs are very rare) (Table 7-1.). Approximately 4% of the population is heterozygous for the normal gene, which controls the production of pseudocholinesterase; these persons have an atypical form of pseudocholinesterase and show slightly reduced SCh hydrolysis. One person in 3200, however, is homozygous for the atypical esterase and will show respiratory inadequacy for 4 to 8 hours after an intubating dose of SCh. Because of the finding that serum with a full complement of normal pseudocholinesterase is inhibited in vitro by the local anesthetic dibucaine to a greater degree than serum lacking the normal enzyme, determination of an individual's dibucaine number (the percentage of inhibition of enzyme by dibucaine) may elucidate that person's ability to produce normal pseudocholinesteraze.

Dual block (non-depolarizing or phase II block) occurs after the administration of high doses (or multiple doses) of succinylcholine, which exceed the therapeutic window. It is followed by desensitization at the nerve endings, and the myocyte becomes less sensitive to acetylcholine; membrane is repolarized and can not be re-depolarized.

The level of pseudocholinesterase can be determined in laboratory (male 1800-4400 ij/L; female 20-50 yo 1650-3670 ij/L, female >50 yo 1960-4140 ij/L)

Table 7-1. Genetic variation of the pseudocholinesterase

Type of pseudocholinesterase	Genotype	Incidence	Dibucaine number	Response to SCh
Typical homozygous	EuEu	Normal	70-80	Normal
Atypical heterozygous	EuEa	1/480	50-60	50-100% longer
Atypical homozygous	EaEa	1/3200	20-30	4 to 8 hours longer

7.3.2. Nondepolarizing block

Nondepolarizing muscle relaxants act principally by binding to the postsynaptic nicotinic cholinergic receptor on the motor end-plate as competitive antagonists to ACh. Nicotinic acetylcholine receptor is a pentameric transmembrane protein which belongs to the group of ligand-gated ion channels. It is synthesized in muscle cells, and is located in skeletal musculature (15 to 20.000/mm3). The activation of acetylcholine receptors leads to changes in the spatial position of the amino acid chain; therefore the channel in the center of the protein opens and cations can pass through it (Figure 7-3).

According to chemical structure nondepolarizing muscle relaxants, can be steroids (pancuronium, pipecuronium, vecuronium, rocuronium), tetrahydroisoquinoline derivatives (d-tubocurarine, metocurium, atracurium, cisatracurium, mivacurium), and others (galamine, alcuronium).
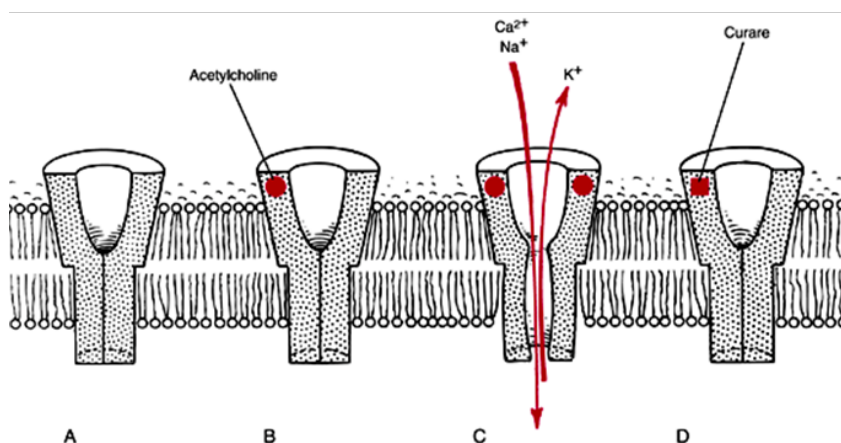
Figure 7-3. Nicotinic acetylcholine receptor

7.3.3. Reversal of neuromuscular blockade

Recovery after SCh induced blockade is generally spontaneous (because of pseudocholinesterase) and does not require pharmacologic antagonism. On the other side, nondepolarizing neuromuscular blockade may be antagonized by anticholinesterase drugs. These drugs inhibit acetylcholinesterase and therefore indirectly increase concentration of ACh on neuromuscular end-plate. Neostigmine is the most frequently used drug (dosage 0.04-0.08 mg/kg, up to 5 mg), but also edrophonium (0.5-1mg/kg) and pyridostigmine (0.1-0.4 mg/kg) are used in clinical practice. These drugs can have muscarinic side-effects (bradycardia, salivation, bronchospasm, myosis…) and these effects can be blocked by prior or simultaneous administration of anticholinergic drugs (atropine).

Sugammadex (Bridion) is the new drug for reversal of neuromuscular blockade, introduced in 2006. It is modified cyclodextrin, which binds nondepolarizing neuromuscular blocking drugs (vecuronium and rocuronium). It's faster in action than neostigmine and has no muscarinic side-effects. The problem may be its availability, mainly due to high prices.

7.4. Review of some relaxants

7.4.1. Succinycholine

It has the fastest onset of action (less than 1 min) and it's short-acting (5-10 min after administration of 1-1.5 mg/kg iv.). This is an ideal drug for rapid sequence endotracheal intubation.

However, there is an increasing debate whether to use succinyl-choline at all. SCh has serious side-effects (rhabdomyolysis, hyperkalemia and cardiac arrest) especially in children with undiagnosed myopathies. Therefore, FDA recommends SCh only for the rapid sequence intubation in this population. Bradycardia is the most frequent side-effect of SCh, because of stimulation of muscarinic receptors of the

heart, usually after successive administration of bolus doses. After administration of SCh fasciculations of the skeletal muscles are frequent, which leads to muscle pain afterwards. SCh-induced depolarisation of normal muscle results in serum K^+ elevation for 0.5 mmol/L, and sometimes hyperkalemia can induce cardiac arrest refractory to CPR. Hyperkalemia can be seen in trauma patients and patients with burns. SCh usage increases intraocular, intragastric and intracranial pressure, and it can provoke malignant hyperthermia and allergic reactions.

The continuous search for the adequate substitute to SCh is therefore understandable, but the results are still disappointing. Rocuronium is, at the moment, the best alternative to SCh considering rapid sequence intubation.

7.4.2. Nondepolarizing muscle relaxants

They are quaternary ammonium compounds as ACh, highly ionized and are readily excreted mainly by kidneys. They do not pass the placenta and the blood-brain barrier According to duration of action they can be divided to:

- Long-acting (d-tubocurarine, pancuronium, pipecuronium) 60-120min
- Intermediate-acting (atracurium, vecuronium, rocuronium) 30-60min
- Short-acting (mivacurium) 12-20min

Classification by chemical structure:

- Steroids – no histamine release, potent, vagolytic: pancuronium, pipecuronium, vecuronium, rocuronium
- tetrahydroisoquinoline derivatives – potent, histamine release, no vagolytic effect (d-tubocurarine, atracurium, cisatracurium, mivacurium)
- Others (galamine, alcuronium)

Pancuronium is cost-effective, suitable for longer surgical procedures (3-4 hours), increases heart rate.

Vecuronium is intermediate-acting drug, suitable for facilitation of endotracheal intubation. It can be administrated as continuous infusion, with no cardiovascular side-effects.

Rocuronium has the fastest onset among nondepolarizing relaxants which is dose-dependent. It has mild vagolytic effect.

Atracurium has specific Hoffman elimination pathway, and has advantage for use in patients with renal and hepatic failure, since its metabolism proceeds independently of both kidney and liver.

Cisatracurium is intermediate-acting, one of 10 atracurium isomers, more potent than atracurium and causes no histamine liberation.

Mivacurium is short-acting nondepolarizing muscle relaxant metabolized by pseudocholinesterase (like SCh).

Regarding side effects of relaxants one should count on their autonomic side effects due to mechanism of action (see later), as well as the anaphylactic and anaphylactoid reactions during anesthesia. It is believed that the relaxants are implicated in 50-80% of cases of all allergic reactions during anesthesia, with approximate mortality from 3.4 to 6%. They are most commonly occurring after SCh, followed by rocuronium.

7.5. Clinical use of muscle relaxants

The goal is to apply the lowest possible dose to achieve adequate skeletal muscle relaxation. Additional doses are 1/4 to 1/3 of the initial dose. The continuous infusion of intermediate-acting relaxants is possible.

IMPORTANT!

Muscle relaxants are not anesthetics!!!

Skeletal muscle paralysis does not mean that patient is anesthetized, amnesic or painless!!!

7.5.1. Endotracheal intubation - dosage

For facilitation of endotracheal intubation good skeletal relaxation is required (usually 2-3x ED_{95}). Time to intubation: 1-3 min for nondepolarizing agents and < 1min for succinylcholine.

7.5.2. Rapid sequence intubation

Rapid sequence intubation is needed in patients who are at high risk of pulmonary aspiration, i.e.

a) where general anesthesia must be induced in the patient that could not fast long enough to empty the stomach;

b) where the patient has a medical condition that makes aspiration more likely during induction of anesthesia, regardless of how long they have fasted (such as gastroesophageal reflux disease); or

c) where the patient has become unable to control their own airway even before anesthesia (such as after a traumatic brain injury).

Patient has to be pre-oxygenated. Pre-oxygenation is usually performed by giving 100% oxygen via a tightly fitting face mask. The opioid and intravenous anesthetic are applied, than follows muscle relaxant, succinylcholine 1-1.5 mg/kg or rocuronium 0.6-1.2 mg/kg. The Sellick's maneuver (or cricoid pressure), may be used to occlude the esophagus with the goal of preventing aspiration. The manual ventilation before tracheal intubation has to be avoided.

7.5.3. Autonomic effects of muscle relaxants

Muscle relaxants can stimulate autonomic ganglia and increase transmission in both sympathetic and parasympathetic limbs of autonomic nervous system (Table 7-2).

Table 7-2. Acethylcholine receptors in human body

Receptors	Nicotinic	Muscarinic
Location	Autonomic ganglia (simp., parasimp.) Skeletal muscles	Exocrine glands (salivary, lacrimal) Smooth muscles Heart
Agonists	ACh Nicotine	ACh Muscarin
Antagonists	Muscle relaxants	Antimuscarinic agents (atropin, glycopyrrolate)

Succinylcholine stimulates nicotinic (hypertension, tachycardia) and muscarinic receptors (bradycardia). Bradycardia is usually seen after the subsequent dose od SCh. Nondepolarizing relaxants block nicotinic receptors of autonomic ganglia, but it has no clinical consequences because much higher dose is needed for blocking autonomic ganglia than for skeletal relaxation. For example, pancuronium induces vagal blockade, which leads to tachycardia, but heart rate increase is 10-25/min. However, it is necessary to be careful in patients with heart disease. Rocuronium also has a mild vagolytic activity. Atracurium and mivacurium may lead to histamine release.

7.5.4. Reversal of neuromuscular blockade

The main determinants of reversal are:
- Intensity of neuromuscular blockade
- Type and dosage of reversal drug
- Spontaneous recovery rate

The time for recovery is directly related to the intensity of neuromuscular blockade at the point of reversal. Clinical criteria for evaluating adequacy of muscle function include: assessment of a patient's ability to maintain adequate head lift, jaw clench, grip strength, and tidal volume. Although, a peripheral nerve stimulators are theoretically the most reliable monitoring method, it's not always available in clinical practice- the most certain sign of adequate reversion is head lift for 5 sec.

Awake patient with adequate muscle strength has the following:
- Eyes wide open
- Coughs effectively
- Holds tongue protrusion
- Has grip strength
- Head lift >5 sec
- Vital capacity > 15ml/kg
- Negative inspiration strength >25 cmH$_2$O

Patient with inadequate reversion of neuromuscular blockade:
- All the movements against gravity are hard to maintain
- Can't lift the head
- Abdominal breathing
- Can't open eyes
- Can't protrude the tongue

- Can't speak
- Masseters are relaxed, partial airway obstruction is possible
- The accumulation of saliva

What to do if you have administered the maximum dose of anticholinesterase, and reversion is not complete?

- Sedate and intubate the patient, or if not extubated maintain endotracheal tube in place
- Maintain adequate ventilation
- Temperature and blood gases correction
- Explain the situation to the patient; give him anxiolytic
- Wait for complete reversal and extubate

7.5.5. Monitoring neuromuscular blockade

The most satisfactory method for monitoring neuromuscular function reliably is the stimulation of an appropriate nerve using a peripheral nerve stimulator and observation of evoked response in the muscle supplied. It gives us information when is the right time for intubation and extubation, about dosage of neuromuscular blocking drug and appropriate time to start reversal of the blockade.

Indications for neuromuscular monitoring are:

- Unpredictable pharmacokinetics of relaxants (liver, kidney dysfunction)
- Change of pharmacodynamics (myasthenia gravis)
- To avoid reversal with neostigmine (in patients with heart disease, asthma)
- When it is important that muscle strength is maximized after surgery (lung disease)
- Long surgical procedures
- Continuous infusion of relaxants

Placement of neuromuscular monitoring (ulnar nerve): the distal electrode is placed at the level of the wrist on the ulnar surface at the flexor crease, as close to the nerve as possible. The second electrode should be placed 1-2 cm proximal to the first, parallel to the flexor carpi ulnaris tendon. The expected response is to see the thumb adduction (Figure 7-4.).

Figure 7-4. Technique for placing neuromuscular monitoring (ulnar nerve), electrode and lead placement.

8. ANALGESICS

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8.1. Non-opioid analgesics

Non-opioid analgesics represent a varied collection of analgesic agents, many of which also possess antipyretic or anti-inflammatory actions. As a group, they represent first-line analgesics for a variety of mild to moderate painful conditions and also often may be useful in conjunction with other analgesics (eg, opioids) for a numerous of severe painful conditions.

Non-opioid analgesics and antipyretics include:
- Aniline products (paracetamol, acetaminophen);
- Salicylic acid products (acetylsalicylic acid);
- Pyrazolon products (metamizole, propyphenazone).

Non-steroid anti-inflammatory drugs include ibuprofen, ketoprofen, diclofenak, etodolac, indomethacin, ketorolac, sulindac, naproxen, piroxicam, meclofenamate, meloxicam. This group of drugs also includes coxibs (celecoxib, rofecoxib, valdecoxib, etoricoxib, parecoxib).

Weak opioids include codeine, nalbuphine, pentazocine, butorfanol, tramadol and pethidine.

Strong opioids include morphine, heroin, hydromorphone, hydrocodone, buprenorphine, oxycodone, thebaine, levorphanol, butorfanol, methadone, fentanyl, sufentanil, alfentanil, remifentanil.

Analgesics and antipyretics

These drugs are used in treatment of mild to moderate pain and as fever reducer. This group of drugs includes acetylsalicylic acid, paracetamol and other NSAIDs. Although they have similar mechanisms of action and similar indications for use, they mostly vary in their chemical structure. Drugs from this group don't act through opioid receptors and they can't cause tolerance and addiction. They are usually administered orally, but can also be administered rectally, locally, intramuscularly, subcutaneously, and some of them can be administered intravenously. Pain treatment usually begins by prescribing one of the analgesics from this group of drugs.

Their mechanism of action involves inhibition of prostaglandin synthesis which leads to analgesic and anti-inflammatory effect. They also act on hypothalamic center that controls body temperature (antipyretic effect).

Aniline products

Paracetamol (acetaminophen in USA)

Paracetamol is classified as a mild analgesic and it's also one of the most widely used medications in the world. Paracetamol is active metabolite of phenacetin, aniline derivate. In contrast to aspirin, paracetamol does not prevent blood from clotting (it is not an antithrombotic), and thus may be used in patients where failure of blood coagulation is a concern. Paracetamol also has central mechanism of action. It inhibits brain cyclooxygenase and nitric-oxide synthesis.

Paracetamol is metabolized primarily in the liver. As a product of its metabolism, sulfates and glucuronides are produced and excreted by the kidneys. Acute overdoses of paracetamol can cause potentially fatal liver damage.

Paracetamol used for treatment of mild to moderate pain whether it is acute or chronic. It is generally safe for use at recommended doses. It has fewer adverse gastrointestinal effects and it does not cause gastric irritation so it can be safely administered in patients with gastric diseases, like ventricular or duodenal ulcer. Paracetamol is also safe to use in children and it is usually drug of choice for reducing fever in people of all ages. It can be administered as syrup for oral use or as suppositories. It is recommended to take 1 gr every 6 hours, but it can also be given every 4 hours, usually in palliative care centers. When given rectally, dosage should be increased by 30-40%. Paracetamol is completely absorbed in upper gastrointestinal tract. Analgesic effect occurs after 30-60 minutes. Its plasma half-life is 2-3 hours.

Acute toxicity is related to dosage and can lead to fatal liver failure. For this reason there have been attempts to ban paracetamol from further use. However, toxic reaction is a rare adverse effect when taken in daily dosage up to 4-6 gr (for adults). Care should be taken when prescribing paracetamol to patients with some genetic disorders and to those who take anticonvulsants as well as with alcohol. In those patients dosage should be reduced. Chronic toxicity occurs in patients who take paracetamol for longer

periods of time, especially when combined with other medications with phenacetin as a compound. It can be manifested as liver or kidney function impairment. Therefore, caution is necessary when prescribing paracetamol to patients with known liver or kidney diseases. Anaphylactic reactions can also occur, but they are very rarely seen. In patients with known allergy to aspirin, allergic cross-reaction to paracetamol can be seen in approximately 5% of cases.

Acetylsalicylic acid

Acetylsalicylic acid has analgesic, antipyretic, anti-rheumatic and anti-inflammatory effect. It also has effect on blood coagulation. It is successfully used for treatment of headache, toothache, muscle pain and rheumatic pain. Small doses (100 mg) are used for prevention of cardiovascular events.

However, acetylsalicylic acid has its disadvantages. It often causes gastric pain and bleeding. Therefore, patients with gastric or duodenal ulcers should be careful when taking this drug. Also, this drug should **not be given to children under age of 12** because there is great possibility of developing dangerous and potentially fatal Reye's syndrome.

Aspirin

Aspirin is semisynthetic product of salicylic acid. When metabolized it is hydrolyzed to salicylates and acetates. Salicylic part is one responsible for analgesic, antipyretic and for weak anti-inflammatory effect. Mechanisms of action are not entirely known but what is known is that it irreversibly inhibits cyclooxygenase acetylation process that converts arachidonic acid into cyclic endoperoxydes.

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Aspirin can be administered orally or rectally. It is usually administered peroral, together with food (milk, water) that reduces stomach mucosa irritation. When administered peroral it is absorbed rapidly and completely from upper gastrointestinal tract. Maximum effect is reached after 15 minutes to 2 hours after intake, which mainly depends on dosage and the form of the drug. Analgesic effect lasts for 4-6 hours. Its plasma half-life is 15-20 minutes. In case of rectal administration, absorption is less predictable and can be slower and incomplete so larger doses are needed. It is usually given as 2-3 suppositories every 4 hours, maximum of 12 suppositories in 24 hours.

Aspirin is usually used for treatment of mild to moderate pain (e.g., acute and chronic headache, musculoskeletal pain, dysmenorrhea). It is also used as antirheumatic and antipyretic. In small dose it is given for secondary prevention of myocardial infarction and stroke.

Aspirin (or aspirin-containing products) should not be given to anyone under the age of 12 because of Reye's syndrome which is a rare but severe illness characterized by acute encephalopathy and fatty liver.

Metamizole

Metamizole is pyrazolon product. It has strong analgesic effect and it is most commonly given orally or parenterally to prevent and treat pain related to surgery or for the treatment of acute pain.

It also has antipyretic effect through action onthalamic thermoregulatory center. Today, metamizole is rarely used because of its known bone marrow depression which can, in some cases, be lethal.

Propyphenazone

Propyphenazone is a derivative of phenazone with similar analgesic and antipyretic effects as metamizole. Today it is commonly used in combination with other analgopyretics.

8.2. Non-steroidal anti-inflammatory drugs (NSAID)

This is heterogeneous group of drugs with similar characteristics: they are weak acids and have high affinity for plasma proteins. They are widely used medications. Gastrointestinal absorption is nearly complete. They are metabolized in liver and usually excreted via kidneys. They can be classified based on their chemical structure, but that classification can't be used for comparison of their analgesic effects. These drugs are classified as one of the following chemical compounds:
- Acetic acid products: diclofenac, sulindac, alklofenak, indomethacin, acemetacin, tolmetin, lonazolac…;
- Oxicams: piroxicam, meloxicam, tenoxicam, lornoxicam, droxicam;
- Fenamates: mefenamic, tolfenamic, flufenamic, meclofenamic acid;

- Propionic acid products: ibuprofen, ketoprofen, naproxen, fenoprofen, flurbiprofen, taiprofenic acid, alminoprofen…;
- Coxibs: rofecoxib, celecoxib, valdecoxib, parecoxib.

Table 8-1. Analgesics and non-steroidal anti-inflammatory drugs (NSAID)

Drug	Dosage (mg)	Maximum daily dosage (mg)	comment
Analgetics/antipyretics			
Paracetamol	500-1000	4000	Hepatotoxic (high doses)
Metamizole	500	5000	Agranulocytosis
Aspirin	325-650	4000	Reye's syndrome (children < 12 years)
NSAID			
Ibuprofen	200-800	3200	
Ketoprofen	25-75	300	
Ketoprofen SR	200	200	
Diclofenac	50-100	200	
Etodolac	200-400	1200	
Indomethacin	25-50	200	Gastrointestinal bleeding, renal function impairment
Ketorolac	10	40	
Sulindac	150-200	400	
Naproxen	200-400	1200	
Piroxicam	10-20	20	
Meclofenamate	50-100	400	
Meloxicam	7.5-15	15	
Coxibs			
Celecoxib	100-200	400	
Etoricoxib	120		Cardiovascular system impairment
Parecoxib	5		

NSAIDs generally have following effects:
- Anti-inflammatory
- Antirheumatic
- Antipyretic
- Analgesic

Mechanism of action

NSAIDs inhibit prostaglandin synthesis by irreversibly inhibiting cyclooxygenase enzyme (COX) in arachidonic acid cycle. Prostaglandins are responsible for sensitization of nociceptors, which then leads to pain impulse generation and feeling of pain.

There are three known cyclooxygenase enzymes: COX-1, COX-2 and COX-3. COX-1 is normally found in many tissues and cells (stomach, kidneys, and platelets) as housekeeper enzyme. It has effect on gastric mucosa protection, regulation of renal blood flow, platelets aggregation and vascular homeostasis. COX-2 is usually found after induction by vasoactive hormones, endotoxins, some cytokines, mitogens and growth factors. Although it can normally be found in some tissues (central nervous system, bones and kidneys), it is mostly induced during inflammation. COX-3 enzyme is encoded by the same gene as COX-1. It seems that it is primarily located in central nervous system, but can also be found in heart. Non-opioid analgesics inhibit COX-1 and COX-2 enzymes depending on the type of NSAID administered. Adverse effects will depend on level of inhibition of COX-1 and/or COX-2.

Most of the NSAIDs inhibit both COX-1 and COX-2 enzymes, therefore leading to inhibition of all prostaglandins synthesis. However, some of these prostaglandins have important physiologic functions. For example, by inhibiting these enzymes, synthesis of prostacyclin, which has important function in gastric mucosa protection, is also stopped leading to stomach pain and bleeding. Coxibs, unlike other NSAIDs, selectively inhibit COX-2 enzyme and therefore have less gastrointestinal adverse effects. However, use of these selective COX inhibitors is yet to be determined since the experience of their use is still

insufficient. It has been shown than although coxibs are safer for use in patients with stomach ulcers, there is increased incidence of cardiovascular adverse effects associated with their use (rofecoxib, *Vioxx*, has been recalled from market). Also, the price of treatment with coxibs is much higher than with other NSAIDs.

There are many NSAIDs that can be administered as suppositories. That way gastric adverse effects are reduced. Furthermore, liver is also better protected and drug effect is prolonged and more efficient.

Pharmacokinetics

All NSAIDs are well absorbed in upper gastrointestinal tract, usually by passive diffusion. Adequate plasma levels are achieved after 30 min and peak plasma concentration usually occurs 2 hours after intake. Different preparations can have variable absorption levels. All NSAIDs have high affinity for serum albumins, usually up to 90%. Only free fraction, which is not bound to plasma proteins, is pharmacologically active. Since many patients that take NSAIDs have different chronic conditions associated with lower albumin levels, and therefore increased fraction of free, unbound form of drug, a care has to be taken when determining the right dosage for those patients.

Indications

- Inflammations: arthritis, rheumatoid arthritis, lupus…;
- Pain associated with malignant disease, metastases;
- Renal and biliary colic;
- Osteoarthritis, bursitis, gout, soft tissue injury;
- Postoperative analgesia;
- Dysmenorrhea;
- Backache, headache, migraine.

Hematologic effects

NSAIDs inhibit platelets aggregation and increase time of bleeding. These effects are related to COX-1 inhibition. They are reversible and present only while drug is present in certain plasmatic concentrations. In platelets, COX-1 enzyme induces thromboxane A2 (TXA2) synthesis. TXA2 is prostaglandin associated with thrombosis. Small doses of Aspirin (75-325 mg) are used to prevent cardiovascular events, myocardial infarction or stroke. These small doses inhibit COX-1 and TXA2 synthesis while having minimal gastrointestinal effects. Endothelial cells synthetize PGI_2 in COX-2related process. This prostaglandin inhibits platelets aggregation and stimulates vasodilation leading to antithrombotic effects. Selective COX-2 inhibitors, by inhibiting PGI_2 synthesis, have prothrombotic effect, which can potentially be harmful in some situations (malignant disease, connective tissue disorders).

Gastrointestinal effects

These include dyspepsia, gastric erosions that can be asymptomatic (during gastroscopy these changes can be found in 20-40% of patients who take NSAIDs), gastrointestinal bleeding and perforation.

Chronic use of NSAIDs eventually leads to intestinal and colon strictures, colitis, exacerbation or existing colitis, hypoproteinemia and microscopic bleeding. Furthermore, protective barrier of intestinal mucosa is damaged, which leads to increased permeability. Potential hepatic damage is usually manifested as transient increase in hepatic enzymes levels, but nevertheless, these drugs are best to avoid in patients with liver disease if possible.

These adverse effects can be prevented, or at least minimized, by prescribing only one NSAID instead of combination, by choosing a medication with least toxic effects, by prescribing minimal effective dose of medication and by taking the drug as short a time period as possible**.** Ibuprofen has the most favorable GI safety profile of all NSAIDs, while diclofenak and naproxen have moderate effect. Piroxicam and azapropazone have most toxic gastrointestinal effects.

Renal effects

PGI_2, PGE_2 and $PGF_{2\alpha}$ are synthesized in kidneys. These prostaglandins are part of mechanisms that regulate renal blood flow, glomerular filtration, renin excretion, urine concentration and electrolyte excretion. In healthy person these prostaglandins don't have much effect on those processes, but in patients with impaired renal blood flow and reduced urine output their influence is significant.

Renal adverse effects of NSAIDs occur because of decreased prostaglandin synthesis. NSAIDs can lead to acute nephritis, nephrotic syndrome and/or renal failure. They can also interfere with water, sodium and potassium excretion. Also, these drugs can have effect on antihypertensive medications and diu-

retics. Long term use of NSAIDs can lead to so called analgesic nephropathy. It is considered that 1-5% of patients who take NSAIDs develop some kind of renal adverse effects.

Central nervous system

NSAIDs can cause headache, confusion (indomethacin), vertigo (indomethacin), extrapyramidal symptoms (tremor) and worsening of Parkinson's disease (sulindac, naproxen).

Respiratory system

Asthma attack can occur when NSAIDs are used, especially in patients who have bronchial asthma. This effect is similar to the one of aspirin.

Pregnancy and breastfeeding

NSAIDs are best avoided during third trimester. Their use in this period can lead to prolonged labor and early ductus arteriosus occlusion. If these drugs are used while breastfeeding they can cause cyanotic crisis in babies.

Route of administration

NSAIDs are usually administered per oral. They can also be administered rectally. In that case dosage should be increased 30-40%. This way of administration can cause mucosal irritation, proctitis, ulcerations and stenosis of colon. Parenteral administration (intravenous, intramuscular, subcutaneous) is an option for some of NSAIDs (diclofenak, ketoprofen, ketorolac). Intramuscular administration is mostly used for treatment of postoperative pain and renal colic. Diclofenak, ibuprofen, ketoprofen and piroxicam can be administered as transdermal patches. NSAIDs can also be administered locally (gel).

Contraindications

Some of contraindications for NSAIDs treatment include gastrointestinal bleeding, gastric and duodenal ulcers, concomitant use of anticoagulant drugs, diuretics (possible renal function impairment), corticosteroid therapy, liver and kidney diseases, severe atherosclerosis and heart failure (increased risk of renal tubular necrosis). NSAIDs are also contraindicated in patients with known hypersensitivity (asthma, angioedema, urticaria, and rhinitis). They should be used with caution in elderly patients because of possible gastrointestinal and renal complications and increased risk of bleeding.

Interactions of NSAIDs with other drugs are shown in table 8-2.

Table 8-2. NSAID interactions with other drugs

Drug interaction	Effect
Anticoagulants, warfarin	Metabolism inhibition, increased anticoagulant effect
Oral hypoglycemics, sulphonylurea	Increased effect
Antiepileptics, phenytoin	Increased effect, increased plasma concentration
Antihypertensives	Antagonistic effect; risk of hyperkalemia, increased risk of renal failure (captopril)
Cardiac glycosides	Glomerular filtration reduction, increased digoxin plasma concentration, heart failure
Methotrexate	Slower excretion
Diuretics	Increased risk of nephrotoxicity, reduced urine output

Diclofenac

Diclofenac is acetic acid product, and it can be in a form of sodium or potassium salts. Potassium salts are more soluble than sodium salts, and therefore have faster onset.

This drug is used for treatment of pain after injuries, headaches, toothaches and menstrual pain. It is also used as anti-inflammatory drug as well as fever reducer. In these conditions diclofenac is used in smaller doses. For treatment of rheumatoid arthritis, osteoarthritis, ankylosing spondylitis, acute gout and posttraumatic pain larger doses are used. It has stronger antirheumatic effect than propionic acid.

Diclofenac is one of the most popular non-steroidal anti-inflammatory drugs. However, this drug is not harmless as it can lead to gastrointestinal bleeding and stomach ulcers so its use in patients with known stomach disease is not recommended. Furthermore, it should not be used during pregnancy, especially during the last trimester. Diclofenac should not be used for longer periods of time and it is recommended not to take it for longer than 2 months. It should be used with caution in patients with known hepatic or renal function impairment.

Diclofenac can be administered as coated tablet, pill or suppository.

Indomethacin

Indomethacin is also acetic acid product. It has strong anti-inflammatory and antirheumatic effect and it is mainly used in the treatment of rheumatic inflammatory diseases, especially those that don't respond to treatment with other NSAIDs (rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis and osteoarthritis. It is also used to treat acute gout, pseudo gout, bursitis, tendinitis, synovitis and humeroscapular periarthritis. Indomethacin is a potent drug with many serious side effects and should not be considered an analgesic for minor aches and pains or fever. The medication is better described as an anti-inflammatory, rather than an analgesic. The frequency and severity of side effects and the availability of better tolerated alternatives make indomethacin today a drug of second choice. Its use in acute gout attacks is well-established because the duration of treatment is limited to a few days only, therefore serious side effects are not likely to occur. Possible adverse effects include stomach ulcerations and GI bleeding, headache, liver and kidney damage, changes in blood count, hallucinations. It can also worsen depression symptoms and increase sodium and potassium retention. It is usually administered as capsules or suppositories.

Oxicams

Piroxicam

This drug has similar anti-inflammatory effect as indomethacin, and its analgopyretics effect is comparable to acetylsalicylic acid. It is used for treatment of various rheumatic diseases: rheumatoid arthritis, spondyloarthrosis, ankylosing spondylitis, psoriatic arthritis, osteoarthritis, acute uric arthritis, bursitis, tendinitis and synovitis. Adverse effects include GI bleeding, which are less marked than with indomethacin use. Piroxicam is administered one daily, usually 10-30 mg, in a form of capsule, injection or suppository.

Ibuprofen

Ibuprofen is one of the most widely used medications and it is usually sold as over-the–counter medicine. It has effect similar to acetylsalicylic acid. It is used to reduce fever and treat pain orinflammation. However, propionic acid products have less antirheumatic effect compared with other NSAIDs. If possible, ibuprofen should not be used in patients with stomach ulcer, hepatic or renal disease, bronchial asthma and during pregnancy. It can be administered as tablets, coated tablets or syrup. It should be taken 3-4 times a day and recommended daily dose is 600-1200 mg. If necessary, daily dosage can be increased to 3200 mg.

Ibuprofen is safe to use in children. It is administered 3-4 times a day up to recommended daily dosage of 20mg/kg. For treatment of juvenile rheumatoid arthritis daily dosage can be increased up to 40mg/kg. For children <30 kg daily dosage should not exceed 500 mg.

Common adverse effects include gastrointestinal (ulcerations, bleeding), central nervous system (headache, vertigo, insomnia, irritability, tiredness) and other (vomiting, fever, neck stiffness, impaired consciousness). Use of ibuprofen for longer periods of time can cause serious hepatic and renal function impairment.

In June 2005, British study showed that ibuprofen, similar to coxibs, may increase the risk of heart attack. However, no undisputed evidence can be found to confirm that finding.

Ketoprofen

This drug has similar effect as ibuprofen. It is generally prescribed for arthritis-related inflammatory pains(rheumatoid arthritis, ankylosing spondylitis, gout, reactive arthritis, osteoarthritis, tendinitis, and bursitis). It can also be used to treat postoperative pain, painful conditions after injuries, pain associated with malignant disease and dysmenorrhea.

Caution should be taken when considering treatment for some groups of patients (stomach ulcer, liver and kidney disease). Ketoprofen should not be used during pregnancy and while breastfeeding. Also, it is not recommended to use in children. Suppositories should not be used in patients with proctitis. It should be mentioned that in our market there is no registered form of ketoprofen that could be bought over-the–counter.

Naproxen

Naproxen is a NSAID of the propionic acid class and is commonly used for relief of a wide variety of pain, fever, swelling and stiffness. It is also used for the treatment of many rheumatic conditions.

As other propionic acid products, it should be avoided in patients with stomach and duodenal ulcers, in cases of gastrointestinal bleeding, severe hepatic and renal impairment, heart failure and during preg-

nancy, especially during the last trimester. Naproxen should not be used in children younger than 1 or under 13 kg. Adverse effects are similar to those described with other NSAIDs.

Coxibs

Coxibs are non-steroid drugs of new generation. They are mostly used in treatment of rheumatoid arthritis and osteoarthritis. These drugs selectively inhibit COX-2, an enzyme responsible for synthesis of factors, which mediate processes of inflammation, pain and fever. Selective targeting for COX-2 reduces the risk of peptic ulceration. COX-2 inhibitors appear to work as well as nonselective NSAIDS. .

After several COX-2 inhibiting drugs were approved for marketing, data from clinical trials revealed that COX-2 inhibitors caused a significant increase in heart attacks and strokes, with some drugs in the class having worse risks than others. In September 2004 rofecoxib was withdrawn from market after it was related to possible increase of risk for cardiovascular complications (myocardial infarction). A study has shown that rofecoxib does actually increase risk for cardiovascular complication and after that the drug has been finally withdrawn. Valdecoxib is another drug from this group that has been withdrawn from market. An effect of coxib use is still a matter of debate. For now, coxibs are not recommended for use in patients with heart disease.

8.3. Narcotics (opiates and opioids)

Opiates are substances produced from opium, *Papaver somniferum.* They act through opioid receptors. Drugs that belong to this group are morphine and its products (papaverine, codeine, and thebaine). Opioids, on the other hand, are synthetically produced compounds with same mechanism of action (binding to opioid receptors). This group includes pethidine, pentazocine, tramadol, methadone, fentanyl, alfentanil, remifentanil. These drugs are also called narcotics, from Greek word meaning stupor. Therefore, narcotics can be defined as drugs that cause sleepiness.

Human body also produces endogenous opioids, compounds whose effect is similar to morphine. Those peptides include methionine-enkephalin (met-enkephalin) and leucine-enkephalin (leu-enkephalin), endorphins (β), dynorphins (A and B) and endomorphine 1 and 2. They all bind to opioid receptors.

Opioids are classified as agonists, partial agonists, agonist-antagonists and antagonists.

- Agonists: morphine, diamorphine, diacetylmorphine, codeine, pethidine, fentanyl, methadone, oxycodone, hydromorphone;
- Partial agonists: buprenorphine;
- Agonist-antagonists: nalbuphine, pentazocine, butorfanol;
- Antagonists: naloxone, naltrexone, nalmefene.

Table 8-3. shows op ioid analgesics and their main characteristics.

Table 8-3. Opioid analgesics

Drug	Receptor activation	T$_{\frac{1}{2}}$ (h)	Dosage (mg)	Duration of effect	Strength (compared to morphine)
Morphine	μ	3	2-5	4-6	1
Hydromorphone		2-3			5-10
Oxycodone	μ, κ	4-5		4-6	2
Methadone	μ	15 (8-80)		6-8	1.5
Meperidine	μ, κ, δ	2.5	25-50	2-4	0.1
Fentanyl	μ	2		0.4-0.5	80-100
Tramadol	μ, κ, δ	4-6	50-100	6	
Pentazocine	mixed	2		2-4	
Butorfanol		2.5-3.5	2	4-6	

Sufentanil has 1000 times stronger effect compared to morphine, buprenorphine 10-40, remifentanil 200 and alfentanil 40-50 times stronger effect.

Mechanism of action

Opioid achieve their analgesics effect by binding to G-protein coupled receptors located primarily in central nervous system (brain and spinal cord). These receptors are located in areas responsible for transmission and modulation of pain. There are three main classes of opioid receptors: μ, κ and δ. By binding to these receptors, endogenous and exogenous opioids inhibit adenyl cyclase enzyme, which leads to lowering of intracellular cAMP concentration and potassium channels activation. Furthermore,

opening of calcium channels is inhibited. These changes lead to hyperpolarization of cellular membrane and reduction of neurotransmitters release. Opioids have both presynaptic and postsynaptic effect. Presynaptic effects include inhibition of neurotransmitters release (acetylcholine, norepinephrine, serotonin, substance P and glutamate). Postsynaptic effects include neuronal inhibition by opening potassium channels, which leads to cellular membrane hyperpolarization.

Alternative mechanisms of action

It has been shown that NMDA receptors have a role in transmission of nociceptive stimuli in dorsal horn of spinal cord. Also, norepinephrine, serotonin and sodium channels have certain roles in these processes. Methadone, meperidine and tramadol, among other, inhibit reuptake of serotonin and norepinephrine. Methadone, meperidine and some other opioids act as NMDA receptors antagonists. Meperidine blocks sodium channels and therefore has effect as local anesthetics.

Pharmacodynamics

Central effects of opioids include analgesia, sedation, euphoria or sedation, respiratory depression, miosis, tolerance, antitusic and emetic effect..

Effects on **peripheral** organs include delayed gastric emptying (pyloric contraction), decreased peristalsis and increased sphincter tonus, contraction of gall bladder sphincters, increased tonus of bladder, decreased vascular tonus and histamine release.

Rapid infusion of large doses of strong opioids can cause muscle rigidity of chest. This is usually seen when fentanyl, sufentanil and alfentanil are used. The mechanism of this phenomenon is not clear but it can be reversed with muscle relaxant or opioid antagonist.

Even therapeutic doses of opioids can cause ureter and bladder contraction with urine retention. However, tolerance to these effects usually occurs over time.

Furthermore, therapeutic doses of morphine can cause skin vasodilation. Histamine has similar effect. After morphine injection histamine release can occur with localized urticaria, bronchoconstriction and vasodilation. Itching can occur after neuraxial block if opioids were administered. Long term use of opioids can cause immunosuppression.

If morphine, or other opioids, are repeatedly administered in therapeutic doses, their efficiency decreases. In that case we say that **tolerance** has occurred. At the same time physical **dependence** also develops. It is defined as occurrence of withdrawal symptoms after opioids are withdrawn from therapy or after antagonist is administered. The mechanisms underlying the development of tolerance and physical dependence are not entirely understood. What is known is that permanent activation of μ-opioid receptors during chronic pain treatment has significant role in development of these syndromes.

Pharmacokinetics

Most of opioids are well absorbed when administered subcutaneously, intramuscularly or *per os*. However, because of first-pass metabolism, initial does of drug administered *per os* should be much larger than when drug is administered parenterally in order to have the same effect. There are significant individual differences regarding first-pass metabolism.

Certain analgesics, like codeine and oxycodone, are efficient when administered *per os*. These drugs have reduced first-pass metabolism because of methyl group attached to aromatic hydroxyl group.

Nasal administration of some opioids can result in rapid increase in plasma concentrations of drug because first-pass metabolism is avoided.

Although opioids have different affinity for plasma proteins, they all relatively fast leave vascular compartment and accumulate in well perfused tissues like brain, lungs, liver, kidneys and spleen. Drug concentration in skeletal muscle compartment can be relatively low, but this compartment is main reservoir of opioids because of its large mass. Even though the blood flow through fat tissue is low, opioids can still accumulate in fat if administered in large doses.

Opioids are mainly metabolized via glucuronidation or the P450 (CYP) system. The molecules and their metabolites are usually excreted by the kidneys. Morphine is primarily conjugated to morphine-3-glucuronide that has neuroexcitatory effect. Around 10% of morphine is metabolized to morphine-6-glucuronide, an active metabolite that is more potent and longer-lasting opioid agonist than morphine. In patients with kidney failure or in cases when large doses of morphine are administered, this metabolite is accumulated and adverse effects can occur. These include central nervous system excitation caused by morphine-3-glucuronide and prolonged effects of morphine-6-glucuronide. Hydromorphone is also

metabolized to morphine-3-glucuronide. However, this opioid does not metabolize to morphine-6-glu-curonide.Esters (heroine, remifentanil) are rapidly hydrolyzed by tissue esterases. Heroine is metabo-lized to monoacetate morphine and then into morphine, which is further conjugated by glucuronic acid.

Hepatic oxidative mechanisms are primary degradation pathways for phenylpiperidine opioids (fen-tanyl, alfentanil, sufentanil) and only small amounts of these drugs are excreted unchanged. Fentanyl is metabolized in liver by P-450 isoenzyme CYP-3A4. So far, no active metabolites of fentanyl have been found. This isoenzyme can also be found in the guts. Codeine, oxycodone and hydrocodone are also metabolized in liver (P-450 izoenzyme CYP-2D6) and their metabolites are somewhat stronger.

Accumulation of normeperidine, a meperidine metabolite, can occur in patients with impaired renal function or in cases when large doses of this drug are administered. Normeperidine can cause restless-ness and convulsions.

Opioid metabolites are mostly excreted via kidneys. However, small amounts of unchanged drugs can also be found in urine. Glucuronide conjugates can be found in bile, but internal excretion is only a small part of drug elimination.

Indications

Indications for morphine use are:
- Treatment of severe nociceptor pain (malignant pain), severe acute pain (burns, postoperative pain), severe chronic non-malignant pain and pain syndromes and in some cases neuropathic pain;
- Acute myocardial infarction (supplemental therapy);
- Acute cardiogenic pulmonary edema (supplemental therapy);
- Premedication, supplement to local or general anesthesia;
- Cough, lung cancer;
- Bowel peristalsis reduction, intestinal bleeding.

Contraindications

Opioids are contraindicated in patients who are allergic to morphine, to those with increased intracra-nial pressure, in patients with biliary colic, acute hepatic porphyria, patients with asthma or COPD, dur-ing pregnancy and while breastfeeding and in patients who take MAO inhibitors.

In patients allergic to Aspirin, opioid use can cause asthmatic attack.

Special consideration is needed when administering opioids to patients with hypothyreosis, increased intracranial pressure, prostate hypertrophy and when acute abdomen is suspected.

Adverse effects

Adverse effects range from sedation to somnolence. Occasionally, dysphoria, confusion or excitation can occur. Respiratory depression is the most serious adverse reaction associated with opioid use, but it usually is seen when drug is administered by fast intravenous injection. Central vagal stimulation results in miosis and bradycardia. In addition, smooth muscles tonus is increased (spastic obstipation, urine retention, Odi sphincter spasm with possible biliary colic or pancreatitis). Other adverse effects include nausea, vomiting, sweating, hypotension, hallucination, insomnia, dry mouth, itching, eyesight distur-bances, rash, urticaria, bronchoconstriction and sedation. Morphine can paradoxically cause "opioid-in-duced hyperalgesia" in which patients become more sensitive to painful stimuli. Patients treated with opioids can develop physical dependence and drug addiction. Substitution therapy includes methadone administration. Psychological addiction is main problem when dealing with addiction treatment.

Caution

Opioids should be used with great **caution** in patients with hepatic and renal disease, respiratory sys-tem disease, head injuries and allergic reactions. Impaired hepatic function can have influence on opioid metabolism and, therefore, can lead to metabolite accumulation (e.g., morphine -6-glucuronide, norme-peridine, norpropoxyphene). Morphine-6-glucuronide is morphine product with 2x stronger effect than morphine. Normeperidine is meperidine metabolite, which can cause central nervous system excitation with tremor or restlessness. Norpropoxyphene is a product of propoxyphene metabolism and can have cardiac toxic effect.

In patients with impaired respiratory reserve (emphysema, extreme obesity, kyphoscoliosis) opioids should be carefully administered. They can cause bronchospasm, especially in asthmatics. Cough sup-pression can have deleterious effect in patients with heavy bronchial secretions (pneumonia, bronchiec-tasis, posttoracotomy).

Table 8-4. Treatment of morphine adverse effects

Symptom	Cause	Treatment
Respiratory depression	Direct effect on μ-opioid receptors in pons and medulla	Naloxone IV/SC; Ventilatory support if necessary; Naloxone dose should be titrated to desired effect
Nausea, vomiting	Stimulation of chemoreceptors in trigger zone (central effect); delayed gastric emptying	Haloperidol 1.5 mg; Metoclopramide 10-20 mg
Nausea and vomiting caused by movement	Vestibular apparatus stimulation	Cyclizine 50-100 mg PO/SC
Obstipation	Direct effect on GI smooth muscles	laxatives
Urine retention	Increased tonus of muscles of urinary tract	Catheterization (if necessary)
Sedation	Central effect of morphine	Reduction of dose, be aware of possible interactions with other drugs
Psychotomimetic effect	Dysphoria, hallucination	Haloperidol 3-5 mg PO/SC
Itching	Central effect; Histamine release	Ondansetron 8 mg iv and 8 mg PO for3-5 days
Bronchoconstriction	Histamine release in bronchial tree	Antihistamine IV/IM; Change opioid or give other analgesic; Bronchodilators
Morphine induced pain	Morphine-3-glucuronide accumulation	Change opioid (e.g., methadone)
Myoclonus		Diazepam or midazolam 2.5-5 mg PO/SC; Check other medications; reduce morphine dosage
Hallucination/delirium	Possibly by activation of σ-opioid receptors	Haloperidol 1.5-3 mg, titrated to effect; stop with opioids

Table 8-5. Treatment of nausea and vomiting

Medication	Mechanism of action	Dosage	Administration
Haloperidol	Antidopaminergic	0.5-5 mg/4-8 h	PO, SC, IV,
Scopolamine	Anticholinergic	1-2 patches; 0.3-0.6 mg/4-8 h	PO, SC, transcutaneous
Cyclizine	Antihistamine	25-50 mg	PO, SC
Metoclopramide	Antidopaminergic, prokinetic	5-20 mg/6-8 h	PO, IV, SC
Diphenhydramine	Antihistamine, anticholinergic	25-100 mg/4-6 h	PO, IV
Ondansetron	Antiserotonergic	8-32 mg/day	IV, PO
Lorazepam	Anxiolytic	0.5-2 mg/4-8 h	SL, PO, IV, SC
Dexamethasone	Unclear	4-20 mg/day	IV, PO

Table 8-6. Laxatives

Medication	Starting dose	Time to effect (hr)
Senna	15 mg/day (maximum 8 tablets/day)	6-12
Bisacodyl	50-200 mg/day PO; 10-20 mg/pr	6-12 1
Docusate	100-800 mg/day	25-72
Lactulose	15-60 mL/day	1-2
Magnesium citrate	200 mL	0.5-3

In patients with head injuries carbon dioxide levels can increase to a level that cause increase in intracranial pressure. Miosis, vomiting and mental confusion are important signs of this condition and opioids should be avoided in these patients if possible.

True allergic reaction to opioids, although possible, is rarely seen. Usually some kind of adverse effect occurs and patient is convinced that it is actually allergic reaction.

Drug interactions

When opioids are combined with sedatives (hypnotics), central nervous system depression and respiratory depression can occur. Also, when combined with antipsychotics, increased sedation and respiratory depression can occur as well as increased cardiovascular effects like antimuscarinic effect and effect

of α-adrenergic receptors blocators. When opioids are administered in patients who take MAOIs hyperpyretic coma and serious hypertension can occur.

Some drugs can increase opioids effects. Those include antihistamines, anxiolytics and antiemetics. Amphetamine and analeptics can decrease sedative effect and depression caused by opioid use.

Especially serious interactions can occur when meperidine is combined with MAOIs. In those cases delirium, hyperpyrexia and convulsions can be seen.

Furthermore, interactions between methadone and desipramine, antiviral drugs and antibiotics were described.

Opioids are often **combined** with non-steroidal anti-rheumatics or other non-opioid analgesics. In order to decrease incidence of adverse effects, opioids can be combined with antiemetics (metoclopramide, thiethylperazine, dimenhydrinate and ondansetron) and laxatives (lactulose, bisacodyl).

If opioids are used for longer periods of time, tolerance can develop, meaning dosage should be increased in order to have the same effect. Since there is no ceiling effect, doses of opioids can be substantial. To avoid large doses, different way of administration can be used or other opioid can be administered.

Administration

Opioids can be administered in different ways: *per os (PO),* rectally, intravenously (IV), subcutaneously (SC), intramuscularly (IM), intrathecally or epidurally, sublingually (SL) and transdermal.

Oral doses are usually 3 times larger than those administered parenterally. Bioavailability of orally administered morphine is only 25%. Furthermore, orally administered opioids have longer effect because of slower absorption. When administered orally, dosage of opioids can be easily titrated.

Parenteral administration includes IV, IM and SCs ways. Patient controlled analgesia (PCA) can be used in all these cases, although IV is most common. Subcutaneous PCA is often used for patients treated in their home.

When administered intrathecally or epidurally opioids cause selective spinal analgesia. Small doses of opioids with prolonged effect and minimal adverse effects are usually used. However, respiratory depression can still occur, especially when morphine is administered. Most of opioids are lipophilic and therefore can easily pass through lipid barrier. Neuraxial administration of opioids is used for treatment of postoperative pain, and rarely for malignant pain.

If opioids are administered rectally, same doses as oral administration apply.

Fentanyl is mainly administrated transdermal. Drug diffuses through skin into the blood. Patch should be replaced after 72 hours and quick titration to effect is not possible when this way of administration is used.

Opioids can also be administered transmucosaly (buccally, nasally, gingival). First pass metabolism is avoided this way and fast onset of action occurs. By this way fentanyl, buprenorphine, butorfanol and sufentanil can be administered.

Morphine

Morphine is an alkaloid derived from opium (Sertuner, 1803.), dried juice from opium poppy (*Papaver somniferum*). This drug is a referent drug when potential and profile of opioid action is compared. It is widely used all over the world and relatively inexpensive. It acts as pure opioid agonist with analgesic, sedative and antitusic effect. It binds primarily to µ-opioid receptors and activates them. Additionally, euphoria or dysphoria, sleepiness and dizziness can occur. Morphine causes respiratory depression, suppresses cough reflex, reduces fear and feeling of tiredness. It also causes miosis, increases tonus of smooth muscles in gastrointestinal and urinary tract.

Morphine comes in form of brown powder, which is hydrolyzed and inactivated in stomach. Therefore, it is not recommended to administer it in usual tablets because of very weak effect. It has been used only parenterally for long time, but now acidoresistent formulations are available which made oral morphine administration reliable.

Pharmacokinetics

Morphine is well absorbed in GI tract, mostly in proximal parts on intestines. Around a third of morphine is bound to plasma proteins and unbound fraction is ionized at physiologic pH. Morphine is strongly lipophilic.

Plasma half-life of morphine is around 3 hours and analgesic effect lasts for 4-6 hours. When administered IV, plasma levels increase rapidly, but peak concentration in brain and spinal cord is achieved

15-30 minutes later. Initial doses of intramuscular or subcutaneous morphine are variable, but 10 mg is usually recommended for person of 70 kg. Epidural or intrathecal administration showed good analgesic long lasting effect (12-24 hours).

Pharmacologic effects of morphine depend on dosage. Morphine shows no ceiling effect and increase in dosage will lead to increased effect but also to an increase of adverse effects.

Metabolism

Morphine is metabolized in liver by processes of glucuronidation and oxidation. Its metabolites are morphine-3-glucuronide (inactive) and morphine-6-glucuronide (2x more potent than morphine).

Glucuronides are excreted via kidneys. In patients with impaired renal function those metabolites are accumulated and prolonged effect occurs, including respiratory depression. Patients with hepatic function impairment tolerate morphine well up until the point when hepatic insufficiency leads to coma (glucuronidation is rarely affected until terminal liver disease). Extrahepatic metabolism occurs in central nervous system.

Administration, indications and contraindications for morphine use are described above.

Therapeutic doses

Morphine sulphate
- PO: 10-30 mg every 4 hours
- SC/IM for adults: 10 mg (5-20)/70 kg every 4 hours; for children: 0.1-0.2 mg/kg (up to 15 mg) every 4 hours;
- IV for adults: 2.5-15 mg/70 kg; continuous infusion: 0.1-1 mg/mL 5% glucose;
- Rectally: 10-20 mg every 4 hours;
- Epidural: 4 mg diluted in 10-15 mL 0.9% NaCl (maximum 10 mg/24h);
- Intrathecal: 1/10 of epidural dose (0.2-1 mg/24h) diluted with 1 mL 0.9% NaCl.

Other opioids:
- Meperidine: IM 75 mg, SC 75-100 mg;
- Methadone: IM 10 mg, PO 10-20 mg;
- Levorphanol: IM 2 mg, sc 2 mg, PO 4 mg;
- Hydromorphone: IM 1.3-1.5 mg, PO 7.5 mg;
- Codeine: IM 120-130 mg, PO 200 mg;
- Fentanyl: IM 0.1-0.2 mg, transdermal 12.5-100 µg/h

Diphenylpropilamine products

Methadone

Methadone is synthetic opioid with prolonged effect. It acts by binding to the µ-opioid receptors located in central nervous system. By activating those receptors, perception of pain is modified on spinal cord level and on higher levels of central nervous system. In addition, emotional reaction to pain is also modified. Methadone suppresses cough reflex by direct effect on centers most probably located in medulla oblongata or pons. **Elimination** of methadone is biphasic, with long β-elimination phase, up to 30-60 hours. This drug has ability to accumulate in organism, so it should be used with caution in order to avoid accumulation. There are inter-individual differences in blood concentration of methadone. In addition, sedative and respiratory depressant effects can overcome analgesic effect. This is possible because analgesic effect depends on α-elimination, which is usually 6-8 hours long. This is why methadone should be administered every 4-8 hours in order to achieve analgesia, but only once a day if given for substitution therapy. When large doses are administered, QT-interval prolongation can be seen in ECG. Methadone also has agonistic effect on δ-opioid receptors and also acts as NMDA antagonist as well as serotonin and norepinephrine re-uptake inhibitor.

Methadone induces hepatic microsomal enzymes. Therefore, if administered over long periods of time its **metabolism** increases and tolerance develops. First sign of tolerance is shorter period of analgesia. Tolerance can also develop to respiratory depressant effect. If dosage is progressively and carefully increased, analgesic effect can be achieved without respiratory depression.

Indications for methadone administration include severe pain treatment, strong persistent cough and treatment of heroin addicts (however, methadone itself can cause addiction).

Theoretically, methadone is ideal medication for treatment of neuropathic pain, but in practice this isn't quite so. Furthermore, methadone can be used for opioids rotation. Withdrawal syndrome is mild-

er than with morphine. Since it has longer duration of effect, methadone is used for detoxification or maintenance therapy in those with opioids addiction. Methadone analogue is levo-alpha-acetyl-methadol (LAAM), which is also used in opioids addiction treatment.

Dosage

Daily dosage should be carefully titrated. Rapid titration is not possible, which means that methadone should be used in treatment of patients with stabile levels of pain. It is relatively inexpensive and can be very efficient. When administered orally its activity is twice weaker than when administered IM or SC.

For treatment of pain it can be administered PO (2.5-15 mg), SC or IM (2.5-10 mg) every 4-6 hours. For maintenance therapy it is administered 40-100 mg a day. After oral administration analgesic effect occurs in 30-60 minutes. After parenteral administration analgesic effect occurs in 10-20 minutes with maximum effect after 1-2 hours.

For suppression of cough usual dosage is 1-2 mg every 4-6 hours. If used for longer periods of time, it is recommended to administer methadone no more than twice a day. Older patients and patients with respiratory diseases can be more sensitive to methadone effects. In those patients, in order to reduce possibility of respiratory depression, lower doses should be administered. These patients are more sensitive to analgesic effects as well. Therefore, lower doses or longer intervals will enable adequate analgesia.

For treatment of heroin addiction only oral administration is used. Treatment is usually started with 10-20 mg (1-2 mL) a day and then increased by 10-20 mg daily until withdrawal symptoms are resolved. Usual dosage for control of withdrawal symptoms is 20-40 mg (2-4 mL) a day. In some cases larger doses are needed, and maximal daily dosage is 120 mg (12 mL). Dosage is progressively decreased for each patient individually on daily basis depending on how patient will respond to treatment. If maintenance dose need to be applied, it is also determined individually. All patients who undergo addiction treatment with more than 100 mg of methadone a day should be checked daily during first three months of treatment. Long term administration of methadone can lead to tolerance development. When treatment is being topped, dosage should be gradually lowered.

In conclusion, dosage and frequency of administration should be individualized depending on pain intensity, patient's comorbidities, other medications being used and treatment effect. Dosage should be adjusted in patients with renal and hepatic disease.

Methadone should be administered with **caution** in patients with head injuries, increased intracranial pressure, prostate hypertrophy, urethral stricture, hypothyreosis, sensitivity to other narcotics and in patients with Addison disease.

It is not recommended to use methadone in patients with acute abdomen, severe inflammatory bowel disease or diarrhea (pseudomembranous colitis, intoxication).

Data about safe methadone administration during pregnancy is insufficient. Since methadone can be found in milk, it is not recommended to use it while breastfeeding.

Adverse effects include nausea, vomiting, obstipation, increased intracranial pressure, miosis, asthma exacerbation, respiratory depression, orthostatic hypotension, tolerance and addiction. It can also cause increased sweating and higher prolactin levels.

Signs of **overdose** are respiratory depression, sleepiness, hypotension, cold skin, confusion, dizziness, convulsions, miosis, bradycardia and unconsciousness. Methadone overdose can result in cardiac and respiratory arrest, coma or death.

Naloxone and naltrexone antagonize methadone effects. If pentazocine is administered with methadone, withdrawal syndrome can occur. Buprenorphine can decrease therapeutic effect of methadone.

Contraindications for methadone use include hypersensitivity to methadone, acute asthma, COPD and MAOIs therapy. It is not recommended to use methadone at the same time with MAOIs or within two weeks after MAO inhibitors are stopped.

When methadone is used with other drugs, various interactions can occur. MAOIs increase respiratory depression as well as central nervous system depression. Anticonvulsants induce hepatic enzymes and therefore increase methadone metabolism and can lead to withdrawal syndrome. Tricyclic antidepressants also increase depressant effects on central nervous system, as well as alcohol. Cimetidine inhibits methadone metabolism. If ciprofloxacin is given to patients who take methadone, sedation, confusion and respiratory depression can occur.

Codeine

Codeine is weaker opioid than morphine. It is metabolized in liver (cytochrome P450) and metabolites are excreted via kidneys. 10% of codeine is actually dimethyl morphine, and its analgesic effect is

probably related to hepatic metabolism. Codeine also has strong antitusic effect. Its plasma half-life is 2-4 hours. If administered alone, dosage should be 30-60 mg PO every 4 hours. Codeine is often administered in combination with other drugs, mostly acetaminophen and acetylsalicylic acid. There are also fixed-dose combinations of codeine (15, 30 or 60 mg) and acetaminophen (300 mg).

Hydrocodone

Hydrocodone is semi-synthetic codeine product with analgesic and antitusic effect. It is usually administered in combination with acetaminophen.

Hydromorphone

This is a strong opioid analgesic mostly used for treatment of malignant pain. It is efficient, easily titrated, with good tolerability and low risk for interactions with other drugs and it shows no ceiling effect. When administered parenterally, blood concentration increases rapidly, but effect on central nervous system is slower. Plasma half-life is 2-3 hours after intravenous injection. Hydromorphone is usually administered in doses 2-5 mg PO or 1.5 mg parenterally, every 3-4 hours.

Hydromorphone is metabolized in liver by glucuronidation process. It has no active metabolites (e.g. morphine-6-glucuronide) and therefore it is safe for use in patients with impaired hepatic and renal function.

This drug is usually used for treatment of malignant pain. It can also be used for treatment of polypathy in older patients, as well as for treatment of various types of pain in patients with liver and renal disease. It is also useful for treatment of patients who can't take medication orally.

Hydromorphone has low risk of interactions with other drugs. It also has low affinity for plasma proteins and it is not metabolized by cytochrome P450.

Oxycodone

Oxycodone is synthetic thebaine product. It has similar strength and other characteristics as morphine. It is usually administered with non-opioid drugs.

Oxycodone hydrochloride can be administered as formulation with controlled release of active substance. This formulation is useful for patients with hepatic and renal function impairment. It has no active metabolites and it bioavailability is 60-87%. It has rapid onset of action (<1 hour) and can be combined with gabapentin, amitriptyline and anticonvulsants.

Phenylpiperidine products

Meperidine

Meperidine has larger plasma protein affinity than morphine, around 70%. Dosage for oral and parenteral administration is the same. Analgesic effect occurs within 15 minutes after oral administration and maximum effect is reached after 1-2 hours from intake. If administered parenterally, effect occurs within 10 minutes and maximum effect is reached within 1 hour. Analgesic effect lasts for 2-4 hours. Usual dosage is 50-100 mg.

Normeperidine is meperidine metabolite. It has plasma half-life 15-20 hours. Both meperidine and normeperidine are excreted via liver and kidneys. In patients with impaired hepatic and/or renal function accumulation of normeperidine can occur. Normeperidine also has toxic effects, which can manifest as tremor, myoclonus, pupils dilation and hyperreflexia. If meperidine is combined with MAOIs, respiratory depression or excitation, hyperpyrexia and convulsions can occur. Meperidine also has weak local anesthetic affect.

Fentanyl

Fentanyl is a strong opioid receptor agonist. It has strong analgesic, sedative and antitusic effect. It is used for intravenous balanced anesthesia, analgesia of mechanically ventilated patients, for treatment of severe pain (e.g., myocardial infarction) and for treatment of malignant pain. Dosage of fentanyl administered during anesthesia and in ICU should be carefully titrated and patients general medical condition should be evaluated carefully (bradycardia, hypotension, low volume status). It can be used as an analgesic (2-10 µg/kg) or as an anesthetic (20-100 µg/kg). When administered parenterally it has fast onset of action. Fentanyl can also be administered intrathecally, epidurally, over mucosal membranes or through skin. It has very strong analgesic potential: 0.1 mg of fentanyl is equal to analgesic effect of 10 mg of morphine, making fentanyl 100 times stronger. It causes severe respiratory depression so it should be administered only by physicians who are able to intubate and adequately ventilate patient if that becomes necessary. Fentanyl acts predominantly through µ-opioid receptors. It has short duration of action, around 30 minutes. It is highly lipophilic.

Fentanyl products include sufentanil, alfentanil and remifentanil. These products are used during anesthesia and are not used for acute or chronic pain treatment.

For anesthesia induction fentanyl is usually administered in doses 1.5-4.5 µg/kg (0.1-0.3 mg/70 kg). Repeated doses are usually 1-3 µg/kg (0.07-0.2 mg/70 kg).

Adverse effects include respiratory depression, hypotension, bradycardia, obstipation, urine retention, nausea, vomiting and miosis. Naloxone is used as antidote.

Contraindications include known hypersensitivity to fentanyl, pregnancy and breastfeeding (fentanyl passes through placenta). It should be used with caution in patients with hypovolemia, hypotension and at risk of severe shock.

Fentanyl can be used as **transdermal patch (TTS)** for treatment of severe chronic pain. A patch that contains reservoir of fentanyl, is placed on patients' skin. Fentanyl release is gradual and lasts for 72 hours. After that the patch is removed and replaced by a new one. When using these patches, patients can get from 2.5 mg (25 µg/h) to 10 mg (100 µg/h) of fentanyl per day, depending on strength and number of patches used.

Fentanyl TTS are used for treatment of chronic malignant pain when opioid requirements are stabilized. They are also used for treatment of chronic non-malignant pain when other analgesics have no effect and when VAS (visual analog scale) > 4 (osteoarthritis, cox and knee arthrosis, backache, diabetic neuropathy, rheumatoid arthritis…). Use of fentanyl TTS is contraindicated for treatment of acute pain.

There are various forms of fentanyl TTS:

- TTS 12.5 µg/h – patch for 72 hours (1.25 mg of fentanyl);
- TTS 25 µg/h – Patch for 72 hours (2.5 mg of fentanyl);
- TTS 50 µg/h – patch for 72 hours (5 mg of fentanyl);
- TTS 75 µg/h – patch for 72 hours (7.5 mg of fentanyl);
- TTS 100 µg/h – patch for 72 hours (10 mg of fentanyl).

Adverse effects of fentanyl TTS include respiratory depression, addiction, intracranial pressure increase, bradycardia, hypotension, nausea, vomiting, sedation, obstipation, itching, sweating, urine retention, rash, erythema and hallucinations. When treatment is stopped withdrawal symptoms can occur. Those include nausea, vomiting, diarrhea, anxiety and shivering. In order to avoid those symptoms, therapy should be stopped gradually rather than suddenly.

It is not recommended to use fentanyl TTS during pregnancy and while breastfeeding. It is recommended that patients with these patches don't operate with motor vehicles.

Opioid agonist-antagonists

Benzomorphane products (Pentazocine)

Pentazocine is synthetic opioid analgesic. It acts through δ- and κ-opioid receptors as agonist and through µ-opioid receptors as antagonist. Therefore, pentazocine is partial opioid receptor agonist-antagonist. Analgesic effect of 30-60 mg of pentazocine administered IM or SC is comparable to administration of 10 mg of morphine. Pentazocine is used for treatment of different types of moderate to severe pain.

This drug should not be used for treatment of patients with known opiate addiction because it can lead to withdrawal symptoms. If pentazocine is administered after anesthesia where fentanyl, alfentanil or sufentanil were being used, analgesic effect of those drugs will be reversed. Pentazocine should also be avoided in patients with pulmonary or systemic hypertension, weak cardiac function and in patients with porphyria.

Same adverse effects and contraindications are applied for pentazocine as for morphine.

Pentazocine is usually administered orally in doses of 50-100 mg every 3-4 hours (after meal). Maximal daily dosage is 600 mg. If administered IM, 30-60 mg is usually given and for IV administration 30 mg every 3-4 hours is applied. In children 7-12 years old, 25 mg can be administered orally every 3-4 hours. In those children pentazocine can also be applied SC or IM (1 mg/kg) as well as IV (0.5 mg/kg).

Oripavine products

Buprenorphine

Buprenorphine is highly lipophilic semisynthetic thebaine product. It has both agonistic and antagonistic effects on opioid receptors. It is has partial µ-receptor activity and small κ- and δ-receptor activity. It has similar effect as morphine regarding analgesia, central nervous system and cardiovascular effects.

Buprenorphine also exerts partial agonist effect on *opioid receptor-like receptor* (ORL-1). Activation of this receptor is related to hyperalgesia. Buprenorphine can reduce effect of opioid receptor agonists (morphine, fentanyl).

Indications for buprenorphine administration include malignant pain, neuropathic pain and severe chronic musculoskeletal pain.

Buprenorphine has strong analgesic effect. Dose of 0.4 mg has equivalent analgesic effect as 10 mg of morphine but has much longer duration of action. It is usually administered IM or IV in doses 0.3 mg every 6 hours. After IM administration, analgesic effect occurs after 15 minutes and maximum effect follows after 1 hour. If administered IV analgesic effect occurs very quickly. If administered sublingually dose is usually 0.2-0.4 mg every 6-8 hours. For IM or IV administration usual dosage is 0.15-0.3 every 6-8 hours. Buprenorphine can also be administered epidurally in doses of 0.15-0.3 mg. When administered this way, analgesic effect occurs within 10 minutes with duration of 15-20 hours. Maximal recommended daily dosage is 1.6 mg if administered sublingually, and 1.2 mg if administered parenterally.

When starting therapy, patches with lower amount of drug are used. Therapeutic dose is then gradually titrated until adequate analgesic effect is reached. Buprenorphine can be additionally administered sublingually in cases of breakthrough pain. In case of opioid rotation, dosage of buprenorphine should be calculated from table of equivalent opioid dosages. Maximum of 0.32 mg of buprenorphine can be given per prescription.

Buprenorphine has shown ceiling effect. That means when maximal recommended daily dosage is administered, further increase of dose will not lead to increased analgesic effect.

In patients with renal insufficiency buprenorphine is safe to use because pharmacokinetics remains unchanged. In patients with hepatic disease buprenorphine should be used with caution since it's metabolized in liver.

For treatment of addiction FDA recommends sublingual use of buprenorphine in combination with naloxone. In USA buprenorphine is a drug of choice in treatment of patients with heroin or methadone addiction. Because it has great affinity for opioid receptors, withdrawal symptoms can occur with 1-2 week delay. Furthermore, because of such affinity, naloxone has little effect on reversal of buprenorphine effects. Instead, central analeptic doxapram (Dopram amp (20mg/mL)) is much more efficient. Doxapram is administered IV in doses 0.5-1.5 mg/kg. It is usually given as continuous infusion (200 mg/50 mL 0.9% NaCl; 60-180 mg/h, 15-45 mL/h).

If buprenorphine is administered in patients addicted to opiates, it can lead to withdrawal (restlessness, anxiety, insomnia, hyperkinesia, tremor and GI symptoms). In addition, buprenorphine itself can lead to addiction development. If administered sublingually (Subutex) for rehabilitation treatment it has 6-8 hours effect. If administered as patch its effect lasts for 96 hours. Naloxone can only partially antagonize buprenorphine effects.

Same contraindications for use apply as for morphine. It is not recommended to use it for treatment of persons <18 years of age. Furthermore, contraindications include known hypersensibility to buprenorphine, pregnancy and breastfeeding, MAOIs treatment, use of drugs that cause central nervous system depression (anesthetics, hypnotics, and neuroleptics), myasthenia gravis and delirium tremens. Buprenorphine should be used with caution in cases of head injury, shock, loss of consciousness, increased intracranial pressure, respiratory system disease and acute alcohol intoxication. Buprenorphine use can decrease ability to operate with motor vehicles.

Adverse effects are similar to those seen with other opioids: nausea, vomiting, spastic obstipation, urine retention, headache, erythema, pruritus, confusion, sleep disorders, sedation, hypotension, respiratory depression and lowering of pulmonary artery blood pressure. Furthermore, delayed hypersensitivity reaction can occur on place where patch is applied. These side effects are less pronounced than those caused by morphine.

Buprenorphine Transtec
- Transtec 35 µg/h – patch for 96 hours (20 mg);
- Transtec 52.5 µg/h – patch for 96 hours (30 mg);
- Transtec 70 µg/h – patch for 96 hours (40 mg).

Tramadol

Tramadol is synthetic opioid analgesic of newer generation. It has central effect and has somewhat unusual mechanism of action. Tramadol is weak µ-opioid receptor agonist. Furthermore, it inhibits serotonin and norepinephrine re-uptake. Analgesic effect of tramadol is much weaker than that of morphine

(10-20% of morphine analgesic effect). Analgesia is achieved by combination of indirect postsynaptic $\alpha 2$ adrenoreceptors activation and opioid activity. In US, tramadol is registered only for oral administration. It has low potential for causing addiction as well as respiratory depression. It is used for treatment of moderate pain and in combination with non-opioids for treatment of severe pain.

Tramadol has great affinity for tissues with volume of distribution 200-300 L. It has low affinity for plasma proteins (20%). It is metabolized in liver, where O-desmethyltramadol is created. 90% of excretion is via kidneys and 10% via liver. Dosage should be adjusted in patients with renal and hepatic function impairment. Elimination half-life is 5 hours.

Tramadol is used for treatment of moderate to severe pain: neck pain, acute low back pain and lumboischialgia and for nerve radiculopathy. It is also used for treatment of chronic pain: osteoarthritis, rheumatic disease, chronic regional pain syndromes and regional fascial painful syndromes.

Tramadol can be administered as capsules, tablets, tablets with prolonged release, suppositories, drops and injections. For adults and children >14 years of age tramadol is usually administered orally in doses 50-100 mg every 4-6 hours. Maximal recommended daily dosage is 400 mg (used to be 600 mg). If administered in form of drops, 20 or 40 drops (50 or 100 mg) can be given every 6 hours. Tramadol can also be administered as suppositories: 100 mg every 4-6 hours. There are also tablets with prolonged release: 100-200 mg 1-2 times a day. Dosage should be reduced in patients with renal and/or hepatic function impairment. For treatment of moderate postoperative pain tramadol is administered orally 50-100 mg every 4 hours, or intravenously 40-100 mg titrated until analgesia is achieved.

Tramadol is particularly useful analgesic for treatment of patients who have any kind of problems related to opioid or non-steroidal analgesics treatment. It can be used as monotherapy or in combination with NSAIDs.

Adverse effects include nausea, dizziness, headache, sweating, dry mouth, tiredness, vomiting, obstipation, GI symptoms, itching and skin rash. Rarely, palpitations, tachycardia, bradycardia, orthostatic hypotension, blood pressure increase, respiratory depression convulsions, paresthesias, tremor, confusion, sleep disorders and allergic reactions can occur. When tramadol is stopped, withdrawal symptoms can occur but this is rarely seen. Withdrawal symptoms include agitation, anxiety, insomnia, hyperkinesia, tremor and gastrointestinal symptoms.

Tramadol is contraindicated in patients with known allergic reactions to tramadol-hydrochloride. It should not be administered in patients with acute alcohol intoxication, intoxication with central nervous system depressants, patients taking MAOIs and patients with untreated epilepsy. It should be used with caution in patients with opioid addiction, in patients with loss of consciousness, head injury, severe hepatic and renal function impairment, patients with respiratory disease and those with increased intracranial pressure. It is not recommended to use tramadol during pregnancy and while breastfeeding. Tramadol can decrease ability to operate with motor vehicles.

Long term use of tramadol can lead to development of tolerance, physical and psychical addiction. Cross tolerance with other opioids can also develop.

Tramadol administration can have serious adverse effects if some other drugs are being used (MAOIs, antipsychotics, antidepressants). When tramadol and other serotonergic drugs (SSRIs, triptans, MAOIs) are used at the same time, serotonin syndrome can develop. It is manifested as confusion, agitation, increased body temperature, sweating, ataxia, hyperreflexia, myoclonus and diarrhea. Alcohol increases central nervous system depression effect. Furthermore, tramadol should be used with caution in patients who take oral anticoagulants.

Tramadol + paracetamol

This fixed-dose combination is used for treatment of mild to moderate pain. Usual combination is 325 mg of paracetamol with 37.5 mg of tramadol. It can be administered 2-3 times a day.

Opioid antagonists

True opioid antagonists are naloxone, naltrexone and nalmefene.

Naloxone

Naloxone is pure opioid antagonist, which can bind to all types of opioid receptors. It has greatest affinity for μ-receptors. Even small doses of naloxone administered IM or IV will prevent or reverse effects of μ-receptor agonists. Sedative effect is also reversed and increase in blood pressure can occur. Sudden reversal of narcotic depression with large doses of naloxone can cause nausea and vomiting, tachycardia, sweating, hypertension, restlessness and even cardiac arrest. Other adverse effect includes

hypotension, ventricular tachycardia and fibrillation and pulmonary edema. In patients with opioid addiction, acute withdrawal syndrome can occur. In order to avoid those effects, naloxone should be administered gradually.

Plasma half-life of naloxone is 60-90 minutes in adults and up to 3 hours in newborns. It action can last 1-4 hours. Naloxone should be administered IV, IM or SC. If given orally, it is rapidly metabolized and inactivated. After IV administration, effect occurs within 1-2 minutes. If administered IM or SC, effect occurs after 2-5 minutes. Volume of distribution is 5 l/kg, and 50% of the drug is bound to plasma proteins. Naloxone is metabolized in liver (oxidation and glucuronidation). Non-metabolized naloxone and its metabolites are excreted via kidneys. Duration of its effects depends on opioid concentration.

Naloxone is used for reversal of respiratory depression caused by opioids (addiction, anesthesia). Naloxone antagonizes opioid adverse effects and therefore patients normalize respiration, regain consciousness, their pupils return to normal size and bowel function is normalized. However, if naloxone is administered at the end of anesthesia, it will reverse analgesic effect of opioids and patient will feel pain. Since naloxone has short half-life, patients should be carefully monitored and if necessary, dose should be repeated (rebound effect).

As already mentioned, naloxone is indicated in cases of respiratory depression (bradypnea) and consciousness disturbances caused by opioids.

Usual dosage is 0.8-2 mg, maximum 10 mg. For treatment of postoperative respiratory depression, 0.1-0.2 mg of naloxone is administered and, if necessary, repeated every 2 minutes, depending on patients' response. Also, continuous infusion can be given starting with 2.5 µg/kg/h. In cases of severe respiratory depression in newborns starting dose is 5.10 µg/kg. Dose is repeated if necessary up to maximum of 25 µg/kg.

Relative contraindications include pregnancy (naloxone passes through placenta) and heart disease.

It is important to mention that most opioids have longer effect than single doses of naloxone so it is usually necessary to repeat dose of naloxone after 15-90 minutes, depending on clinical signs (e.g., respiratory depression). Naltrexone and nalmefene have longer half-lives than naloxone with 8-10 hours. In addition, naltrexone can be given orally. Single dose of 100 mg can be sufficient to block heroin effects for up to 48 hours. Nalmefene is administered only IV.

9. GENERAL ANESTHESIA

Ivan Agnić**, Mladen Carev*, Igor Vuković*

9.1. Introduction

The term "general anesthesia" includes medical procedure aiming to eliminate the patient consciousness (hypnotic effect), suppress the pain stimulus (analgesic effect), deprive unpleasant memories of the procedure (amnesic effect), and, depending on the need, to ensure patient immobility, in order to provide the surgeon optimal working conditions before and during invasive diagnostic or therapeutic intervention. The application of general anesthesia is inseparable from patient care and maintenance of its vital functions within the normal limits.

The patient may be induced and maintained in anesthesia with the application of the pharmacologic agents intravenously, inhaled or balanced/combined. The key to the planning lies in understanding the pharmacokinetics of available drugs. The pharmacokinetics of intravenous hypnotics allows quick onset of unconsciousness, however concentration of anesthetic in the plasma depends on the dosage and its metabolism requiring anesthesiologist's constant estimation of the length of pharmacodynamic action. On contrary, inhalational anesthetics metabolism is minimal, their removal from plasma depends on the interaction between the plasma concentration and the alveolar concentration. In daily practice, therefore, the most common procedure is induction with intravenous anesthetics and maintenance with inhalational. General categories of drugs that are commonly used in the process of general anesthesia are:

- Intravenous anesthetics (thiopental, propofol, etomidate, ketamine, midazolam)
- Inhaled anesthetics (N_2O, sevoflurane, isoflurane, sevoflurane, halothane)
- Opioids (morphine, fentanyl, sufentanil, alfentanil, remifentanil)
- Muscle relaxants (succinylcholine, pancuronium, vecuronium, vecuronium, atracurium ...)
- Adjuvant drugs (anti-emetics, anti-arrhythmic drugs, sympathomimetics, parasympathomimetics...)

Anesthesia is actually the art of giving certain drugs in order to achieve the patient 1) unconsciousness, 2) amnesia, 3) analgesia, 4) immobility and 5) the weakening of the autonomic nervous system response to painful stimulation. Accordingly, if the patient is not conscious it does not apply automatically that there are no present painful stimuli, in addition, if the patient is immobile it does not necessarily mean that he is not conscious, and vice versa. All of these components of the general anesthesia process should be understood by anesthesiologist, therefore, he can approach them separately in order to combine and achieve the satisfactory conditions. From the repertoire of available drugs, the aim is to choose the combination that best suits the requirements of the patient, the type of invasive procedures and conditions, bearing in mind the potential synergies and antagonisms that are possible between different substances applied.

9.2. General anesthesia - mechanism of action

The mechanisms of action of anesthetics are still not completely known. Some key points are identified as the focus of anesthetics action, such as synapses of neurons in the reticular formation, which is considered an important hub in the process of consciousness. The receptor for γ -aminobutiric acid (GABA), is one of targets for anesthetics such as thiopental, which potentiates its activation and causes the extension of chloride channel patency, whereas propofol and etomidate increase the affinity of these receptors for GABA. Ketamine antagonizes N-methyl-D-aspartate (NMDA) action on receptors and functionally "separates" the thalamus from the limbic lobe (which is important in the functions related to the awareness and sensation). Some inhalational anesthetics have a multifunctional range of effects - depending on the amount (expressed in MAC value - minimal alveolar concentration) provide amnesia, hypnosis and relaxation by acting not only on the central nervous system but also on a reflex arcs level of the spinal cord. Many of the effects are also attributed to the modulation of the GABA and modulation of the reuptake of other neurotransmitters such as dopamine and 5-hydroxytryptamine. In general, the scope of understanding general anesthesia will surely be developed in parallel with the emergence of new pre-clinical findings in neuroscience.

9.3. Ensuring ventilation during general anesthesia

Since most of the anesthetics have a pronounced effect on the autonomic nervous system, with particular emphasis on respiration, there is always a need to ensure adequate ventilation, which is in practice almost synonymous with general anesthesia. The anesthesiologist can choose from mask ventilation,

supraglottic devices (eg. laryngeal mask) or endotracheal tube. The choice depends on the requirements of the patient, type of surgery, and the assessment of the anesthesiologist. The choice itself can dictate the further strategy of general anesthesia conduction, as various drugs provide specific conditions, mostly dose dependent. For example, endotracheal intubation usually requires the prior administration of neuromuscular relaxants, while the use of laryngeal mask is usually designed to enable spontaneous breathing of the patient. In any case, securing the airway is a basis of the general anesthesia procedure, as well as the obligatory application of venous cannula (regardless of the type of general anesthesia).

9.4. General anesthesia - indications and complications

Indications for general anesthesia include patients facing a therapeutic or diagnostic (mostly endoscopic) procedure unsuitable to be performed under local anesthesia. General anesthesia is also administered in cases of some therapeutic methods of non-invasive nature, which would be unpleasant for patients, such as cardioversion in atrial fibrillation, or the application of electric current for the purpose of psychiatric treatment.

General anesthesia as a choice in the 21st century in the Western world countries slowly give its place to methods of regional anesthesia, which are declared as a safer, faster, cheaper and sometimes easier. All types of surgical procedures below the level of the neurocranium have been successfully performed under regional anesthesia. Complications related to the procedure of general anesthesia are numerous with a very broad spectrum of possible events. They can be classified as general complications which can occur in all anesthesiology procedures and specific complications, which are associated with a particular type of surgery or anesthesia. The most important general complications include:

- Allergic and anaphylactic reactions to administered drugs
- Failure to establish the airway patency
- Other complications during the procedure of endotracheal intubation, such as breakage of a part or the whole tooth or traumatic lesion of soft tissue
- Gastric content aspiration
- Cardiac arrest/arrhythmia, hemodynamic instability
- Postoperative respiratory depression
- Postoperative cognitive dysfunction syndrome, particularly in the elderly
- Lesions of peripheral nerves due to inadequate position of the extremities on the operating table
- Awareness during anesthesia (where the immobile patient becomes aware during the procedure and remembers the incident postoperative)
- The emergence of deep vein thrombosis
- Improperly positioned venous access (pain, hematoma, swelling, muscle lesions)
- Incidents caused by unsafe equipment / devices

9.5. The importance of monitoring during general anesthesia

Keeping in view the possible and unpredictable complications which can happen to an anesthetized patient, the importance of 1) preoperative preparation of patients and 2) intra- or perioperative monitoring of the patient's condition and function must be emphasized.

Preoperative preparation includes an interview with the patient in order to inform him about the type of anesthesia and the possible risks; it includes patient's informed consent. The medical history, physical examination and laboratory results give the anesthesiologist the opportunity to assess the likelihood of a certain type of complication, to take preventive measures, and to adopt perioperative strategy. He should look for a history of allergic diathesis data, especially about any previous allergic incidents; in addition, information about coagulopathy (prolonged bleeding) is very useful. Furthermore, the anesthesiologist should always check the patient's fasting in order to avoid pulmonary aspiration. On the other hand, in the procedure of general anesthesia, most time is spent on monitoring the vital functions of the patient (especially the blood oxygenation), with an automated monitoring together with anesthesiologist's observation, auscultation and manual examination methods (checking pulse, blood pressure, monitoring the color of the skin, the width of the pupil, etc.). Standard monitoring for each procedure include ECG, SPO_2 (pulse oximetry - measurement of hemoglobin oxygen saturation along with pulse waveform display), the measurement of blood pressure and capnometry. Information provided by monitoring methods are often layered, i.e. normal capnometry suggest normal metabolic production of CO_2 and also adequate tissue perfusion. Vigilance and a proactive approach of an anesthesiologist are essential to avoid many of the complications.

10. MONITORING OF VITAL SIGNS

Nenad Karanović*, Toni Lozančić**

10.1. Introduction

With the occurrence of the first intensive care units (ICU) some 50 years ago, the need has arisen for more intensive monitoring of patients' vital signs. Unfortunately at this stage of development of the ICU's, the most difficult patients were monitored only intermittently by nurses and other medical staff. Continuous measurement was unavailable or required a number of invasive procedures.

The rapid development of technology and the wide use of computers have significantly changed the potentiality of intensive care and monitoring within a few decades. There is no single part of the hospital where the patient is monitored better, more intense and with more continuity than in ICU's and operating theatres. Today all the vital signs can be tracked accurately and continuously, either by invasive or non-invasive procedures. The role of most of the surveillance and monitoring of patients is to alert the staff, physicians and nursing staff about possible threatening disorders to the patient's condition.

10.2. Monitoring

Monitoring represents the process by which medical staff, primarily physician, identifies and evaluates (estimates) the physiologic and pathophysiologic changes, noting trends during treatment. Efficient monitoring reduces any unfavourable treatment outcome, suggesting disturbances before they result in serious or irreversible damage. With their appearance the monitors increased specificity and accuracy of clinical assessment.

The first goal of monitoring is to point out the pathophysiological events (abnormalities) in patients at high risk of developing these events and disturbances. Another equally important role of monitoring is enabling timely and meaningful treatment. Final, but not the least important role in monitoring is the assessment of improvement of the patient condition.

The monitoring itself may be clinical supervision, with the help of various technical and technological resources, or conducted via laboratory tests.

Clinical supervision (or monitoring) is carried out with the help of our own senses (sight, hearing, touch, smell, etc.). The main characteristic is that it is always available, but unfortunately not sufficiently objective. It depends on many factors, such as the speed of perception, the ability of individual senses, fatigue etc.

Monitoring with the help of technical and technological means is more accurate, provides more data, is continuous and devoid of subjectivity. With certain computer software it is also capable of very complex diagnosis, not just surveillance. The possibility of malfunction is a risk. However, there are certain programs that warn of such a situation.

Laboratory monitoring with the aforementioned types of monitoring also enables the review of the complete state of the patient.

Selection of monitoring depends on the general status of the patient, the type of illness or injury and the intended way of treatment or possible intervention.

Basic monitoring: ECG and pulse, non-invasive measured blood pressure, body temperature, oxygen saturation of peripheral blood and state of consciousness.

10.3. Monitoring of the cardiovascular system

10.3.1. Electrocardiography

It monitors cardiac electrical activity. Continuous electrocardiography provides observation of heart rate, rhythm disturbances detection and tracking the function of pacemakers. It can help with the spotting of cardiac ischemia and some electrolyte imbalances.

Indications:

- In cardiac patients and all others with possible development of arrhythmias, myocardial infarction or angina pectoris. Patients in whom there is a possibility of bleeding to death or the need for replacement of fluids, blood and blood derivatives.
- In diabetics (due to damage to blood vessels (coronary and other arteries)) – possible arrhythmias, and electrolyte disturbances.
- All others likely to expect any kind of rhythm disturbances (bradycardia, tachycardia, other arrhythmias)

Placement: Leads II and V5 are most commonly used (3 electrodes). They are positioned on the shoulders and the front axillary line at the level of the xiphoid process.

Complications: Malfunction due to possible technical errors; old, dry or insufficiently well attached electrodes. Interruptions of the cables that disturb the signal from the electrodes are possible.

Normal values of heart rate: 60-100 beats/min. Lowering or raising the ST up to 1 mm.

10.3.2. Blood pressure measurement

Because the systemic blood pressure is dependent on cardiac function and peripheral circulation, arterial blood pressure monitoring provides "rough data" on the total cardio-circulatory function.

Blood pressure measurement is a standard procedure and an absolute requirement for all endangered patients.

However, the type and frequency of measurements depend on the individual condition and diagnosis of individual patients. Blood pressure depends on cardiac output (CO) and the systemic vascular resistance (SVR). Blood pressure can be measured either directly - with the instrumentation vascular areas (invasive) or indirectly (non-invasive) - techniques that include cuff for arterial occlusion.

a) Non-invasive blood pressure measurement
- Palpation - method is limited, insufficiently precise and enables only the measurement of systolic blood pressure.
- Auscultation (Riva-Rocci method) - more reliable than palpation, but still not precise enough. In comparison to the intra-arterial measurement, systolic blood pressure varies from 1-8 mm Hg, while the diastolic differs 8-10 mmHg. In comparison to intra-arterial measurement auscultatory method shows higher values at a pressure lower than 120 mm Hg, and lower values at the systemic pressure higher than 120 mmHg.
- Oscillometry - uses two cuffs. This method is the only non-invasive one that allows determination of the mean arterial pressure. The disadvantage is the inability of accurate measurement in patients with arrhythmias and those with poor circulation and reduced volume.
- Plethysmography - based on the fact that arterial pulsations lead to changes in the volume of the limb. Such changes may be determined by finger plethysmograph. Insufficient accuracy in stress situations (vasoconstriction) and at reduced intravascular volume.
- Doppler - ultrasonography. It is measured by ultrasound probe placed onto the artery distal to the cuff. Arterial pressure obtained by this method are often higher than those obtained by palpation and lower than those obtained by invasive measurements. However, they give very good data at low pressures. Sensitivity to movement is a drawback, as well as the need for exact placement of the probe and the use of ultrasound gel.
- Tonometry - based on the detection of occlusive pressure required to stop the flow through surface artery compressed to the bone structures. The good side is the continuous monitoring where the resulting wave pulsations are very similar to those obtained by invasive measurements.

b) Invasive blood pressure measurement

A catheter placed into an artery provides the most accurate blood pressure measurement nowadays. Such catheters are connected to pressure transducers, which convert pressure into electrical signals. Care must be taken that the air does not reach the system, which can lead to incorrect measurements since the air is easier to pressurize than water.

Indication: The need for continuous monitoring of pressure and its variations in different clinical settings, and during the use of vasoactive drugs.

Clinical application: Radial, ulnar, dorsalis pedis, posterior tibial, femoral and axillary arteries are used most frequently. Radial artery is preferred for ease of puncture and less possibility of severe complications (vascular insufficiency of the hand caused by thrombosis or arterial vasospasm). These complications are more common when using cannulae larger than 22 G. Women have less potential for development of arterial thrombosis than men, for unknown reasons. Infection is frequent complication.

Advantages: possibility of frequent blood sampling

10.3.3. Measurement of central venous pressure (CVP)

CVP reflects changes in the right heart, and only secondary may indicate the state of pulmonary circulation and left heart (only in cardiac and pulmonary uncompromised persons)

Indications: Assessment of the volume load (in patients without heart disease). Assessment of the right heart's condition.

Placement: internal jugular, subclavian and both sides femoral veins. Femoral vein is avoided because of frequent thrombosis and greater risk for infection.

Complications: arterial puncture, pneumothorax, perforation of superior vena cava (mortality 67%), laceration of the right ventricle (100% mortality), cardiac tamponade, damage to the brachial plexus, ganglion stelatum and phrenic nerve, air embolism (rare), venous thrombosis, infection.

10.3.4. Catheterization of the pulmonary artery

It was initially used as a way to measure intra-cardiac pressures and to assess the left heart function, supplemented with CVP measurement. Today it is considered a "golden standard". Provides information regarding the condition of the left heart, and also indirectly, of certain other hemodynamic values.

Indications: From cardiac disease to various pulmonary and circulatory disorders. Complications: the same as when placing a central venous catheter, along with the additional possibility to cause significant cardiac arrhythmias (VF and VES), knotting of the catheter, and rupture of the pulmonary artery (41% mortality).

Subtype of hemodynamic monitoring, not invasive as the one obtained by pulmonary catheter are PiCCO (Pulse Contour Cardiac Output) and LIDCO (Lithium Dilution Cardiac Output) method. Cardiac output (CO) can be observed together with various other values necessary for the proper supervision of circulatory system.

10.3.5. Doppler echocardiography

Ultrasound diagnostic of cardiac function. Recently constantly used by trans-oesophageal approach during cardiac surgical procedures. Unlike other methods, this one can diagnose acute myocardial infarction within ten seconds, which is significant. However, there are contraindications to its use (trans-oesophageal).

10.3.6. Monitoring of tissue perfusion

For now, there are two well-established methods:

a) *Tonometry of the gastrointestinal tract mucosa*: Allows an indirect measurement of the partial pressure of mucosal carbon dioxide (pCO_2) and pH calculation.

b) *The saturation of mixed venous blood*: To be taken from the pulmonary artery with the assistance of Swan-Ganz catheter. Based on the obtained values it provides estimation of the state of consumption of oxygen and perfusion.

10.4. Monitoring of the respiratory system

10.4.1. Auscultation using a stethoscope

The oldest method that is also very often used nowadays. Not objective enough.

10.4.2. Pulse oximetry

Allows for a non-invasive assessment of arterial oxygenation of peripheral blood. It is based on the change in the light absorption (red and infrared) which passes through the pulsating arterial vasculature. It belongs to the usual and standard patient monitoring. Not disabled by hyperpigmentation (black race), hyperbilirubinemia or anaemia (with exception of severe anaemia).

Limitations: Incorrect values in serious hypoxemia (below 75%), in cases of abnormal arterial pulsations, hypoperfusion, vasoconstriction, hypotension. In case of carbon monoxide poisoning cannot demonstrate appropriate values (shows higher values). It cannot completely replace the arterial blood gases analysis.

Indications: broad application in ICU's, such as control of oxygenation in patients on mechanical ventilation, and during the various procedures and interventions such as bronchoscopy, gastrointestinal endoscopy, electrocardioversion, etc.

Sensor placement sites: the peaks of the nose and fingers and ears.

10.4.3. Monitoring of CO_2 – capnography

Continuous monitoring of CO_2 concentration during each exhalation. The concentration of carbon dioxide at the end of exhalation ($ETCO_2$) is approximately equal to the concentration of this gas in arterial blood ($PaCO_2$) in patients with normal pulmonary function. Large differences between $ETCO_2$ and $PaCO_2$ can be caused by poor lung perfusion or intrapulmonary shunts. The progressive increase in $ETCO_2$ may indicate hypoventilation, airway obstruction or increased metabolism.

10.4.4. Transcutaneous measurement of blood gases

It is based on the determination of the partial pressure of oxygen and carbon dioxide in the tissue using the infrared part of the light (CO_2) while heating the electrodes to 43-45°C (O_2). Correlates well with the partial pressure of oxygen in arterial blood. Routinely used in the neonatal intensive care unit.

Note: Monitoring location needs to be changed every 4-6 hours because of possible thermal injury.

10.4.5. Respiratory mechanics monitoring

Includes directly measured values and those calculated from these values. The most commonly measured values are tidal volume, minute volume, airway pressure, intrathoracic pressure. Typical derived values are lung compliance, airway resistance, work of breathing.
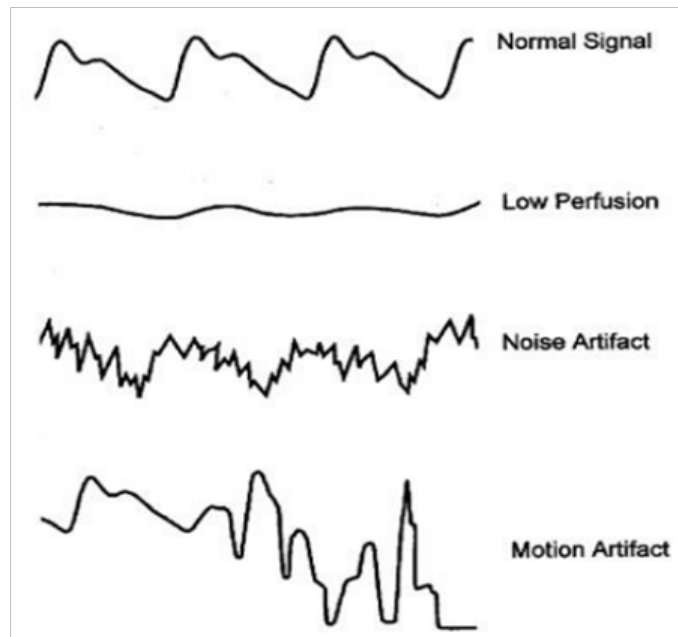
Fig. 10-1. Various signals received by pulse oximetry

10.5. Monitoring of the nervous system

10.5.1. GCS - Glasgow coma score

A scale that allows evaluation of the state of consciousness. The minimum number of points is 3, and the maximum 15. It is estimated on the basis of eye opening, motor activity and verbal responses (*Tbl. 10-1*).

10.5.2. Neurological status

Observes and notes the presence or absence of reflexes, pathological phenomena, pupil width and reaction to light, motor power.

10.5.3. Intracranial pressure

This measurement is used to confirm the diagnosis of elevated intracranial pressure and to monitor the success of treatment. It is indicated in head injury with GCS <7 or pathologic CT.

Complications: Infection, bleeding, especially in patients with coagulopathy, or during difficult insertions.

10.5.4. Electroencephalography

EEG reflects changes in cortical electrical activity. It records spontaneous activity. This activity is dependent on cerebral perfusion and oxygenation (*Fig. 10-3*). Conventional EEG can be used intermittently, but is expensive and impractical. Therefore the so-called Cerebral Function Monitor (CFM) is often used in the ICU. CFM is single channel. The so called "Bi-spectral index" monitoring or BIS (anesthesia depth monitor) is also designed on the basis of the EEG. It is used during anesthesia in surgical procedures.

10.5.5. Evoked potentials

Electrical signals that occur in the nerve pathways after periodic external stimulation. They are divided into auditory, visual and somatosensoric.

10.5.6. Cerebral blood flow

a) *Trans-cranial Doppler ultrasound* is based on ultrasound, like other echo-based diagnostic tools. It is used in certain cardiac surgery procedures.

b) *Radioisotope imaging*: usually xenon, which is administered intravenously or by inhalation. The drawback is a need of patient transportation to the laboratory with the gamma camera, which is highly impractical, so far used only as a diagnostic tool.
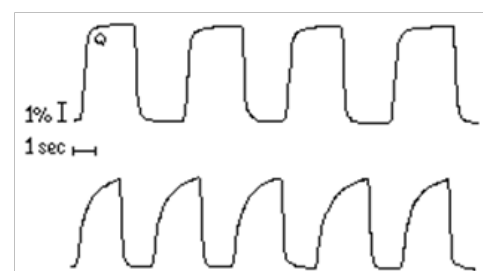
Fig.10-2. Capnograph measured normally (above) and during an asthmatic episode (below)

10.5.7. Cerebral oxygenation monitoring

It's performed in two ways:

a) Measurement of saturation of venous blood in the internal jugular bulbus

b) "Near-infra-red" spectroscopy (NIRS) based on the absorption of infrared light wavelengths of 700-1000 nm, by haemoglobin, myoglobin and cytochrome aa3.

10.6. Laboratory monitoring

- Different biochemical tests associated with particular organs function (liver, kidneys, heart, brain), the degradation products, electrolytes, enzymes in the blood
- Condition of the immune system
  - specific and non-specific indicators and acute phase proteins (eg. CRP: C-reactive protein)
- Coagulation status
- Circulatory condition - exsanguination
- Nutritional status
- Blood gas analysis
- Microbiological and toxicological tests
- Biochemical markers of cardiac and brain injury
- Etc.

10.7. Other monitoring methods

10.7.1. Body temperature

Detecting increased or decreased body temperature. It has significance in diagnosing certain conditions and pathological processes (sepsis, hyper- or hypothermia).

10.7.2. Diuresis

Along with partial kidney function it often indicates the state of cardio-vascular system (low blood pressure or low volume - exsanguination, low urine output).

Complications: The possibility of infections due to urinary catheters.

10.7.3. Presence of peristalsis

Tube retention (naso- or oro- gastric) refers to the condition and possible complications of the gastrointestinal system, particularly after surgical procedures. Intra-abdominal pressure facilitates decision making for surgical procedure, for example in pancreatitis.

Table 10-1. Glasgow Coma Score

Eye opening	score
Spontaneous	4
On call	3
On pain stimulus	2
Absent	1
Best motor response	
Following commands	6
Localising pain	5
Retraction on pain stimulus	4
Decortication flexion	3
Decerebration extension	2
Absence of response	1
Best verbal response	
Oriented	5
Confused	4
Inadequate	3
Indistinguishable speech	2
Absence of response	1
Total	**3-15**

Fig. 10-3. EEG waveforms, from top to bottom. .

11. AN APPROACH TO PATIENTS WITH LIFE-THREATENING CONDITIONS

Sanda Stojanović Stipić**, Mladen Carev*

11.1. Importance of a systematic approach to patients with life-threatening conditions

Life-threatening conditions can be caused by trauma (often) or another medical condition (respiratory problems, cardiac problems, alterations in mental status, an allergic reaction, poisoning, environmental factors, obstetric problems, etc.). Clearly, the procedure will be strictly individual with respect to the size of the problem; however, there are procedural rules common to all these conditions.

Firstly, patient or his/her accompanying person(s) should always be asked about the medication that the patient takes or has just taken, and about any allergies. It is important to know what led to the disease or trauma. It is equally important to know when the patient last had food or fluids orally.

The procedure with the life-threatened patient should follow the ABCDE rule (**A**irway; **B**reathing; **C**irculation; **D**isability; **E**xposition). In life-threatened patients it is advisable as early as possible to use monitoring, primarily ECG, non-invasive blood pressure measurement and oxygen saturation measurement (SpO_2), if possible.

Initial assessment should be quick, yet complete. Only after life-threatening conditions have been removed, can the next step be taken. The effect of treatment and/or other interventions should always be assessed. You must not forget that it always takes a few minutes for resuscitation measures to be effective. One should not be afraid to ask for help when treating life-threatened patients; on the contrary, all members of multidisciplinary team should be included.

For a start it is very good to ask the patient a simple question: 'How are you?'
- If the patient answers, it is a very valuable piece of information and it means that the patient:
  - has a functional airway
  - is breathing
  - has preserved brain perfusion
- If the patient is talking intermittently, it is most probably due to
  - Respiratory distress
- If the patient is not answering – the case is very serious

Then ABCDE procedure follows.

Airway(A)

Regarding the airway it is necessary to LOOK, LISTEN, and FEEL.
1) LOOK for the movement of the ribcage, possible intercostal retraction, movement of nostrils
2) LISTEN for the sounds of breathing, possibly stridor, obstruction
3) FEEL the flow of air.

Airway obstruction is a medical emergency of greatest degree, because, if left untreated, there will be very quickly:
- Hypoxia
- Damage to the brain, kidney and heart
- Cardiac arrest
- Death.

Airflow obstruction may be indicated by:
- Paradoxical movements of the abdomen and chest
- The use of auxiliary respiratory muscles
- Various sounds (stridor, wheezing) – with partial obstruction
- Central cyanosis is a late sign

Important! In life-threatened patients the decreased level of consciousness usually leads to airway obstruction! In case of an airway obstruction a specialist (an anesthesiologist, an intensivist) should be asked to help. One can try head-tilt with or without chin-lift and jaw-thrust maneuvers, inserting oropharyngeal airway or laryngeal mask. Moreover, one can try to clean the oral cavity in order to possibly remove the foreign body. In all cases of airway obstruction, endotracheal intubation is the golden standard. Administration of oxygen in any manner is not an error.

Breathing (B)

Regarding the breathing, this should be done at all times:

1) Determine the adequacy of ventilation
2) Inspect the chest – to exclude open pneumothorax, chest wound, and flail chest
3) Auscultation - whether bilateral breathing sounds are heard
4) In case of respiratory failure, begin support with mechanical ventilation.

The signs of respiratory distress may be:

- Sweating
- Central cyanosis
- The use of accessory muscles, abdominal breathing
- Rapid, shallow breathing.

If at any point we assess that breathing is not sufficient, one should try to ventilate patient using bag-mask ventilation, and call for help. The best solution is endotracheal intubation and mechanical ventilatory support.

Circulation (C)

Circulation check should include:

1) Check of peripheral pulse, capillary filling and blood pressure
2) Electrocardiogram (ECG)
3) Classifying a possible shock according to the vital signs (Table 11-1.)
4) Correction of hypovolemia
5) Determination of blood type, Rh factor, laboratory findings.

Frequency and the quality of the pulse (peripheral and central) are determined first. In the assessment of patients the special attention should be paid to the extremities, i.e. color of hands and fingers. They can be pink, which is a good option, but also pale and/or mottled as well, indicating serious conditions. The temperature of nose, fingers, toes, and ears is also important. Capillary filling time is assessed by pressing on the fingertip. It is normally < 2 seconds. Regarding the blood pressure, it is usually decreased in shock; however one should be cautious in the assessment because in the initial stages of shock it can be almost normal (due to compensatory vasoconstriction and increase in systemic blood resistance).Low diastole may indicate sepsis and anaphylaxis (vasodilatation, decrease in systemic vascular resistance). Decreased pulse pressure (systole *minus* diastole) can indicate hypovolemia or cardiogenic shock. Jugular veins can also reveal important information. Collapsed jugular veins usually indicate hypovolemia, and when engorged they indicate cardiac problems (heart failure, tamponade) or pneumothorax. Auscultation of the heart can also be useful. It is important to recognize the signs of decreased cardiac output; decreased level of consciousness and oliguria (urine output<0.5 mL/kg/h). The symptoms of heart failure are dyspnea, tachycardia, increased jugular venous pressure, third heart sound, crepitations over the lungs. In that case it is important to decrease the fluid intake and administer certain drugs: inotropes that enhance the myocardial contractility and diuretics that stimulate fluid elimination.

It is never wrong to insert several wide intravenous cannulas (14, 16 Gauge). The fluids are given quickly: for instance, 500 mL of crystalloids, if the patient is normotensive, and 1,000 mL, if the patient is hypotensive. The measurement of the central venous pressure should be considered. It is also necessary to measure the pulse and blood pressure continuously (every five minutes) and make attempts to maintain systolic pressure above 100 mmHg.

Definition of shock: Shock is an acute circulatory failure with inadequately or inappropriately distributed tissue perfusion leading to generalized tissue hypoxia. It is always necessaryto consider hypovolemia as the first cause of the shock, unless proven differently. Intravenous fluids should be quickly administered (unless there is an obvious heart cause). In surgical patients, bleeding site(s) should be identified. Caution: tension pneumothorax can also lead to circulation collapse.

Disability (D)

This mostly refers to the assessment of the level of consciousness. The most common causes of unconsciousness should be taken into consideration:

- Severe hypoxemia
- Hypercapnia (CO_2 narcosis)
- Sedatives/analgesic drugs
- Brain hypoperfusion

Table 11-1 Evaluation of hemorrhage (*American College of Surgeons Committee on Trauma 1983/1984*) – adult, 70 kg

	Class I	Class II	Class III	Class IV
Blood loss (mL)	< 750	750-1500	1500-2000	>2000
Blood loss (%)	<15	15-30	30-40	>40
Heart rate (min⁻¹)	<100	>100	>120	>140
Blood pressure	Normal	Normal	Decreased	Decreased
Respiratory rate (min⁻¹)	14-20	20-30	30-40	> 35
diuresis (mL/h)	>30	20-30	5-15	0
CNS – mental state	Mildly anxious	Light anxiousness	Severe anxiousness, confusion	Confusion, lethargy (>50% coma)

The level of consciousness of the life-threatened patient in emergency admission room is usually estimated by Glasgow Coma Scale (GCS). It was introduced into clinical practice in 1974 in order to monitor the level of consciousness during the first six hours after head trauma. It individually assesses best eye opening, verbal and motor responses, and values range between 3 (deep coma) and 15 (normal awake state). GCS is very important as it is included in numerous other scoring systems. Also, it is accepted worldwide and its value on admission in the hospital allows not only for making clinical assessment (severe head trauma is considered when GCS ≤ 8), but also for the outcome. It is, however, unsuitable for infants and children of up to 5 years of age.

Best EYE response (E)

1) No eye opening
2) *Eye opening in response to pain stimul*us (a peripheral pain stimulus, such as squeezing the lunula area of the patient's fingernail)
3) *Eye opening to speech.*
4) *Eyes opening spontaneously*

Best VERBAL response (V)

1) No verbal response
2) *Incomprehensible sounds* (Moaning but no words.)
3) *Inappropriate words* (Random or exclamatory articulated speech, but no conversational exchange. Speaks words but no sentences.)
4) *Confused* (The patient responds to questions coherently but there is some disorientation and confusion.)
5) *Oriented* (Patient responds coherently and appropriately to questions such as the patient's name and age, where they are and why, the year, month, etc.)

Best MOTOR response (M)

1) No motor response
2) *Decerebrate posturing* accentuated by pain (extensor response: adduction of arm, internal rotation of shoulder, pronation of forearm and extension at elbow, flexion of wrist and fingers, leg extension, plantar flexion of foot)
3) *Decorticate posturing* accentuated by pain (flexor response: internal rotation of shoulder, flexion of forearm and wrist with clenched fist, leg extension, plantar flexion of foot)
4) *Withdrawal from pain* (Absence of abnormal posturing; unable to lift hand past chin with supra-orbital pain but does pull away when nail bed is pinched)
5) *Localizes to pain* (Purposeful movements towards painful stimuli; e.g., brings hand up beyond chin when supra-orbital pressure applied.)
6) *Obeys commands* (The patient does simple things as asked.)

Example: a patient who opens his eyes in response to the pain stimulus, responds with confusion and localizes pain stimulus has a GCS of 11; it can be written down as GCS=11 (E2 V4 M5). (http://en.wikipedia.org/wiki/Glasgow_Coma_Scale)

In case of cranial trauma:

GCS ≤ 8 = deep coma, severe cranial trauma, life-threatening prognosis

GCS 9–12 = conscious patient with a moderate injury

GCS > 12 = mild injury

At this level, ABC needs to be re-checked at any moment. Important information can also be found in the patient's therapy list (administer naloxone if the patient was taking opioids or flumazenil in case of benzodiazepines overdose). Pupils need to be examined (size, symmetry, light reaction). It is helpful to determine blood glucose using test strips; if the values are < 3 mmol/L – administer 25–50 mL 40% glucose. If the patient is not intubated the recovery position is recommended.

Exposition (E)

This step includes the examination of the complete body. Skin changes need to be observed, as well as open fractures, deformities, contusions, etc. It is necessary to undress close-fitting trousers carefully in order not to cause additional trauma. Prevention of hypothermia is also important.

After all this, the triage can be done, i.e. whether the patient will be referred to a ward or to the intensive care unit (ICU). It is advisable to keep medical record about the administered medications and performed procedures.

Conclusion: Treating life-threatened patients is a vast area due to a number of conditions, but the initial approach is generally the same. Resuscitation and preservation of optimal blood volume is of permanent priority, accompanied by treating breathing disorder (mechanical ventilation). Only after the initial resuscitation and provided circulatory and respiratory support the early diagnosis and treatment is given.

11.2. The life-threatened patient in intensive care unit

Intensive care unit (ICU) is a hospital ward which provides life support or support of organ systems in critically ill patients who usually require constant and invasive surveillance. Physicians who work at ICU are called intensivists; they are most frequently anesthesiologists, internists, surgeons and emergency medicine physicians. Furthermore, there is a highly educated nursing staff to work with the most difficult patients.

Patients are admitted to the ICU in several ways: directly from emergency room after diagnostic examination and surgical treatment, from other departments if their clinical condition is significantly deteriorated, or it is possible immediately after surgery, if it is a demanding and/or the patient has multiple risk factors for postoperative complications.. Most frequent patient conditions treated in ICU are *trauma, sepsis and multiple organ dysfunction syndrome*. Patients admitted to ICU usually require support due to hemodynamic instability (hypertension/hypotension, life-threatening arrhythmia), inability to maintain airway or sufficient breathing (i.e. require mechanical ventilation), acute kidney failure, and, very often, due to complete clinical effects of multiple organ failure.

12. ADULT LIFE SUPPORT

Ana Šarić**, Mihajlo Lojpur *

12.1. Causes and patophysiology of cardiorespiratory arrest

Cardiac arrestis a common namefor an acutecessationof blood flow. However, the term is imprecisebecausearrestcan be caused bythree differentmechanismsthat are not alwaysassociated with a complete lack of mechanical action of the heart. These mechanismsare:

- **Ventricular fibrillation and puseless ventricular tachycardia(VF/VT)** – the heart does not stand still, ventricles contract too fast, in an unsynchronized and anarchic way. That is the reason why valves are unable to ensure the anterograde blood flow.
- **Asystole** – conduction system of the heart does not generate electrical impulses necessary for the myocardial contraction. That is why the heart does not contract.
- **Pulseless electrical activity (PEA)** – there is electrical activity that would normally be associated with a palpable pulse, but there is no mechanical response of the heart. Patients often have some myocardial contractions. However, these are too weak to produce a detectable pulse or blood pressure.

In approximately 80% of cardiac arrests VF is the primary mechanism of cardiac arrest in adults.

The most common reasons for cardiac arrest are heart disease, but it can be a respiratory diseases and other conditions that interfere with the normal functioning of the organism.

Coronary disease (Ischemic heart disease) is the most most often (75%) cardiac cause of cardiac arrest. In other 25% of cardiac arrest, causes are: changes of the myocardium that can result in a carrdiac arrest (hypertrophy, dilatative cardiomyopathy, myocarditis,…), valvular diseases (aortal stenosis, prolaps of mitral valve), electrophysiologic disorders (elongated QT interval, WPW syndrom,...), acute pulmonary oedema, etc.

Respiratory causes of cardiac arrest are:

1) Inadequate inhalatory atmosphere (e.g. carbon monoxide or dioxide poisioning)
2) Hypoventilation and apnea due to the opstruction of airway (bronchospasm, foreing body in the airway), lung diseases that decrease respiratory surface (eg. pneumonia, …), neurological diseases resulting in decreased respiratory movements (e.g. muscular dystrophy, …), thoracic diseases and injuries (e.g. pneumothorax, haematothorax, …)

The third group of cardiac arrest causes is called general causes. It combines:

1) Metabolic causes – hypoxia, hypokalaemia, …
2) Toxic substances and poisonings – eg. intoxication with proarrhythmogenic drugs (eg. digitalis, antiarrhythmics, …)
3) Physical causes – electric shock injuries, trauma, hypothermia, …
4) Reflex causes – stimulation of parasympaticus (pressure onthe eyeballs, massaging of sinuscarroticus, intubation, bronchoscopy, aspiration of tracheobronchial tree) and sympathicus with emotions, pain, etc.

In adults the most often causes of cardiac arrest are primarily cardiac (coronary disease above all), and in children respiratory and general causes dominate.

Regardless of the primary cause of arrest, the consequences are always the same. In the end the complete cessation of blood flow happens and oxygen is not delivered to the tissues making them hypoxic.
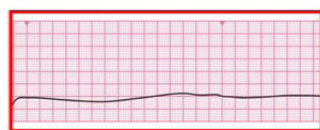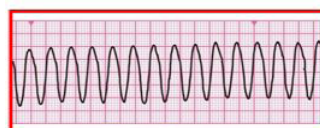
Fig. 12-1. The cardiac arrest rhythms.

The brain, being the most differentiated organ, is the most sensitive to the lack of oxygen (eventhough it weights only 2% of the complete body weight, it uses more than 20% of the oxygen that is delivered via blood for organs and tissues to use). After the complete cessation of blood flow, brain cortex stops functioning after 5 – 15 seconds („cortical death") and the patient stops responding. Shortly after that vital centers in brainstem stop working as well, respiratory center being one of them. As a result, the patient stops breathing shortly after the cardiac arrest („brainstem death"). If the blood does not start to flow in any way, spontanious or as a result of chest compressions, in approximately 5 minutes most brain cells die and the brain becomes irreversibly damaged („brain death").

There are factors that decrese the brain`s need for oxygen, for example hypothermia and some medications (barbiturates, benzodiazepins, calcium chanell blockers, …) They can postpone the brain death!

After the death of the brain, in different intervals the other organs and dissues die as well, leading to complete biological death that is caracterized with rigor and livor mortis. However, eventhough few kinds of death have been mentioned in order to emphasise the course of events, there is only one death: death of the brain is the death of the patient!

12.2. Clinical characteristics of cardiorespiratory arrest

Urgent medical assessment is required, one should identify arrest in no more than 10 seconds, without wasting to much time. The most important symptoms of cardiac arrest are :

1) **Unresponsiveness** – loss of consciousness happens 15 seconds after cardiac arrest. If patient does not respond to gently shaking his shoulders and asking if he is all right, he is unconscious. Seizures can sometimes be seen prior to the loss of conscious, especially if a patient has Adams Stokes syndrome.

2) **Cessation of breathing or abnormal breathing** – respiratory arrest follows quickly after cardiac arrest. Complete cessation of breathing is called apnea, but sometimes agonal breething (occasional gasps, slow, laboured or noisi breathing) can also be seen. One should open airway and check for no more than 10 seconds to determine if the victim is breathing normally:

   - Look for chest movement
   - Listen at the victim`s mouth for breath sounds
   - Feel for air on your cheek

While checking if the victim is breathing normally, one should always keep the victim`s head tilted. In that way the tongue and anterior neck structures (soft palate and epiglottis) are streched, and the commonest site of airway obstruction is relieved.

3) **Cessation of blod flow** – it is determined indirectly, based on the loss of consciousness and on victim`s not breathing normally. However, healthcare providers that are able to determine the presence or absence of a puls in less than 10 seconds can add direct pulse palpation in a recognizing cardiac arrest sequence. It is the best to palpate a puls simulatenously while checking if the victim is breathing normally, always on a rescuers side.

Because of its location, it is easier to palpate puls on a carotic artery (you do not need to undress the victim). One should identify laryngeal cartilage and pull fingers to the lateral, until they fell into a hole in front the anterior edge of sternocleidomastoideus muscle.

Femoral artery is palpated below inguinal ligament, in the middle between iliac crest and pubic bone. It is not as easy awailable as carotic artery, especialy when victims are obese and muscular. While resuscitating, the rescuers occupy the upper body. However, if there are enough rescuers, one could palpate the femoral artery to check if the chest compressions are properly done.

In infants it is difficult to palpate carotid artery because of their short neck. That is why brachial artery should be palpated.

Above mentioned are the most important elements of recognising cardiac arrest. One should spend no more then 10 – 15 seconds to decide if the cardiac arrest is present and if cardiopulmonary resuscitation is needed.

12.3. Treatment of cardiac arrest

Essential treatment algorithms for the resuscitation of adults are, based on didactic reasons, divided into three sections:

- Adult BASIC LIFE SUPPORT and the use of automated external defibrilators (BLS)
- Adult ADVANCED LIFE SUPPORT (ALS)

- POST-RESUSCITATION CARE – intensive care and treatment of the pacients who developed postacardiac arrest syndrome (complex pathophysiological processes that occur following whole body ischemia during cardiac arrest and the subsequent reperfusion response following succesful resuscitation) .

Basic life support refers to recognition of sudden cardiac arrest and maintaining airway patency and supporting breathing and circulation without the use of equipement other than a protective device. It also includes the use of an automated external defibrilator (AED), the recovery position and management of choking (foreign-body airway obstruction).

Advanced life support refers to more complex, invasive actions that can be performed only if the additional and advanced adjuncts, equipement and medications are available. That is why only experienced rescuer should perform ALS.

However, BLS and ALS are connected and both are part of the Chain of survival. The first link of this chain indicates the importance of those at risk of cardiac arrest and calling for help. The central links depict integration of CPR and defibrilation as the fundamental components of early resuscitation in an attempt to restore life. The final link is about post-resuscitation care. Only if all chain links are performed in a timely manner, one can expect that the goal of resuscitation will be fulfilled: a patient discharged from hospital as a healthy person that sees, hears and feels.

12.3.1. Resuscitation procedures

Airway management

Pharynx is the commonest site of airway obstruction in unconscious patients. The reason for obstruction is relaxation of hyoid and neck muscles. As a concequence, the tongue is shifted backwards, on the posterior wall of pharynx.

Foreign-body airway obstruction is an uncommon but potentially treatable cause of accidental death. As most choking events are associated with eating, they are commonly witnessed. Thus, there is often the opportunity for early intervention while the victim is still responsive.

Foreign bodies may cause either mild or severe airway obstruction. Victims with mild obstruction should be encouraged to cough, and should remain under continuous observation until they improve, as severe airway obstruction may subsequently develop. Victims with severe airway obstruction ad ineffective cough should be treated using abdominal thrusts and back blows. If a victim becomes unconscious, rescuers should start with CPR. The purpose od chest compressions is primarily to remove the airway obstruction and secondarily to promote circulation.

Complete airway obstruction quickly causes apnea and cardiac arrest, while partial opbstuction causes hypoxic brain damage, brain od pulmorany oedema, arrhythmias or other complications, and at the very end, cardiac arrest as well. That is why it is important to master procedures that ensure airway patency.

Procedures that improve patency of an airway obstucted by tounge or other upper airway structure are:

1) Head tilt and chin lift

This is the first positional method that ensures the airway patency, and in most cases, where airway obstruction results from relaxation of soft tissues, no other procedure is needed. The rescuer`s hand is placed on the patient`s forhead and the head is gently tilted back. The fingertips of the other hand are placed under the point of the patient`s chin, which is lifted gently in order to strech the anterior neck structures. This procedure is to be avoided if there is cervical spine injury (or if there is suspicion that cervical spine has been injured)!

2) Jaw thrust

This is a method of choice when there is a risk of cervical spine injury. The rescuer`s index finger and other fingers are placed behind the angle of the mandible and pressure is applied upwards and forwards. Both tumbs are used to slightly open the mouth. Rescuer`s elbows should rest at a flat surface.

3) Oropharyngeal and nasopharyngeal airways

Oropharyngeal and nasopharyngeal airways are often helpful, and sometimes essential to maintain an open airway. They overcome the backward displacement of the soft palate and tongue in an unconscious patient. In conscious patients, that still have their glossopharyngeal and laryngeal reflexes, their insertion can cause vomiting or laryngospasm. Nasopharyngeal airway is tolerated better than oropharyngeal airway in patients that are not deeply unconscious.

Oropharyngeal airways are available in sizes suitable for the newborn to the large adults. Their length correspondens to the vertical distance between the patient`s incisors and the angle of the jaw. Nasopharyngeal airways are sized in milimeters according to their internal diameter, the length increases with diameter.

Oropharyngeal airway is inserted in a way that the tip is placed behind the front upper teeth, it is promoted towards the pharynx while rotating it for 180° about longitudinal axis.

Nasopharyngeal airway is inserted into wider nostril below lower nasal turbine, with gentle rotational movements, after being lubed with anesthetic gel. Insertion can cause damage to the mucosal lining of the nasal airway, resulting in bleeding. That is why it is not as often used as oropharyngeal.

4) Recovery position

This position is recommended if the patient does not respond, but is breathing normally. There are several variations of the recovery position. All of them have in common the fact that this position should be stable, near to the true lateral position with the head dependant and with no pressure on the chest that could impair breathing. The head should be tilted backwards to ensure airway patency and mouth should be open to allow liquid material to drain from the mouth. It is usually performed with following sequence of actions :

- Kneel beside the victim
- The arm nearest to you should be placed at right angles, elbow bent with the hand palm uppermost
- The far arm should be placed with the back of the hand against the victim`s cheek
- The far leg should be grasped above the knee and pulled up in order to roll the victim towards the rescuer.
- The far leg can then be adjusted so that both knee and hip are bent at right angles.

If there is a risk of cervical spine injury, the head should be held all the time while rolling the patient. At the end of sequence, something should be placed below the head in order to ensure that the head is stable.

5) Endotracheal intubation (ET)

Tracheal intubation is a procedure of placing the tube into trachea in order to ensure airway patency. Intubation can be done through the victim`s nose or mouth:

Nasotracheal intubation has manyadvantages(it is better tolerated, it is more suitable for longer transport and etc.), but is difficult to perform and is often accompanied with serious epistaxis. That is why it is rarely performed while resuscitating. However, when patients have difficult mouth and oral cavity injuries or trismus it is a method of choice.

Orotracheal intubation is performed with rescuer standing above the victim`s head. Rescuer uses his right head to hold the occiput and tilt the head. Laryngoscope is hold in left hand. The blade enters the mouth and moves tongue to the left, while the blade goes deeper into oral cavity in order to show epiglottis. If the curved blade is used (adults, bigger children), the tip of a blade should be positioned in valekula above the epiglottis. The laryngoscope is then lifted upwards. It the straight blade is being used, its tip reaches the epiglottis and lifts it directly. In both cases the tracheal entrance is shown. However, the curved blade does not touch it and provokes less trauma and leaves more space for insertion od the tube in trachea.

When the tube goes through vocal cords, the cuff ends up below the cords. The cuff is inflated with air, lungs are auscultated and after the breathing sounds are heard on both sides of thorax, the tube is fixated using tape or bandage.

General indications for tracheal intubation are:

- The rescuer is unable to ventilate unconscious victim with others, less invasive methods
- Lack of victim`s protective reflexes .

Tracheal intubation has many advantages over other methods of airway management, the most important being:

- Enables the administration of high oxygen concentrations and adequate tidal volumes particular when lung and/or chest compliance is poor
- Enables artificial ventilation that does not require interruption of chest compressions
- Minimizes gastric inflation and therefore the risk of regurgitation
- Enables aspiration of tracheobronchal route.
- Endotraheal route for drugs administration.

Because of all the above mentioned, tracheal intubation is perceived as the optimal method of providing and maintaining a clear and secure airway. However, it should be used only when trained personnel are available to carry out entire procedure with a high level of skill and confidence. There are evidence that without adequate training and experience,

- Tracheal intubation can harm the patient (lips, teeth, tongue and trachea can get injured; epistaxis as a side effect if nasal intubation is performed)
- Incidence of complications, such as oesophageal intubation and dislogdement is unacceptably high
- Prolonged attempts are harmful: cessation of chest compressions during this time will compromise coronary and cerebral perfusion.

Table 12-1. ET sizes for patients of different age

Age /Weight	Internal diamether of ET tube (mm)	Length of ET tube, measured from incizors (cm)	Size of aspiratoin catheter (F)
0–1years /3–10 kg	3,5–4,0	11–12	8
1 year old infant/ 10–13 kg	4,0	12	8
3 years old /14 –16 kg	4,5	12,5	8–10
5 years old /16–20 kg	5,0	13–13,5	10
6 years old /18 –25 kg	5,5	14	10
8 years – junior (24–32 kg)	6,0 cuffed	15	10 or 12
12 years – adolescent (32–54 kg)	6,5 cuffed	16–16,5	12
16 years – grown up (≥50 kg)	7,0 cuffed	17–17,5	12
Adult female	7,0–8,0 cuffed	17,5–21	12 or 14
Adult male	8,0–8,5 cuffed	21–22	14

There are alternative airway devices, supraglottic airway devices, that are easier to insert than a tracheal tube and, unlike tracheal intubation, can generally be inserted without interrupting chest compressions.

6) Supraglottic airway devices

These devices are revolutionary when it comes to resuscitation and airway management because they enable less experienced personnel to secure the airway during cardiac arrest.

Laryngeal mask airway (LMA) is a plastic tube with a standard 15mm connector to a self-inflating bag (the ambu bag) ond its upper end and a somethins similar to a face mask on its lower end. This lower part is shaped in a way to cover laryngs and, after the cuff has been inflated, to isolate it from the rest of the structures,

Advantages of LMA:
- Ventilation using LMA is more efficient, in comparison to ventilation with disposable face masks
- It is easier to insert, in comparison to tracheal intubation, one does not need a laryngoscope to insert it.

Disadvantages of LMA, In comparison to tracheal intubation:
- there is an increased risk of aspiration, especially if the patient is ventilated using pressure >20 cm H_2O
- inability to provide adequate ventilation in patients with low lung and/or chest-wall compliance
- generally, <u>LMA does not protect the airway</u> from aspiration of gastric contents!

Before insertion, one must prepare gloves, lubricant and syringe to inflate the mask. After picking out correct size of LMA, one must inflate a mask with only 5mL of air, in order for it to regain it`s shape. Lubricant goes on the back side of the mask. The rescuer stands above the patients`s head, with the head slightly tilted and held with non-dominant hand, while the LMA is held in dominant hand, like a pencil with an opening facing downwards. Laringeal mask is then promoted into oral cavity, pushing through the hard palate. At first, one feels resistance while the mask is being pushed through the base of the tongue. After that, there is no problem to insert LMA even deeper, until the tip of the LMA does not reach the upper part of oesophagus. That means that the LMA is in the right place and it can be inflated with the rest of the air. One must always check ventilation of the patient after LMA has been inserted; if the ventilation is adequate and no air is lost while ventilating, the LMA can be fixed. If the ventilation is not adequate, LMA should be repositioned after deflating it, oral cavity and pharynx could be aspirated.

Table 12.2. Sizes of laryngeal mask airway

Size	1	2	2,5	3	4	5
Weight (kg)	>6,5	6,5–20	20–30	30–50	50–80	>80
Volume of air (mL)	2–4	10	15	20	30	40

It should be mentioned that there is a laryngeal mask with double tube arrangement, LMA Proseal. This inovation with double cuff design (on adult sizes) enables seal pressures of 30 cm H_2O and greater to be achieved, with minimal mucosal pressure. The drain tube opens at the upper oesophageal sphincter and permits drainage of gastric secretions and access to the alimentary tract. It allows easy clinical confirmation of mask position and is intended to prevent inadvertent gastric sufflation.

Combitube (Esophageal –Tracheal Combitube – ETC) is a double lumen tube: one lumen (shorter, transparent tube) resembling a tracheal tube, the other (longer, blue tube) is an esophageal obturator type tube with a distal blocked end and perforations at the pharyngeal level. It does not matter if the combitube enters trachea or esophagus, this device enables ventilation in both positions.

Two sizes of the Combitube are available: they can be used with patients older than 15 years, in smaller and larger adults.

Table 12-3. Combitube sizes

Size	Upper cuff volume (mL)	Lower cuff volume (mL)
37 F	40–85	5–12
41 F	40–100	5–15

Combitube is introduced blindly, without the use of laryngoscope, with the head in neutral position, until two black marks on both tubes reach patient`s incisors. Then the blue cuff is ventilated with 40-100mL of air which moves combitube approximately 1cm out of mouth. After that one should inflate the lower cuff with 5-15mL of air.

After insertion, one should check to see where the tip of combitube really is. There are two possibilities:
- Usually ETC enters the oesophagus, which is the easyer route. When both cuffs are inflated, hypopharynx (the entrance into trachea is located there) is detached from oesophagus with the lower cuff and from oropharynx with the upper cuff.
- Rarely ETC enters trachea. In those cases the lower cuff acts as ET tube`s cuff, and the upper cuff settles between the base of the tongue and soft palate and makes sure that the combitube is fixated.

That means that after the insertion of combitube and inflation of both cuffs, one should try to ventilate lungs via longer, blue tube which has a blind ending, but has a side openings between cuffs. It the ventilation is succesful, combitube is in oesophagus. The other tube can be used for evacuation of gastric contents. If the ventilation is unsuccesful, one should try to ventilate via shorter, transparent tube that has a distal opening. If the ventilation is succesful, ETC is in trachea.

In both cases, the breathing is auscultated bilaterally in order to realise which lumen is used for ventilation.It is good to auscultate abdomen as well to hear if the stomach is ventilated or not (if it does, one should check the cuffs).

I-gel is a laryngeal mask made of thermoplastic elastomer gel that seals pharyngeal, laryngeal and perilaryngeal area without inflation. In that way possible injuries of surrounding tissues are minimized. There are I-gels in different sizes (Table 12.4.).

Table 12-4. I-gel sizes for adults

Size	Patient	Patient`s weight (kg)	Maximum size of NGS (Ch)
3	Small adult	30–60	12
4	Medium adult	50–90	12
5	Large adult	90 +	14

I-gel is very easy to insert, requiring only minimal training and a laryngeal seal pressure of 20-24 cm H_2O can be achieved. While inserting it:
- Water based lubricant is spread over its lower end
- Patient`s head is tilted backwards into sniffing position, chin is liffted to make place for the i-gel that is then promoted into pharynx with hard, but glently movements

- When one feels resistance and its distal end reaches incizors, one should stop pushing
- If patient`s ventilation is inadequate, one should reposition device.

Laryngeal tube (LT) is a single lumen tube with two cuffs. Modified version incorporates an extra lumen for inserting a gastric tube or suction system. It can fit NGS of maximum 16F. There are few different sizes of LT, calibrated according to weight or height, with each size having colour-coded 15mm connector (Table 12.45). Original packaging contains syring for inflation of the cuffs, fixator that acts as a bite block at the same time and a tape for fixation.

Table 12-5. Laryngeal tube sizes

Size	Age	Weight	Recommended volume for cuffs (mL)	Colour-code
0	Newborn	< 5 kg	10	Transparent
1	Infant	5–12 kg	20	White
2	Small child	12–25 kg	35	Green
2,5	Bigger child	125–150 cm	45	Orange
3	Adult	< 155 cm	60	Yellow
4	Adult	155–180 cm	80	Red
5	Adult	> 180 cm	90	Purple

Insertion of LT is easy and requires minimal training:
- Both cuffs have to be deflated and tube has to be lubricated with water based lubricant
- Tube is held like a pen at the level of incizor`s mark

Left hand should open patient`s mouth using „thumb and index finger technique" making sure that tongue doesn`t fold back. Tube is inserted in the midline of the mouth, along hard palate and then promoted until it reaches hypopharinx. If one feels resistance while inserting it, one can move if from the midline to the side and try again. When LT is properly positioned, the middle black line on the upper end of the tube should be in level with the upper teeth of the patient. Both cuffs are connected and inflated through a single small lumen line and pilot balloon. Indicated volumes are indicated on the enclosed syringe, the colour on the syringe maches to the colour-coded connector. Thanks to the special construction, proximal cuff is inflated first to stabilize the tube and seal nasopharynx and oropharynx. Distal cuff seals oesophagus.

- After the insertion, ventilation is checked with inspection of chest movements, auscultation and capnograpy. Reduction of tidal volumes and avoiding high ventilation pressures while ventilating in not necessary when using LT.

The supraglottic airway devices (SAD) are easier to insert then tracheal tube and, when compared to a face mask, they are better when it comes to airway management; providing a patent airway, decreasing the risk of aspiration and increasing chances for adequate ventilation.

They disadvantages are possible gastric inflation and aspiration of gastric contents, as well as the need for repositioning the device in order to maintain patent airway.

While inserting SADs, one can cause injuries to oropharingeal, tracheal and esophageal mucosis which can lead to the formation of oedema.

Contraindications for use of SADs are: preserved gag reflex, oesophageal dieseases, intentional or accidental use of caustics, obstruction of the upper airway (foreign body, oedema glottis, epiglotitis, …)

The supraglottic airway devices are to be used when medical personnel is without adequate training and experience when it comes to tracheal intubation. They should also be used when endotracheal intubation is difficult or impossible.

7) Airway management with foreign-body airway obstruction

When patient is not breathing after opening the airway and can not be ventilated with the use of positive pressure, one can assume that there is a foreign-body airway obstruction. Foreign body in the airway can be removed in several ways:

a) **Using fingers –** one hasto be careful, especially when children are involved, not to push foreign body even further and not to make injuries to the mucosa. Fingers can imitate forceps (index finger and middle finger) or hook (bent index finger). If gauze or handkerchief is put over fingers, sponge effect is created.

b) **Turning head to the side –** to allow liquid material to drain from the mouth (be careful when there is a possible cervical spine injury!).

c) **Using Magill forceps –** this forceps can be used for removing solid materials from oral cavity and pharynx and, if wraped with a gauze, for removing liquid materials as well.

d) **With back blows and Heimlich maneuver when patients are conscious, or with chest compressions when they are in cardiac arrest –** when foreign body is too deep down and can not be removed with above mentioned preocedures.

If the patient is conscious, five back blows have to be done as soon as possible. If those back blows fail to relieve the airway obstruction, five abdominal thrusts (Heimlich maneuver) have to be done as follows: rescuer stands behind the victim, puts both arms round the upper part of abdomen, leans victim forward, clenches fist and places it between the umbilicus and the ribcage, grasps clenched fist with the other hand and pulls sharply inwards and upwards. The pressure that is created with this maneuver can remove foreign body like a cork on a champagne bottle.

Heimlich maneuver, however, is not without complications. It can cause pulmonary *aspiration* of *gastric contents*, damage to the abdominal organs (ruptured liver and spleen). This is why it is not performed when patients are unconscious (they don`t have protective mechanisms that stop development of these injuries). Abdominal thrusts should not be performed on pregnant women and obese patients.

If the victim with foreign-body airway obstuction is unconscious, CPR with chest compressions should start immediately. Chest compressions in these situations are not only to promote circulation, they also generate pressure that could remove airway obstruction. Therefore, there is a general rule to quickly check mouth for any foreign body, each time the airway is opened (after thirty chest compressions and before breathing in) and to remove it if it has been partly expelled.

a) **With aspiration –** while resuscitating, oral and nasal cavity and tracheobronchal area have to be cleaned from secretions, sputum, vomitus and foreign materials (eg. false teeth, blood clots, dirt, …). It is an importantandindispensable part of resuscitation and numerous aspirators have been created so far. Some can generate negative pressure up to 300 mmHg. There are:

- devices that are foot and hand operated
- devices that generate vacuum with principles of Venturi while using compressedoxygenfrombottles(their downside is limited consumptionof larger quantitiesof oxygen)
- devices running on batteries (for max. 2 hours) or other sources of electrical energy.

Note that every above mentioned aspirator needs aspiration catheters – they are attached to the suction tube of aspirators and are available in different sizes, in sterile packages. Bottle of water is also needed for aspiration, in order to flush aspiration catheters and the suction tube (eg. sterile saline), anesthetic gel or spray for rubbing on/spraying catheters.

Aspiration of oral cavity is performed through mouth, with gentle movements of aspiration catheters. Nasal cavity should be aspirated as well, because of the joint anatomy, and is done gently, through nostrils with aspiration catheters that have to be pretreated with anesthetic in order to avoid epistaxis.

Aspiration of trachea and bronchi is performed when patients are unconscious and without gag reflexes and can not be performed blindly. That is why laringoscopes are used, to show the entry into trachea. As opposed to when patients are intubated or have tracheal cannula. Aspiration is always done with gentle movements of aspiration catheters, diamether of those should allow breathing, if patients are breathing of their own, and should be small enough to go through ET tube, if patients are intubated.

8) Cricothyrotomy and tracheotomy

Sometimes patency of airway can not be ensured with none of the abave mentioned procedures (eg. difficult face and oral cavity injuries, airway obstruction at the level of trachea). In those cases, invasive procedures must be performed: cricothyrotomy and tracheotomy. Both methods are part of advanced life support, however, they are rarely used in Croatia. This is completelly unjustified, especially when it comes to cricothyrotomy because it is easy to perform, especially when one has a cricothyrotomy set.

Quicktrach is a needle cricothyrotomy set that contains 10 mm syringe attached to a padded neck strap and a flexible connecting tube. This syringe helps to insert cannula into trachea, with cannula being conical due to anatomical reasons. A removable safety stopper provides a barrier that reduces the chances of perforating the rear wall of the trachea, and the conical needle tip provides the smallest necessary stoma.

Cannula is inserted into trachea as follows:

- Metal needle is connected to the syringe
- Skin is punctuated (with specially grinded needle tip that makes prior incision with scalpel unnecessary and reduces the risk of bleeding) in the middle of cricothyroid membrane, with the top of the needle pointing backwards, towards patient`s legs

- While inserting the needle, the clip of the syringe has to be pulled backwards, to create vacuum inside of the syringe
- When the tip of the needle enters trachea, the air fills the syringe and the clip goes backwards. That is how the rescuer knows that the cannula is in right place (in trachea)
- Metal needle has to be kept in place, and plastic cannula has to be pushed forwards, over the needle, until it enters trachea
- After that, metal introducer has to be pulled out and cannula has to be tied around victim`s neck

Size of canula varies, according to the patient`s age (Table 12.6.)

Table 12-6. Sizing of *Quicktrachcannulas*

	Adults	Children	Infants
Cannula no. (G)	13	14	18
Length (mm)	63	49	37

When it comes to *Quicktrach*, one should mention the possibility of performing translaryngeal jet ventilation. The same manufacturer has created *Manujet III*, a gun that enables oxygen jet insuflation and has the option of limiting the pressure manually. The gun uses oxygen from the canister, and is connected with tracheal cannula through pipes with connectors. Pipes have holes that enable oxygen to exit the system. Entire system is intended for prehospital use, when there is complete obstuction of the upper airway. Oxygen jets can oxygenate the patient for 10-15 minutes without ventilating one, thus keeping him alive until patency of airway is ensured in some other way.

Tracheotomy should be done in an operating room, within sterile conditions. Serious complications are associated with performing tracheotomy in prehospital settings. It is therefore rarely justified, especially because if one needs to ensure a patent airway surgically, one can always perform crycothyrotomy, which is a lot easier, less hazardous and with less complcations.

Breathing management

During CPR, the purpose of ventilation is to maintain adequate oxigenation and to remove carbon dioxide. This can be done via:

- Mouth-to-mouth, mouth-to-nose or mouth-to-tracheostomy ventilation
- Bag-mask ventilation (BMV) with air, with or without supplementary oxygen
- Mechanical ventilation using oxygen or oxygen-enriched air.

When breathing directly into a patient, the exhaled air has 16% of oxygen which is enough for a person at rest. However, the rescuer must inhale adequate volume of air, according for the patient`s age and weight. It is believed that 6-7 mL/kg is enough when it comes to tidal volume. It is necessary for rescuers to give each rescue breath over 1s and to avoid rapid and forceful breaths. Latter could generate pressure that is high enough for oesophagus to open and cause gastric distension with all it`s consequences (regurgitation, vomitting, pulmonary aspiration of gastric contents). Moreover, time taken to take two rescue breaths should not exceed 5s in order not to interrupt chest compressions for too long. Respiratory rate should be around 10/min (hyperventilation is harmful because it increases intrathoracic pressure, which decreases venous retourn to the heart and reduces cardiac output!).

There is more than one technique of artificial ventilation with inhaling air into patient`s lungs:

1) **Mouth-to-mouth ventilation**: rescuer kneels beside victim, opens the airway using head tilt and chin lift, pinches the soft part of the nose closed using index finger and a thumb of the hand that is placed on the forehead. Rescuer than takes a normal breath, places lips around victim`s mouth and blows steadily into a mouth while watching for the chest to rise, taking about 1s as in normal breathing. Respiratory rate is 10/min.

2) **Mouth-to-nose ventilation** is more physiological, but at the same time more difficult method of artificial ventilation. Therefore it is performed when one can not open victim`s mouth, can not place lips around victim`s mouth or when there are excessive face injuries. The head has to be tilted, the hand that lifts the chin pushes it cranially at the same time, in order to close mouth. Rescuer takes a normal breath, encircles patient's nose with his lips and inhales adequate tidal volume. Rising of the victim`s chest is a proof of adequate artificial ventilation. Duration of inhalations and respiratory rate are the same as with mouth-to-mouth ventilations.

3) **Mouth-to-mask ventilation**: The pocket resuscitation masks are used widely. They are similar to anaesthetic facemasks and enable mouth-to-mask ventilation. They have a one-way valve, which

directs the patient`s expired air away from the rescuer. Some masks have a connector for the addition of oxygen. When using them, one has to achieve gas-tight seal between mask and patient`s face and maintain a patent airway with head tilted backwards and chin lifted.

4) **Mouth-to-tracheostomy**: skin around stoma should be clean! Rescuer uses one of his hands to close patient`s mouth and nose, places lips around stomae, making sure that the seal is good and blows steadily. The artificial ventilation is succesful if one can see the patient`s chest rising and falling as the air comes out. There is no need to use head tilt and chin lift maneuver.

Ventilation with self-inflating bag (Ambu bag) is an ideal method of artificial ventilation in prehospital settings. Ventilation in those conditions can be controlled (intermitent possitive pressure ventilation with pauses for exhaling, IPPV) or assissted (patient starts to inhale and rescuer deepens that breath, i.e. force-feeds air or oxygen into the lungs in order to inflate them sufficiently). Ambu bag can be attached to facemasks and to other airway adjuncts; LMA, Combitube, ET tube and tracheal cannulas.

There are self-inflating bags of different sizes with different volumes. Depending on the manufacturer, the volume for adults can be 1,1 or 2,2 L, and those for children can have volume of 0,2 to 0,9 L. They have connections for oxygen and additional reservoir for oxygen. They also have unidirectional valve that does not allow rebreathing of patient`s expired air.

Without supplemental oxygen, the self-inflating bag ventilates the patient`s lungs with ambient air (21% oxygen). If oxygen is connected, without reservoar, delivered oxygen concentration is about 30-50%. The delivered oxygen concentration can be increased to about 85% (even to 100%) by using reservoar system that is as big as patient`s tidal volume and with attaching oxygen at flow 10L/min, meaning that the flow equals minute ventilation.

Bag-mask ventilation is performed as follows:

• The facemask of appropriate size is chosen (adult women need numbers 2 or 3, adult men need 4 or 5, children need numbers 0, 1, 2 or 3) and attached to self-inflating bag. The best facemasks are transparent ones because one can timely notice vomit, blood or other secretions.

• Rescuer should stand above patient`s head which should be tilted, with lifted chin, and the mask should adequately seal with the patient`s face. Wider part should cover mouth, and narrower part should cover nose.

• Holding facemask tightly against patient`s head is a virtue and it is clear that ventilation of the patient depends on the adequate seal. Rescuer`s left thumb and index finger should hold the mask at the connection with self-inflating bag, while other fingers are at the mandibular ramus.

• Self-inflating bag should be in rescuers right hand, squeezing the bag ventilates the patient with adequate volume. One breath should not exceed 1s, and respiratory rate should be 10/min. Rising of the victim`s chesti is a secure sign that the ventilation is adequate.

• Moderate gas leakage is acceptable. However, if leakage is excessive and results in inadequate ventilation of the patient`s lungs, mask has to be repositioned, head has to be tilted even more, mandible has to be brought even more forward. One can also use oropharyngeal airway. If that does not help, one may need some halp form the assisstent. That is why two-person technique for bag-mask ventilation is preferable. One person holds the facemask in place using jaw thrust with both hands, and an assistant squeezes the bag. In this way, a better seal can be achieved an the patient`s lungs can be ventilated more effectively and safely.

• When chest compressions have to be done at the same time, compressions and ventilations have to be synchronized: after 30 chest compressions 2 rescue breths into patient`s lungs have to be done. If self-inflating bag is used with ET tube, tracheal cannula, LMA or Combitube, synchronization is not needed.

• If patient is breathing on his own, but his breathing is not adequate, his breaths should be assissted with additional volumes from self-inflating bag, or he should be given additional breaths that are synchronized with his spontaneous ones.

Mechanical ventilation and insuflation of oxygen or oxygen enricher air into patient`s lungs can be done via transport ventilators – those devices are driven by pressure of air in oxygen canister or in the hospital`s central oxygen supply. They are small, light and easy to operate. Ventilation hose has unidirectional valve on it`s end (towards the patient); the valve disables rebreathing (patients inhale the air from the circuit, but exhale into the environment). They can deliver minute volume ranging from 2 to 20L/min, with positive pressure from $\geq$50cm H_2O. Respiratory rate can range from 10 to 35/min, with inhale-exhale ratio (I:E) 1:1,5. Inspired oxygen concentration can vary from 50 to 100%. Patient has to be intubated if portable mechanical ventilation is to be use.

c) Maintaining circulation

While performing CPR, chest compressons generate blood flow to the brain and myocardium and increase the likelihood that defibrillation will be successful (external vs. internal chest compressions; enternal are done when the thorax is closed and internal while thorax is open). Optimal chest compressions compress the heart between spine and sternum („cardiac pump") and make blood go from the heart, lungs and large vessels directly into the aorta. Moreover, blood flow depends on the increased intrathoracic pressure that affects every intrathoracic organ and indirectly ensures blood flow into the aorta. The heart is filled with blood in between compressions, when there is no external pressure. Elasticity of the thorax brings everything back into the original condition and generates negative pressure inside of the thorax, the pressure that sucks the blood back into large vessels and heart („thoracic pump").

Chest compressions should be done as follows:

- The patient should be undressed (it is not a must) in order to accurately determine site of compressions – centre of the victim`s chest
- Rescuer should place the heel of one hand on the lower half of the sternum, with one heel of the hand on top of the first hand and with fingers interlocked. It is important to ensure that the pressure is not applied over the victim`s ribs, to minimise the possibility fractures.
- Rescuer should be positioned vertically above the victim`s chest, with elbows extended, and should press down on the sternum at least 5cm.
- After each compression, one should release all the pressure on the chest without loosing contact between the hands and the sternum. It is really important that compressions and releases take equal amounts of time and that compressions are repeated at a rate of at least 100/min (but not exceeding 120/min).

The blod flow will be efficient if chest compressions are done in a way that maintans 50%:50% compression-decompression ratio during one cycle (compressions create „cardiac pump" that ejects blood from the heart and releases create „thoracic pump" that sucks blood into the heart). Although only compressions were recently in the spotlight, today we are well aware that without adequate releases the heart can not be filled up and subsequently cardiac output can not be maintained.

There is an advanced device that doubles the blood flow during CPR by increasing negative intrathoracic pressure. The device is called ResQPOD and it acts as a generator of negative pressure that prevents unnecessarily entrance of air. In that way, while the release phase is on, negative pressure doubles and blood flow back to the heartdoubles as well. Improved venous return results in increased cardiac output during the subsequent compression phase of CPR, providing greater blood flow to the brain. ResQPOD increases the opportunity for survival and normal neurological outcome. It is easy to use – it has a patient port that allows fast and easy connection to an endotracheal tube or other airway adjunct, resuscitation technique with ResQPOD is the same as without one.

Another device that works at the same way is manual active compression decompression (ACD) pump. It has a double-grip handle that attaches to patient's chest with a suction cup. The suction cup allows the expansion of the chest during decompression phase to a greater extent than is normal reducing pressure inside the chest. By reducing intrathoracic pressure during the decompression phase, more blood is drawn back to the heart, and this greater volume of blood can be pumped to the body on the next compression.

It is designed with a metronome and force gauge to aid in chest compressions. The timing mechanism helps responders maintain the correct compression rate while the force gauge helps assist in achieving the correct compression depth.

Cardiopulmonary resuscitation **ALWAYS** begins with chest compressions that are followed with rescue breaths (CAB sequence). One should always keep in mind following rules:

- After 30 chest compressions, 2 rescue breaths follow, no matter how many rescuers are involved in CPR.
- If tracheal tube or SAD has been inserted, chest compressions and rescue breaths don`t need to be synchronized in 30:2 ratio. One should deliver continuous chest compressions at a rate of 100/min, uninterrupted during ventilation.
- If there are two rescuers and they are experienced enough to exchange roles without interrupting compressions, they should do it every 2 minutes (5 cycles of CPR). If they don`t, decrease in compression quality is expected due to rescuer fatigue.
- One should check patient only it the victim starts to wake up, move, open eyes and breath normally.

Chest-compressions only CPR may be as effective as combined ventilation and compression in the first 4 - 5 minutes after non-asphyxial arrest. If that is the case, chest compressions should be performed at a rate of 100-120/min. This technique, however, is not as effective as conventional CPR for cardiac arrests of non-cardiac origin in adults and children.

d) Defibrillation and other electrical therapies

Electrical therapy that is applied during CPR consists of following elements:

1) Defibrillation

2) Synchronised cardioversion

3) Noninvasive, transcutaneous pacing

Defibrillation requires the delivery of sufficient electrical energy to a critical mass of myocardium. It can be done directly when the thorax is open („internal defibrillation") or, most often, indirectly („external defibrillation") across the closed chest.

Optimal defibrillation technique aims to deliver current across the fibrillating myocardium in order to abolish the waveforms of VF or pulseless VT and enable restoration of spontaneous synchronized electrical activity in the form of an organized rhythm.

The current, if strong enough, causes depolarization of myocardium (more than 75%) and enables sinus node to regains coordinated electrical activity. The sinus node (or any other intrinsic pacemaker) is likely to regain control over the heart is in direct relation with duration of VF. Each minute of delay before defibrillation reduces the probability of survival to discharge by 7-10%!

Electrical current that is needed for defibrillation is generated by defibrillators – devices that consist of:

- Capacitor that stores a large amount of energy in the form of electrical charge, then releases it over a short period of time
- Two electrodes - When the paddles (or pads) are applied to the patient's chest and a circuit is completed. Electrons stored on the capacitor are able to pass through the patient and go back to the capacitor. Thus, current flows, stored electrical energy is released (i.e. the capacitor is discharged).
- Defibrillators nowdays often have the option of ECG monitoring.

According to the types of waveform that create, there are two kinds of defibrillators:

1) *Monophasic defibrillators* deliver one direction of current flow. The effectiveness of this type of electric shock depending on transthoracic impendance, the body's resistance to current flow, that varies considerably with body mass, but is approximately 70-80 Ω in adults. Hence in order to have successful defibrillation one has to use higher energies. Higher energies can cause myocardial injuries if impendance is lower than expected. On the other hand, when thoracic impendance is high (obese patients, patients with hairy chest), high energies are insufficient for successful defibrillation. For that reason monophasic defibrillators are no longer manufactured.

2) *Biphasic defibrillators* deliver current that flows in a positive direction for a specified duration before reversing and flowing in a negative direction for the remaining time of the electrical discharge. These defibrillators compensate for the wide variations in transthoracic impedance by electronically adjusting the waveform magnitude and duration to ensure optimal current delivery to the myocardium, irrespective of the patient`s size. This is really important because thoracic impendance is the third factor contributing to the successful defibrillation (the first one is the time from the beginning of the VF until the shock and the second one is electrode placement).

Biphasic waveforms are more effective at terminating ventricular arrhythmias at lower energy levels, they have greater first shock efficiacy than monophasic waveforms and have greater first shock efficiacy for long duration VF/VT. Lower energies for defibrillation cause minimum myocardial damage. That is why there are less post-shock arrhythmias when biphasic defibrillators are used.

According to the way they operate, defibrillators can be :

1) *Manual defibrillators* can be classical or computerized. Rescuers need to analyze rhythm on their own when classical manual defibrillators are used. However, computerized defibrillators analyze rhythm on their own and alert that the defibrillation is needed. Rescuer is to adjust the energy of electrical shock, to charge and to deliver shock while using paddle or self-adhesive electrodes. They are obviously not so easy to use and one has to be well acquaintedwith the device in order to use it in a correct and safe way. Their advantages are their numerous possibilities - synchronized cardioversion, external pacing, noninvasive blood pressure measurement, pulse oxymetry, capnography and etc.

2) *Automated external defibrillators* are sophisticated devices that have automated rhythm analysis, they are charged on their own, somethimes even deliver shock on their own. Hence the rescuer only needs to tape self-adhesive electrodes and turn the device on. These devices use voice and visual prompts to guide rescuers to safely attempt defibrillation and are especially useful for lay rescuers.

Automated external defibrillators are reliable computerized devices that enable lay rescuers and health professionals to attempt safe defibrillation in cardiac arrest victims many minutes before professional help arrives. Therefore, they should be available throughout all hospitals, at general practitioners` and dentists consulting rooms, in outpatient medical facilities and public areas of mass gathering. They are able to analyse several features of ECG, including frequency and amplitude, and are extremely accurate in rhythm analysis. They recognise shockable rhytms and use visual and vocal prompts to emphasize when shock is to be delivered (semi-automated AED) or they deliver it on their own (automated AED), in a safely manner (they alert rescuers to stay clear prior to shock).

Automated external defibrillators deliver efficient, biphasic electroshocks. They are relatively cheap devices that are easy to maintain and to use with minimal previous training. Their main advantage is the ability to deliver early defibrillation (within 5 min. of collapse) and the fact that they can be used by trained lay responders.

Although there are different AED manufacturers, they are all used in the same sequence:

1) Switch on AED

2) Attach the electrode pads on the victim`s bare chest. Electrodes can be placed anterolaterally (right electrode is placed to the right of the sternum, below the clavicle and left is placed in the left mid-axillary line, approximately level of V6 ECG electrode) or anteroposteriorly (one electrode is anteriorly, over left precordium and the other posteriorly to the heart, just inferior to the left scapula). However, conventional antero-apical position is believed to be better because it records II lead and is less prone to errors while rhythm is interpretated.

3) Sometimes button ANALYZE is to be pressed in order to analyze rhythm. However, in most cases it is done automatically as soon as electrodes are attached. Ensure that nobody is touching the victim while AED is analyzing the rhythm.

4) If a shock is indicated, some AEDs will start to charge on their own and with some rescuers need to press CHARGE button.

5) Rescuer that handles with AED should make sure that nobody is touching the victim. The AED will use visual and vocal prompts to ensure safe defibrillation.

6) After AED has been charged, the device will alert that shock is to be delivered. Automated devices deliver the shock on their own, while semi-automated prompt the rescuer to press the SHOCK button.

7) Rescuers need to immediately restart CPR and keep doing so for the next 2 minutes. Device will start to analyze rhythm after 2 minutes have elapsed. The AED will also monitor victim`s rhythm during postarrest period which is often complicated with cardiac arrhythmias ane rearrests. That is why electrodes must stay on the patient`s chest and AED must not be turned off even after the retourn of spontaneous circulation.

Recommended initial energy level for the first shock using a monophasic defibrillator is 360J and the initial biphasic shock should be between 120 or 150 and 200J (the shock energy for a particular defibrillator should be basedon the manufacturer's guidance). If VF/pVT still continues, energy level for the second and each subsequent shock should be betwen 150 and 360 J for biphasic shock and 360 J for monophasic shock.

Energy levels for children follow this simple formula: 4J/kg, for both monophasic and biphasic defibrillators.

In an oxygen-enriched atmosphere, sparkling from poorly applied defibrillator paddles or pads can cause a fire. The risk od fire during attempted defibrillation can be minimised by taking off any oxygen mask or nasal cannulae and placing them at least at 1m away from the patient`s chest. Ventilation bag and ventilator tubing should stay connected to the tracheal tube or SAD. Alternatively, they can be disconnected and removed at least 1m away.

Cardioversion is an electrical therapy used to treat atrial ot ventricular tachyarrhythmias, neither VF nor pulseless VT. The shock delivered must be synchronized to occur with the R wave of the electrocardiogram rather than with the T wave. That is why defibrillator has to operate in SYNC mode.

Conscious patients must be anaesthetised or sedated before attempting synchronized cardioversion. However, one must always pay attention to airway management and breathing. The drug of first choice for sedation is midazolam (Dormicum, amp ā 15 mg/3ml), a benzodiazepine that works on the central nervous system and causes, among other things, amnesia. It`s effect can be reversed with flumazenil (Anexate amp. ā 5 mL/0,5 mg).

When it comes to anaesthetics, one can use:
- propofol (Diprivan, amp ā 20 mL/200mg) – it is a relatively new drug with rapid oneset of action and short duration, if not given too quickly patient can continue to breathe spontaneously. However, it decreases arterial blood pressure and is not suitable for hypotensive patients.
- etomidate (Hypnomidate, amp ā 10 mL/20mg) - is ultrashort acting nonbarbiturate hypnotic that has minimal effects on haemodynamics. That is why it is a drug of first choice for hypotensive patients. If administered slowly, a patient can continue to breathe spontaneously.

Energies used for cardioversion are lower than those used for defibrillation and depend on arrhythmias treated. Some arrhythmias, stable VT or atrial flutter, can be converted to synus rhythm with 50J, and others (i.e. atrial fibrillation) usually need 100J or more.

Complications that are associated with cardioversion:
1) Arrhythmias: VF, VT, bradycardia, asystole
2) Hypotension: most often it is a result of deterioration of arrhythmia, rarely it is a side-effect of sedation
3) Respiratory depression: most often it is a side-effect of sedation used prior to cardioversion.
4) Emboly: it is a side-effect of cardioversion of permanent atrial fibrillation, it can be prevented if anticoagulant therapy has been started few weeks prior to cardioversion.

Table 12-7. Drugs used for cardioversion

Drug	Dosage	Oneset of action	Duration
A. Sedatives (benzodiazepines)			
Midazolam	0,025–0,1 mg/kg, iv.	2 min.	30–60 min
B. Anaesthetics			
Propofol	1,5–2 ,5 mg /kg, slowly iv.	< 1 min.	10 min.
Etomidat	0,1–0,4 mg/kg, slowly iv.	< 1 min.	10 min.
C. Antidote to benzodiazepines			
Anexate	2 mL (0,2 mg) iv, ® administer 1 mL increments iv. until the effect is achieved Max. Dose is 1 mg (2 amp)!	approximately 60 sec.	45 min. Sometimes it is neccessary to repeat dose to maintain the effect!

Cardioversion is the most common elective intervention, and when patients with arrythmias present with stenocardia, hypotension, dyspnea and are unconscious as well, it is considered to be an urgent procedure.

Pacing is normally used for patients with symptomatic bradycardia refractory to anticholinergic drugs or other second line therapy. Moreover, whenever a diagnosis of asystole is made, check ECG carefully for the presence of P waves because this will likely respond to cardiac pacing. Do not attempt pacing for asystole unless P waves are present! The pacemaker sends electrical impulses to pace the heart via the pacing lead, self-adhesive electrodes are taped to the patient`s chest, myocardium is depolarized and subsequently contracted.

Noninvasive (transthoracic) pacemakers operate in two modes:
- Demand mode – pacemaker generates and deliveres impulses only when they are needed. These pacemakers demand intrinsic cardiac activity and if they find it, they adjust delivery of impulses. If they don`t find intrinsic activity, they take over as heart`s pacemaker.
- Non-demand mode (asynchronized mode, modus of fixated frequency) – pacemaker delivers impulses according to the previously adjusted frequency, it ignores intrinsic cardiac activity. Sometimes pacemaker`s impuls can occur with T wave of the electrocardiogram, but the risk of inducing VT or VF is only theoretical.

Transthoracic pacing is to be used as follows:
1) ECG monitoring has to be attached to the patients chest (3 electrodes); it is important to ensure the best signal, gel or shaving the chest are optional .

2) Electrodes for pacing are self-adhesive (2 adult electrodes with surface of 150cm^2 and those for children <10kg with surface of 45cm^2), they are taped to clean, dry skin. Both anteroposterior and anterolateral position for placing electrodes are equaly effective.

3) Electodes have to be connected to the device.

4) Pacemaker`s mode is chosen (demand mode enables that the intrinsic signal takes over as heart`s pacemaker as soon as frequency of SA node gets higher than of pacemaker)

5) Frequency of pacing is chosen, it usually is between 60 and 90/min.

6) The strength of impulses are adjusted. Usually the effect is visible when the current is between 50 and 90mA, but individual differences are possible. There is a difference between electrical effect (QRS complexes with tall, wide T waves) and mechanical effect (palpable puls, visible signs of improvement of cardiac output).

Current is increased slowly if patients are conscious and quickly if patients are in cardiac arrest.

Transthoracic pacing is a temporary method, a bridge to definitive solution of a problem. It is easy to use and requires minimal training. It can be applied quickly and the application is without complications that are often associated with invasive techniques. The main problem is that it may be uncomfortable for the patient. Discomfort is because of the electrical stimulation of skin, nerves and muscles. Sedation should therefore be considered. Prolonged transcutaneous pacing may, however, cause burns on the skin. That is why periodic inspection of the underlying skin is strongly advised, if it is necessary to pace for more than 30 minutes.

12.4. Adult basic life support

At the general practicioner`s office ALS procedures should be performed. However, if a physician is on the street, without any equipment, and witnesses a cardiac arrest, he is expected to perform basic life support (BLS). Everything he needs to know and do in an out-of-hospital setting, without any equipment other than protective devices and AED, is summoned up in Fig 12.1.

12.5. Adult advanced life support

12.5.1. The importance of cardiac monitoring

Many of AEDs that are used nowdays have inbuildt single-lead ECG monitors and the ability to recognize shockable rhytms, a huge advantage in comparison with old manual defibrillators. That is why laymen are competent enough to resuscitate patients in cardiac arrest, in a correct and safe manner.

Situation is complicated when patients are in a risk of developing cardiac arrest, especially those with chest pain or periarrest arrhythmias that can evolve into cardiac arrest. In those situations single-lead monitors are not enough because they can not be used to diagnose ishemic cardiac disease (series of 12-lead ECGs are needed to diagnose acute coronary syndrome). However, they provide enough information for recognising rhythm disorders. Obviously, certain amount of knowledge is essential for making a diagnosis, but one does not need to be an expert for ECG. It is important to recognise if the disorder is a bradycardia or tachycardia and to what extent it effects the patient. Here are two examples:

- A patient is bradycardic (has around 40 heartbeats per minute) and we are not sure which bradycardia that is. However, we do know thah the patient is unstable, he is hypotensive, his systolic blood pressure is <90mmHg. HIs heart`s frequency is too slow to maintain appropriate minute volume
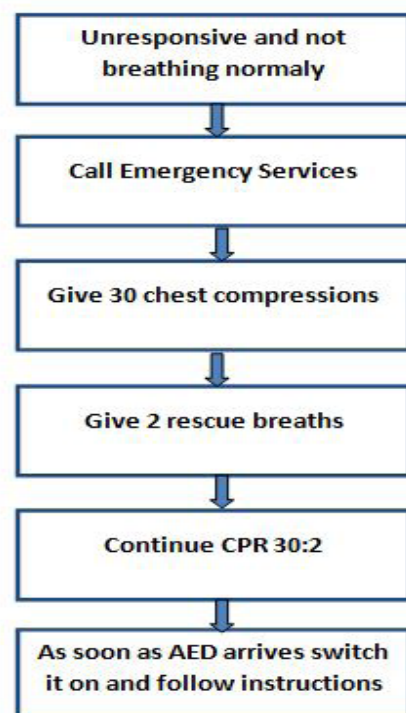
Fig. 12.1. Adult Basikc Life Support algorithm

and is enough for us to start treating him with atropine and/or transcutaneous pacing in order to prevent cardiac arrest.

- The same situation is when a patient is tachycardic. The most important thing is to recognize if the patient is stable or not. If the patient is unstable (with loss of consciousness, hypotension, chest pain and signs of his heart failing), synchronised cardioversion is attempted immediately and, if that does not restore sinus rhythm and the patient remains unstable, amiodarone is given over 10-20 minutes. If the patient is stable, has no adverse signs or symptoms and is not deteriorating, drug treatment is likely to be appropriate. There is time to evaluate rhythm using 12-lead ECG and assess the QRS duration. If the duration is greater than 0.12s it is classified as a broad complex tachycardia. If the QRS duration is less than 0.12s it is a narrow complex tachycardia. Obviously there is still time to seek expert`s help and organize transport to hospital.

12.5.2. Arrhythmias in critically ill patient

Arrhythmias in critically ill patient can be:
- Arrest arrhytmias – seen on the monitor of the defibrillator while the patient is in cardiac arrest
- Peri-arrest arrhythmias – can develop into cardiac arrest if not identified and treated in a timely manner.

12.5.2.1. Arrest arrhythmias

Arrest arrhythmias can be:
- Shockable rhythms that are treated wit defibrillation: VF and Pulseless VT
- Non-shockable rhythms that are not treated with defibrillation: asystole and pulseless electrical activity (PEA).

Treatment od patients with these arrythmias is described in an adult ALS algorithm.

a) Ventricular fibrillation/ Pulseless ventricular tachycardia

It is considered that initial rhythm is VF/ pulseless VT in approximately 80% patients with cardiac arrest. However, often by the time the first ECG is recorded, the rhythm has deteriorated to asystole. Survival rates after cardiac arrest depend on the time of defibrillation. If shock is delivered in the first minute after VF, probability of survival to discharge is more than 90%. Each minute of delay before defibrillation reduces the probability of survival to discharge by 7-10%.

Ventricular fibrillation/ pulseless ventricular tachycardia should be treated as follows:
- When there is VF/ pulseless VT confirmed on the monitor of defibrillator, the defibrillator is charged while another rescuer continues chest compressions and the first shock is delivered (120-or 150 - 200J if biphasic defibrillator is used or 360J monophasic).
- Cardiopulmonary reanimation is resumed immediately after the shock, starting with compressions. Even if the defibrillation attempt is successful in restoring a perfusing rhythm, it takes time until the post-shock circulation is established and is very rare for a pulse to be palpable immediately after defibrillation. What is more, the delay in chest compressions will further compromise the myocardium if a perfusing rhythm has not been restored.
- After 2 minutes, pause briefliy to assess the rhythm; if still VF/ pulseless VT, give a second shock (120 or150 - 360J biphasic and 360J monophasic). Without reassessing the rhythm or feeling for a pulse, resume CPR, starting with chest compressions.
- After 2 minutes, pause briefly to assess the rhythm; if still VF/ pulseless VT, give a third shock (120 or150 - 360J biphasic and 360J monophasic). Without assessing the rhythm or feeling the pulse, resume CPR. Give adrenaline 1mg and amiodarone 300mg once chest compressions have resumed, they will have their effect only if circulation is ensured.
- While VF/ pulseless VT is present, resuscitation continues with adrenaline given every 3-5 minutes until return of spontaneous circulation (ROSC) is achieved (once every two cycles) → electrical shock → CPR for 2 minutes → pause to assess the rhythm.

After 2 minutes of CPR or before delivering the shock, monitor must be checked to assess the rhythm. If there is an organised rhythm that is associated with spontaneous circulation (narrow or regular QRS complexes), pulse must be felt and patient must be checked:
- If there is a pulse, post-resuscitation care follows
- If there is no pulse, CPR continues with sequence for non-shockable rhythms.

If an organized rhythm is noticed during CPR, chest compressions are not interrupted unless the patient has signs of life return (purposeful movement, normal breathing or coughing). If there are any doubt with feeling the pulse in the presence of an organized rhythm, CPR should be continued.
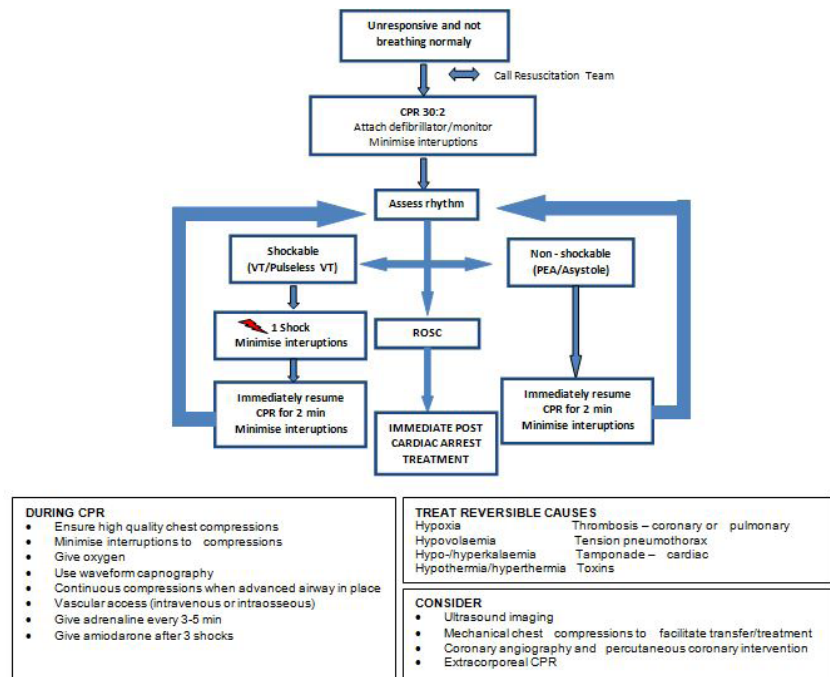
Fig. 12.2. Adult Advanced Life Support algorithm.

b) Non-shockable rhythms

Asystole and pulseless electrical activity (PEA) are arrest arrhythmias that don`t need to be defibrillated.

Pulseless electrical activity is defined as a cardiac arrest in the presence of electrical activity what would normally be associated with a palpable pulse. These patients often have some mechanical myocardial contractions but these are too weak to produce a detectable pulse or blood pressure. ECG is usually normal. Hence, ECG monitoring is not essential for treating a patient, monitoring of patient`s vital signs is.

Asystole is defined as an absence of electrical and mechanical cardiac activity, hence no contractions of the myocardium and no cardiac output or blood flow can be noticed. That is why flatline is seen on ECG. One should check if electrodes or leads are attached correctly and also for the presence of P waves without QRS complexes to follow („P wave asystole"), because this may respond to cardiac pacing.

Note: Sometimes asystole and fine VF can be difficult to distinguish. There are several reasons: if an ECG is not tuned properly (normally 1mV equals to the 1cm deviation from the baseline), electrical interference, respirational movements, resuscitation maneuvers). That is why one should always check minimum two ECG leads and increase the amplitude in order to confirm asystole.

Treatment of asystole and PEA is as follows:
- Comence with chest compressions and ventilations 30:2.
- Give adrenalin 1mg as soon as venous access is achieved.
- Once an advanced airway has been sited, continue chest compressions without pausing during ventilations.
- After 2 minutes of CPR, check the rhythm; if asystole is present, continue with CPR and give adrenaline 1mg iv. every 3-5 minutes (i.e. every alternate cycle).
- If there is an organized rhythm on the monitor, attempt to palpate a pulse. If there is a palpable pulse, begin with post-resuscitation care. If no pulse is palpable (or if any doubt about the presence of a pulse), continue CPR.
- If signs of life return during CPR, check the rhythm and attempt to palpate a pulse.
- If VF is identified on the monitor midway through 2 min cycle of CPR, complete the cycle of CPR before formal rhythm and shock is appropriate.

Note: One should have in mind that non-shockable rhythms, especially PEA, are often caused by one of reversible causes (4H and 4T). Survival following cardiac arrest with asystole or PEA is unlikely unless a reversible cause can be found and treated effectively.

12.5.2.2 Peri-arrest arrhythmias

Peri-arrest arrhythmias usually are a sign that a patient`s contition is deteriorating and can precede a cardiac arrest. It is all about „better safe than sorry" when it comes to peri-arrest arrhythmias. The correct

and timely identification and treatment of arrhythmias in critically ill patient may prevent cardiac arrest from occuring or from reoccuring after succesful initial resusciatation.

The treatment algorithms have been designed to enable ALS providers to treat the patient effectively and safely in an emergency. The initial assessment and treatment of a patient with an arrhythmia should follow ABCDE approach and include:

- Administration of high flow oxygen
- Obtaining intravenous access
- Establishinig monitoring (12-lead ECG, blood pressure, SpO_2)
- Findings of electrolytes in the blood (K^+, Mg^{2+}; Ca^{2+})

Only after above mentioned things are taken care for, we can say whether a patient is stable or unstable and we tray to address the nature of arrhythmia. The presence or absence of adverse signs or symptoms dictates the appropriate treatment. The following adverse factors indicate a patient who is unstable:

- Clinical signs of low cardiac output – pallor, sweating, cold and clammy extremities (increased sympathetic activity), impaired consciousness (reduced cerebral blood flow) and hypotension (systolic blood pressure <90mmHg)
- Deviation from the normal heart rate – tachycardia >150 beats per minute (broad QRS compex tachycardia is more difficult to endure than narrow complex tachycardia), bradycardia <40 beats/ min (patients with impaired cardiac function may be symptomatic and unstable at heart rates <60 beats per minute).
- Signs of failing heart – failure of the left ventricle is manifested by pulmonary oedema and failure of the right ventricle is manifested by raised jugular venous pressure and hepatic engorgement.
- Chest pain – arrhythmias, especially tachycardias, reduce coronary artery blood flow and cause myocardial ischaemia (myocardial oxygen consumption exceeds delivery).

Having determined the presence or absence of adverse signs and the rhythm, there are three options for treatment: anti-arrhytmic drugs, cardioversion or pacing. Tachycardias of unstable patients usually require cardioversion because the anti-arrythmic drugs have slower onset of action. This is why they are used when patients are stable.

Bradycardia

A bradycardia is usually defined as a heart rate of <60 beats/ min. However, it is better to distinguish absolute (heart rate <40/min) and relative bradycardia (heart rate is too slow in regards to the hemodynamic condition of the patient). In that way the definition better suits patients and their conditions.

Bradycardia in adults is treated according to the algorithm (Fig. 12.3.).

Tachycardias

If the patient is unstable and deteriorating, with any of the adverse signs and simproms, attempt synchronized cardioversion immediately. If cardioversion fails to restore synus rhythm and the patient remains unstable, give amiodaron 300mg iv., over 10 – 20 min, and reattempt electrical cardioversion. The loading dose of amiodarone can be followed by an infusion of 900mg over 24h, in order to prevent new episode of tachycardia or to restore sinus rhythm.

If electrical cardioversion is used to convert tachyarrhythmias, the shock must be synchronised with the R wave of the ECG rather than with the t wave. For a broad-complex tachycardia and atrial fibrillation (FA) start with 150-200J biphasic or 200H monophasic and increase in increments if this fails. Atrial flutter and paroxysmal supraventricular tachycardia (SVT) often convert with lower energies: start with 70-120J biphasic or 100J monophasic.

If the patient is stable, there is a plenty of time to evaluate the rhythm using a 12-lead ECG and assess QRS duration and decide on the appropriate pharmacological treatment or even consult a cardiologist. However, if the patient becomes unstable at any point, synchronized cardioversion is immediately attempted.

12.6. Drugs used in cardiac arrest

12.6.1. Routes for drug delivery

During resuscitation route of administration of drugs may be :

1) Intravenous (iv.) – the best and relatively easy to use technique of administration drugs during cardiac arrest. There are periferal and central venous routes.
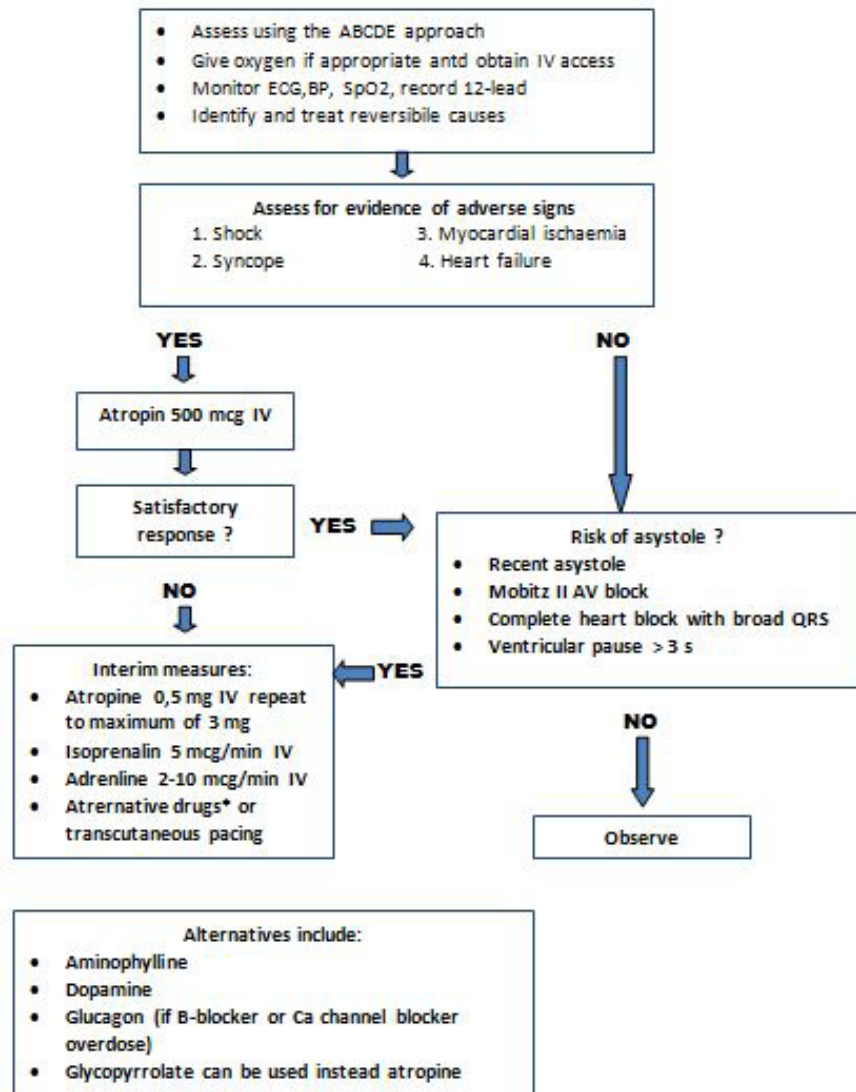
Fig. 12.3. Bradycardia Algorithm

Periferal venous cannulation – a periferal vein is used to administer drugs. The advantages of this route are: it is quicker, easier to perform and safe. The main disadvantage is long circulation time. This is why when drugs are injected peripherally, they must be followed by a flush of at least 20mL of fluid and elevation of the extremity for 10-20s to facilitate drug delivery to the central circulation.

Central venous route – peak drug concentrations are higher and circulation times are shorter (s30s) when drugs are injected into a central venous catheter compared with a peripheral cannula. However, insertion of a central venous catheter requires interruption of CPR and is associated with several complications (unwanted rupture of an artery, haemathoma, haematothorax, pneumothorax, hemopericardium, arrhythmias). Usually v. jugularis interna or v. subclavia, rarely v. femoralis, are used for insertion of a central catheter.

2) Intraosseous – Thanks to the new technical solutions, intraosseous delivery has become fast, safe and easy to use technique for administration of drugs and fluids during resuscitation of both, adults and children.

If intravenous access can not be established within the first 2 minutes of resuscitation, consider gaining intraosseous (io.) access !

12.6.2. The most important drugs used for the management of cardiac arrest

One should have in mind that there are drugs used during the management od cardiac arrest and anti-arrhytmics and a lot more drugs used in the peri-arrest period. All those drugs can be divided into several groups:

1) Inotropic agents/ vasopressors: adrenaline, vasopressin, dopamine, dobutamine, norepinephrine, isoproterenol
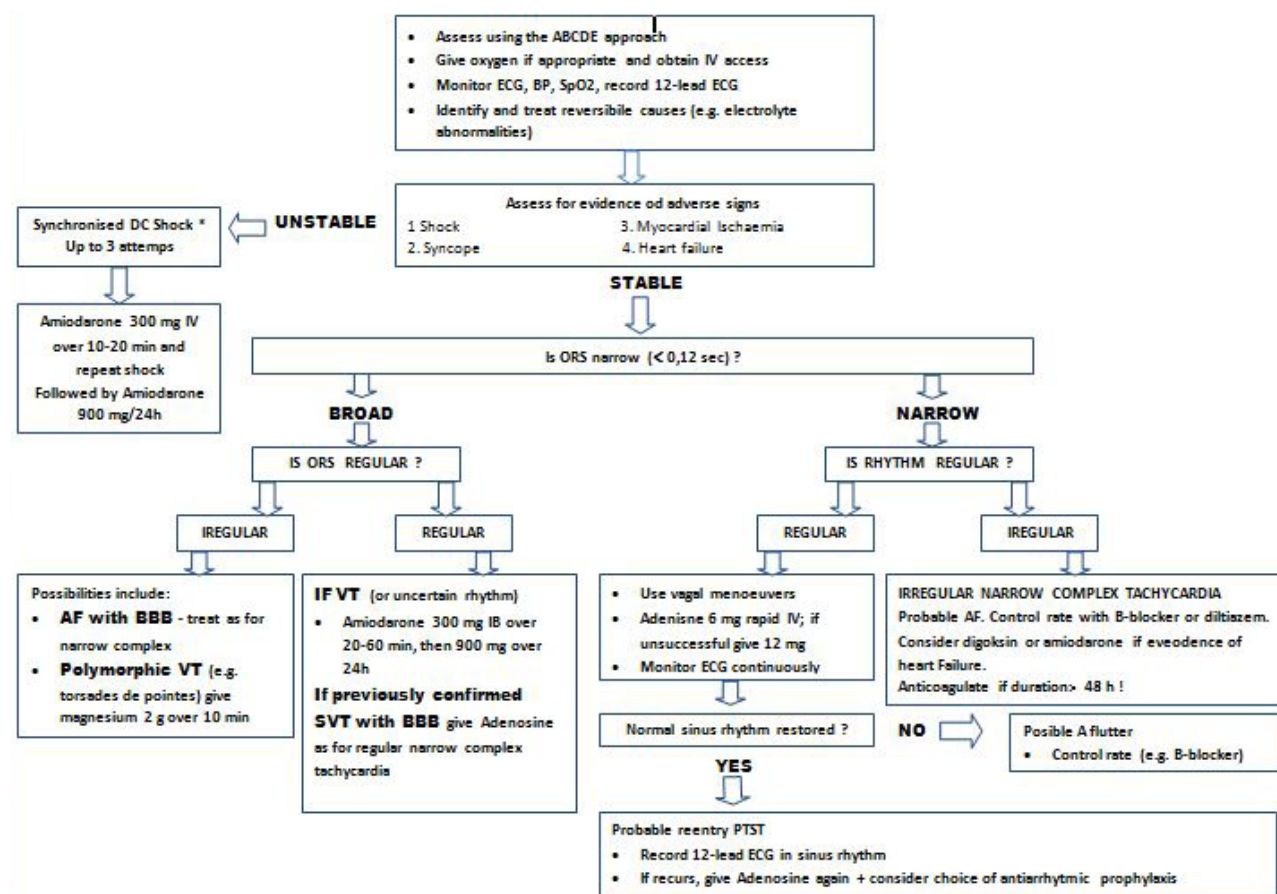
Fig. 12.4. Tachycardia algorithm.

2) Parasympathetic drugs: atropine
3) Anti-arrhythmics: amiodarone, lidocaine, β adrenergic blockers, calcium channel blockers, magnesium, adenosine
4) Others: calcium, sodium bicarbonate, crystalloides, glucose solution

Some of the above mentioned will be discussed further (they are listed in alphabetical order).

1. Adenosine (not registered in Croatia)

Adenosine is a naturally occuring purine nucleotide. It is a product of degradation of ATP or 5-adenosylhomocysteine. It dilates coronary arteries and slows the heart and therefore balances delivery and consumption of oxygen. It`s effect is a result of binding to adenosine receptors A_1 that are located in SA node, AV node, atrial myocardial cells and coronary vessels.

Mechanism of action:

Adenosine binds to it`s receptors in the heart and directly causes hyperpolarisation of atrial myocardial cells. It shortens the duration of action potential and disturbs conduction of impulses in atrial myocardium. At the same time adenosine antagonizes β-adreniergic system and slows down pacemaker within SA node.

Adenosine temporarily slows down conduction through AV node. Hence in can stop reentry mechanism and restore sinus rhythm in patients with paroxismal supravenous tachycardias (PSVT), as well as in patients with Wolf-Parkinson-White (WPW) syndrom.

Hemodynamic effect:

Rapid bolus of 6mg of adenosine is likely to be effective and usually has no hemodynamic effect. Higher doses can cause fall of peripheral resistance.

Indications:

• treatment of PSVT with reentry mechanism at the AV node
• differentiation of narrow-complex and broad-complex tachycardias: adenosine is not effective when it comes to conversion of atrial flutter, FA or ventricular tachycardias into synus rhythm. However, patients with those arrhythmias won`t suffer side effects if given adenosine.

Dosage:

Adults: rapid bolus of 6mg iv. followed with a flush of saline. If unsuccessful this can be followed with up to two doses of 12mg every 1-2 min.

Children: 0,1 mg/kg iv. If there is no response, subsequent doses may be increased to 0,2 mg/kg iv., with maximum single dose of 12mg.

Side effects:

- Cardiovascular – facial flushing, headache, sweating, palpitations, chest pain, seldom hypotension.
- Respiratory – dispnea, chest tightness, hyperventilation.
- Regardind central nervous system (CNS) – dizziness, blurred vision
- Gastrointestinal – nausea, metallic taste in the mouth

Contraindications:

- AV block 2nd or 3rd degree *
- SA node dysfunction – sick sinus sy. or symptomatic bradycardia
- Hypersensitivity to adenosine

*unless patients have a functional artificial pacemaker!

2. Adrenaline (Suprarenin, amp. ã 1 mL / 1 mg)

Adrenaline is a sympathomimetic agent with α and β effects on adrenergic receptors.

Mechanism of action:

- Higher doses used during cardiac arrest act on α receptors and cause vasoconstriction. That increases systemic vascular resistance and arterial blood pressure, and therefore increases cerebral and coronary perfusion.
- When used in lower doses (do 0,03 mcg/kg/min), adrenaline has strong inotropic effect via β1 receptors, it increases myocardial contractility and heart rate and as a result cardiac output. However, after return of spontaneus circulation, it can cause tachycardia, deteriorate myocardial ischaemia because of the increased oxygen consumption in myocardium and causes VF and VT.
- Adrenaline has a strong effect via β2 receptors and causes bronchodilatation.

Indications:

1) VF and pulseless VT that remain after defibrillation
2) PEA
3) Asystole
4) Difficult hypotension with bradycardia
5) Anaphylactic shock

Dosage:

Resuscitation

Adults - 1mg every 3-5 minutes, iv. or io. (tracheal route is recommended only if other routes can not be established, the equipotent dose given via trachea is 3 times higher than the intravenous dose)

Children - 10mcg/kg (0,1 mL/kg of 1:10 000 solution), iv. or io., if tracheal route is needed, the dose is 10 times higher (100 mcg/kg ili 1 mL/ kg of 1: 10 000 solution).

Bradycardia with difficult hypotension

Adults – start with 0,025 – 0,3mg/kg/min (continuous infusion) and increase the dose until effect is achieved (usually between 2 and 10mg(min for adults).

Side effects:

Deterioration of myocardial ischaemia (increased myocardial oxygen consumption), sentricular and supraventricular arrhythmias (accelerated conductivity)

3. Amiodarone (Cordarone, amp 3 mL/ 150 mg)

Amiodarone is a class III anti-arrhythmic agent that elongates effective refractory period and increases duration of action potential in atrial and ventricular myocardium.

Mechanism of action:

- Anti-arrhythmic action as a result of blocking potassium channels, and partially blocking sodium and calcium channels in the membrane of myocardial cells
- As well as α- and β-adrenergic blocking properties amiodarone moderately decreases peripheral resistence, it has mild inotropic and chronotropic effects. The netto effect is a slight decrease of arterial blood pressure and oxygen consumption in myocardium.

Indications:

1) Refractory VF/ pulseless VT
2) Venticular, atrial and nodal arrhythmias
3) Tachycardias in patients with WPW sy.
4) Wide-complex tachycardias

Note: method of choice for treatment of VF is defibrillation!

Dosage in VF/ pulseless VT:

Adults: give 3–5 mg/kg (or 300 mg) amiodarone as iv. bolus or as an infusion diluted in 5% glucose solution to a volume of 20 or 100 mL over 3 min. Additional infusion of 150 mg can be repeated as necessary for recurrent or resistant arrhythmias. This is followed by an infusion of 900 mg over 24 h.

Side effects:

• Deterioration of cardiac decompensation
• Bradycardia (heart rate < 55/min) – stop with administration of amiodarone as soon as possible
• Hypotension
• Neurological problems: paresthesia, tremor, ataxia, headache, fatigue
• Thrombophlebitis when infused into a pheripheral vein, especially in children (veins of smaller diameter!)

Caution: amiodarone is incompatibile with saline and should be used only with 5% glucose solution!

4. Atropine (Atropini sulfas, amp ã 1 mL/0,5 mg i ã 1 mL/1,0 mg)

Atropine is an alcaloide isolated from a plant *Atropa belladonna* with parasympatholytic actions.

Mechanism of action:

• It antagonizes the action of parasympathetic neurotransmitter acetylcholine at muscarinic receptors and therefore blocks the effect of n. vagus on both SA an AV node, increasing sinus automaticity and facilitating AV node conduction
• Decreases excretions of glands
• Relaxes smooth muscles

Indications:

1) Asystole and PEA
2) Bradycardia

Dosage:

Asystole and PEA (heart rate <60/min) of adults: 0,04mg/kg to the maximum of 3 mg (total vagal blocade)

Bradycardia of adults: 500mcg iv., can be repeated to the maximum of 3g.

Children 20 mcg/kg (minumum 100 mcg*), can be repeated to the maximum of 600 mcg.

*doses lower than 500mcg in adults and 100mcg in children can paradoxally cause bradycardia (paradoxal effect of small doses)!

Side effects:

• Tachycardia
• Dry mouth, hot and dry skin, hyperpirexia
• Urine retention
• Midriasis
• Sedation, restlessness, delirium, mania.

5. Bicarbonate (8,4% NaHCO3)

The use of bicarbonates in resuscitation is limited to several indications, because of their many unwanted side effects that are associated with generation of carbone dioxide:

• Carbone dioxide diffuses rapidly into cells and exacerbates intracelullar acidosis
• It produces negative inotropic effect on ischaemic myocardium
• It produces a shift to the left in the oxygen dissociation curve, further inhibiting release of oxygen to the tissues
• It presents a large, osmotically active, sodium load to an already compromised circulatiuon of the brain

Besides that, mild acidaemia causes vasodilatation and can increase cerebral blood flow and full correction of the arterial blood pH may theoretically reduce cerebral blood flow!

Indications:
1) Life-threatning hyperkalaemia or cardiac arrest associated with hyperkalaemia
2) Tricyclic overdose accompanied with ventricular arrhythmias
3) In cardiac arrest, after unsuccessful administation of all prescribed procedures (defirbillation, chest compressions, ventilation with high flow oxygen, administration of vasopressors), especially in children.

However, bicarbonates are used only when ventilation is adequate because of the bicarbonate ion that has to be excreted as carbon dioxide via the lungs.

Dosage:

Adults – 50mL of an 8,4% solution of sodium bicarbonate intravenously

Children – 1-2mL of an 8,4% solution of sodium bicarbonate iv./ io.

6. Dobutamine

Dobutamine is a synthetic sympathomimetic drug. It`s primary mechanism is direct stimulation of β1 receptors of the sympathetic nervous system. However, it has mild α2 (mild vasoconstriction) and β2 (mild vasodilatation) effects.

Mechanism of action:
- Increases contractility, stroke volume and cardiac output.
- Usually slightly increases systemic vascular resistance (SVR) and decreases pulmonary vascular resistance (PVR).

Indications:
- Refractery cardiogenic shock.

Dosage:
- 500 mg diluted in 250 mL of saline (2mg/mL). 2 – 20 mcg/kg are administered per minute.

Adverse effects:
- Nausea, headache, chest pain
- Tachycardia, tachyarrhytmia
- Sometimes hypotension

7. Dopamine

Dopamine is a chemical precursor of noradrenaline, a sympathomimetic with an effect that is dose dependant.

Mechanism od action:

Dopamine stimulates dopaminergic, α- and β-adrenergic receptors, depending on the dose administered:
- Lowest doses of 2–3 mcg/kg/min (dopaminergic action) – vasodilatation of renal and mesenterial vessels
- At low doses of 3–8 mcg/kg/min it acts through the β1 adrenergic receptors to increase heart muscle contraction force and heart rate (positive inotropic and chronotropic action), thereby increasing cardiac output and blood pressure.
- Higher doses than 8 mcg/kg/min cause vasoconstriction via α-adrenergic receptors that further increases blood pressure.

Indications:

Hypotension (not caused by hypovolaemia)

Cardiogenic shock

Low doses are used to maintain perfusion of kidneys

Dosage:

400mg are diluted with 250mL 5% glucose solution (1,6 mg/mL):
- Renal dose – 2 mcg/kg/min – to increase diuresis
- Moderate dose – 3-8 mcg/kg/min – positive inotropic and positive chronotropic action
- High dose 8-20 mcg/kg/min - vasoconstroction

Adverse effects:
- Excessive sympathomimetic activity (nausea, vomitting, headache, restlessness, tremor, tachycardia, tachyarrhytmias, …)
- Increased myocardial oxygen consumption (chest pain is possible)

Contraindications:
- Thyreotoxicosis
- Feochromocitoma
- Tachyarrhytmias
- Angle-closure glaucoma (i.e. narrow-angle glaucoma)

8. Calcium (10% otopina CaCl₂)

Calcium is physiologically active only as free calcium ion (Ca^{2+}). Calcium plays a vital role in cellular mechanisms underlying myocardial contraction. However, there are no data supporting any beneficial action for calcium in cardiac arrest. High plasma concentrations achieved after injection may be harmful to the ischaemic myocardium and may impair cerebral recovery. Therefore, it has to be given only when indicated.

Mechanism of action:
- increases vascular tone (systemic vascular resistance) and arterial blood pressure
- increases heart`s contractility without increasing heart rate (it can even decrease heart rate!)

Indications:
1) Hyperkalaemia
2) Hypocalcaemia
3) Overdose of calcium channel-blocking drugs
4) Overdose of magnesium (e.g. during treatment of preeclampsia)

Dosage:
- The initial dose of 0,2mL/kg (in adults usually 10mL) 10% CaCl₂ in cardiac arrest by rapid intravenous injection. If there is a spontaneous circulation present, it may be given slowly.
- The initial dose may be repeated if necessary (be careful – calcium can slow the heart rate and precipitate arrhythmias)

Caution: don`t administer calcium and sodium-bicarbonate at the same time via the same venous route!

Side effects:
- Bradycardia, seldom AV block
- It can potentiate toxicity of digitalis and effect of hypokalaemia (arrythmias can be caused because of that)
- It inhibits the action of sympathicus (adrenaline, dobutamine).

9. Lidocaine

Lidocaine is an amide local anesthetic with an anti-arrhythmic action (Ib class of anty-arrhythmic).

Mechanism of action:
- It blocks entry of sodium ions into cell, and partially disturbs exit of potassium from the cell,
- It decreases duration of action potential and duration of efective refractory period,
- It decreases conduction of impulses by stopping ventricular arrhythmias that are caused with reentry mechanism

Indications:
- VF and pulseless VT that are refractory after multiple defibrillations and application of adrenaline*
- Wide-complex tachycardia with unknown causes*
- Ventricular extrasystoles that are a consequence of myocardial ischaemia (VES > 6/min), multiple VES, polimorph VES*

*Lidocaine is now recommended only when amiodarone is unavailable!

Dosage:
- Initial bolus of 1 mg/kg as an alternative to amiodarone,
- Additional bolus can be given if necessary after 5-10 minutes, the total dose should not exceed 3mg/kg.

Side effects:
- When it comes to CNS: dizziness, euphoria, anxiety, nausea, vomitting, psychotic behavior, eventually respiratory arrest if high doses are administered.
- When it comes to cardiorespiratory system: rarely SA and AV block, decrease of arterial blood pressure.

10. Magnesium (2mmol i.e. 50% MgSO4)

Magnesium is a main intracellular cation that acts as a cofactor in many enzymatic reactions. Especially important are reactions that generate energy for muscle cells and those involved in neuro-muscular junction (magnesium decreases liberation of acetylcholine and excitability of the motor endplate). Increased concentration of magnesium in blood decreases contractility of muscles, of myocard as well, by acting as a physiological antagonist to calcium (similar as potassium). On the other hand, hypomagnesemia is often combined with hypokalaemia and can contribute to development of cardiac arrhythmias or cardiac arrest.

Indications:

1) Hypomagnesaemia
2) VT in hypomagnesaemia
3) Polimorph VT („*torsades de pointes*")
4) Refractory VF/ pulseless VT

Dosage:

Initial intravenous dose of 25–50 mg/ kg (max. 2g, i.e. 4 mL of 50% magnesium sulphate in 10 – 100 mL 5% glucose solution) peripherally over 5 minutes.

If VF/ pulseless VT are refractory, initial dose may be repeated after 10 – 15 min.

11. Glyceryl trinitrate

Mechanismo of action:

Glyceryl trinitrate is an organic nitrate that has several beneficial haemodynamic effects:

- Dilatation of venous capacitance vessels via released nitrous oxide (venous dialtation > arterial dilatation)
- Decreases volume preload of the left ventricule, and has minor effect in decreasing its afterload
- Decreases end-dyastolic pressure
- Maintains blood flow in deep parts of heart by maintaining coronary blood flow
- Decreases myocardial oxygen consumption

Indications:

- Acute cardiogenic pulmonary oedema
- Chestpain when there is coronary obstruction (angina pectoris, acute myocardial infarction)

Dosage and administration:

Sublingual: 0,15–0,5 mg until desired effect is achieved

Intravenous: 10–20 mg/min, additional 5-10mg can be given, if necessary, every 5-10 minutes.

Side effects:

- Hypotension
- Vasodilatation of small vessels in brain – headache
- Methemoglobineima when high doses are administered
- Reflex tachycardia
- Withdrawal phenomenon is the re-emergence of symptoms because of the discontinuation of the medication.

12. Noradrenaline

Noradrenaline is a strong agonist of α-adrenergic receptors (strong vasoconstrictor) with significant β-adrenergic action.

Mechanism of action:

- Increases systemic vascular resistance and blood pressure
- To a lesser extent increases heart rate and contractility

Indications:

- Extreme hypotension with low systemic vascular resistance

Dosage:

- usually 4mg are diluted in 250 mL of 5% glucose solution (16 mcg/mL)
- at first it is infused at a rate of 1 mcg/min (for adults). The dose can later be titrated until the wanted blood pressure is achieved (90 mmHg), up to maximum of 50 mg/min.

Side effects:

- Visceral ischaemia due to high doses (more than 20mcg/min) – decreased blood flow through skin, kidneys and muscles

- Headache, tremor
- Reflex bradycardia
- Chest pain

12.7. When to stop resuscitation attempts?

The patient should be resuscitated:
- Until the return of spontain circulation (ROSC)
- Until there are evident signs of death
- Until the rescuer gets tired

The decision to declare death and to stop with CPR is somewhat subjective and has multiple elements:
- Duration of cardiac arrest prior to CPR
- Previous health status of the patient
- Some other factors (e.g. age, …)

However, it should be done only after all attempts have been done and unsuccessful, and after they have been properly implemented.

It is generally accepted that ongoing asystole for more than 20 minutes with ongoing advanced life support procedures and in the absence of reversible causes, constitutes grounds for abandoning further resuscitation attempts.

It should be remebered:

Resuscitation should be continued as long as VF/ pulseless VT persists on ECG monitor!

If there is hypothermia, it will enhance the chances of recovery without neurological damage. Therefore normal prognostical criteria are not applicable and CPR should be continued until the patient`s body temperature is at least 34°C!

Table 12-8. Potentialy reversible causes of cardiac arrest

5 H	Hypoxia
	Hypovolaemia
	Hyper/hypokalaemia, hypocalcaemia, Acidosis
	Hypothermia
5 T	Tension pneumothorax
	Tamponade
	Thromboembolia, Pulmonary embolism, thrombosis of coronary arteries
	Toxines

12.8. When not to start resuscitation?

Resuscitation is inappropriate and should not be provided when there is clear evidence that:
- The injuries are incompatible with life
- Too much time has elapsed from the beginning of cardiac arrest (except with hypothermia, intoxications, …)
- There are authentic data that the patient is in terminal phase of incurable disease
- There are sure signs of death.

13. ACUTE CORONARY SYNDROME

Antonela Bunoza**, Mihajlo Lojpur*

13.1. Introduction

Coronary or **ischemic heart disease** is the common name for a disease caused due to reduced blood flow in heart (coronary) arteries . The result is too small supply of oxygen to the heart muscle compared to its needs . Table 13-1. show forms of coronary artery disease .

Table 13-1. The forms of coronary artery disease

Sudden death due to coronary heart disease
Acute coronary heart disease (acute coronary syndrome)
Unstable angina pectoris
Myocardial infarction
With ST segment elevation
Without ST segment elevation
Chronic coronary disease
Chronic stable symptomatic or asymptomatic angina pectoris with previous myocardial infarction or without it
Ischemic cardiomyopathy
Arrhythmia due to coronary artery disease
Heart failure due to coronary artery disease

The most common cause of reduced blood flow through the blood vessels of the heart is atherosclerosis and we can freely say that coronary heart disease is manifestation of atherosclerosis in coronary arteries . Atherosclerosis is characterized by the formation of fibrous plaques and accumulation of fat (cholesterol, lipoproteins , ...) below the surface thereof , so as to gradually narrowing the lumen of blood vessels. It is believed that stenosis of the coronary arteries 50 to 75 % damaging the normal functioning of parts of the heart muscle and that the symptoms in the form of angina pectoris (AP) , attacks of pain in the chest , usually occur when the stenosis is greater than 75 % .The gradual narrowing of the coronary arteries, which are being developed for a long time, often favor the development of collateral circulation, and theeffects of reduced blood flow are less and onset of symptoms is slower. If atherosclerotic plaque ruptures and releases thrombogenic matherials in the lumen of the coronary arteries, follows rapid platelet aggregation and thrombosis of blood vessels. It can cause a critical stenosis of the coronary arteries, with a reduction in the lumen of 75-99% or up to complete occlusion blood vessels (100% stenosis). It is acute event and there is no possibility of any compensation of heart circulation, and without rapid establishment flow through mechanical or medication, leads to acute ischemia and in the further course of the subsequent necrosis (infarction) of heart muscle.

Acute ischemia and / or myocardial necrosis manifested a group of different clinical conditions which are referred to as acute coronary syndrome (Eng. Acute coronary syndrome - ACS). This syndrome involves two entities:
1) Non-ST Elevation ACS, NSTE-ACS:
   a) Unstable angina, UA
   b) Non ST-Elavation Myocardial Infarction, NSTEMI (with Q wave and without it)
2) ST Elevation ACS, STE-ACS
   a) ST-Elevation Myocardial Infarction, STEMI (with Q wave and without it)

13.2. Epidemiology

ACS as an acute complication of coronary artery disease, is one of the most common causes of death worldwid e, especially in developing and middle-income countries.

According to the European Hospital Morbidity Database in 2006 the treatment of acute myocardial infarction (code I21 according to ICD-10) in the Republic of Croatia has generated 0.96% of all hospital admissions. Data from the European Detailed Mortality Database (EDMD) for our country show that same year, acute myocardial infarction was the cause of 4,143 deaths, or that the disease caused 8.22% of all deaths in 2006. Analyzing data on the trend of the share of deaths from acute myocardial infarction in the period from 1995 to 2006. in the Republic of Croatia noticed only slight oscillations (minimum of 8.10% for 2003. to 8.82% for the maximum for the year 2011.)

13.3. Diagnosis

Because it is a syndrome of the highest degree of urgency in which patients are in danger and that the medicine has effective medications and / or emergency treatment, it is extremely important to early diagnosis. In this regard it is essential:

- recognize the clinical picture (symptoms and signs of disease), and ECG parameters, and
- set up early working diagnosis without waiting for arrival of biochemical markers of myocardial necrosis.

For the diagnosis is most important to take a good medical history and do a series of 12 channel ECG, and clinical examination is of minor importance.

The characteristic symptom of ACS is **angina** - pain or discomfort in the chest area caused by ischemia of the heart muscle. It usually occurs in the area behind the sternum, in the form of burning, discomfort, pressure or pain thumping. Sometimes spreads into the neck or arm (usually the left shoulder or left arm), the lower jaw, the back or the epigastrij (diaphragmatic infarction).

Performance of pain can be triggered by physical exertion or emotional stress, but can also occur for no apparent reason. The pain of this kind, which occur during physical exertion and at rest that soothes, is called stable angina pectoris does not belong to ACS.

Unstable angina is different from the stable in that it satisfies at least one of said criteria:

1) it is a newly created AP that occurs on exertion, lasting less than 2 months and limits the physical activity,
2) it is a previously stable AP that becomes more severe and more frequent, which lasts longer and occurs at the minimum effort,
3) it is the AP that occurs at rest and lasting> 20 minutes,

Table 13-2. The differential diagnosis of chest pain

ACS	AP and myocardial infarction
Other cardiovascular causes	Probably ischemic
	Aortic stenosis
	Hypertrophic cardiomyopathy
	Severe hypertension
	Aortic regurgitation
	Anemia / hipokemija
	Non-ischemic causes
	Aortic dissection
	Inflammation of the pericardium
	Mitral valve prolapse
3 Non-cardiovascular causes	Gastrointestinal causes
	Esophageal spasm / reflux
	The rupture of the esophagus
	Ulcer disease
	Nervous – musculoskeletal
	The syndrome thoracic aperture
	Degenerative changes of the cervical and thoracic
	spine
	Costohondritis
	Herepes zoster
	Myalgia chest
	Pulmonary
	Pulmonary embolism, myocardial or without
	pneumothorax
	Pleuropneumonija
	Psychogenic
	Anxiety
	Depression

4) it is the AP that occurs within 2 weeks of myocardial infarction (MI).

In an unstable AP ECG may be normal, show signs of acute myocardial ischemia in the form of horizontal or descending ST connectors leveling or show non-specific abnormalities such as inverted T wave. Cardiac enzymes are usually normal.

Pain in acute myocardial infarction are typically more powerful and longer lasting than those in AP. If it is accompanied by nonspecific ECG changes such as ST depression or T wave inversion and laboratory parameters troponin release we are talking about a myocardial infarction without ST-segment elevation (NSTEMI). If it is accompanied by acute ST segment elevation or new onset left bundle branch block (LBBB), and laboratory indicators of troponin release, we are talking about a myocardial infarction with ST-segment elevation (STEMI).

You must know that in some patients (the elderly, diabetics, ...) can develop ACS without chest pain or with minor symptoms, so doctors often overlook it. Also often belching, nausea and vomiting attributed to stomach problems although the same symptoms seen in inferior IM.

Pain in patients with ACS is often accompanied by other symptoms. These patients are often sweating, pale, tachycardic, and may have other rhythm disturbances (of the FA to VF) and conduction disturbances, with accompanying symptoms (darkening before his eyes, disorders of consciousness, lowering blood pressure, ...). In the event of a massive myocardial ischemia it may develop heart failure with pulmonary edema and / or cardiogenic shock.

Although a clinical examination has limited usefulness in the diagnosis of ACS, it may reveal other significant abnormalities that can focus the doctor on the differential diagnosis of other causes of chest pain. This primarily relates to the aortic dissection, which is especially important to recognize when you are planning thrombolytic therapy. Acute aortic dissection can reveal acute chest pain accompanied by hypotension and without ECG changes that indicate IM, loss or inequality pulse in the upper limbs, acute aortic insufficiency, signs cerebrovskularnog insults in a situation where the affected carotid artery. Table 13-2. given the differential diagnosis of chest pain.

13.3.2. 12-lead ECG recording

The initial 12-lead ECG can confirm the clinical suspicion of ACS, to enable risk assessment and indicate appropriate treatment and repeated ECG can determine the progression of ACS and response to treatment. Eg.:

- The presence of acute ST segment elevation or new onset LBBB in patients with a typical history of acute MI, indicates immediate recanalization of the occluded coronary artery (reperfusion therapy) or percutaneous coronary intervention (PCI) or thrombolysis
- The presence of the sloping ST segment indicates low probability of benefit from thrombolytic therapy, regardless of whether the UA or NSTEMI.
- In the case of UA, the presence of the sloping ST connectors indicates a higher risk further progression of coronary disease, then when there is no leveling, and these patients with higher risk, require prompt drug treatment (low-molecular heparin, aspirin, clopidogrel, a blocking agent, inhibitorglycoprotein IIb / IIIa), emergency coronary angiography and often reveskularization of heart muscle , PCI or surgical coronary bypass set artery.

12 lead ECG provides information about the location and extent of heart muscle damage in case of acute, particularly STEMI. This is important because the place and the degree of ischemia or myocardial affect prognosis and sometimes the choice of appropriate treatment. Table 13-3. stated the localization of cardiac involvement muscle infarction. Denivelation ST segment and T wave inversion, which can be present in NSTEMI, are less related to the site heart muscle damage than is the case in STEMI!

It should be remembered - a normal ECG record does not excludes ACS!

Table 13-3. Localization of cardiac infarction based on 12 channel ECG

Description	ECG Leads With Changes	Artery Occluded
Inferior	II, III and aVF	RCA
Anteroapical	V3 and V4	Distal LAD
Anteroseptal	V1 and V2	LAD
Anterolateral	I, aVL, V5 and V6	Circumflex Artery
Extensive Anterior	I, aVL and V2-V6	Proximal LCA
True Posterior	Tall R in V1	RCA

13.3.3. Laboratory tests in ACS

An important component in the final diagnosis and determine the risk of further disease progression are laboratory tests.

Laboratory tests essential for the diagnosis of ACS are:

- Cardiac troponins, troponin T (TT) and troponin I (TI): these are the components of the contractile structures of heart cells and their growth is the most specific and the most sensitive indicator of myocardial necrosis. Nevertheless, a rise of TT and TI may ocure in some other life-threatening conditions which are accompanied by chest pain (pulmonary embolism, aortic dissection, myocarditis, acute or chronic heart failure, prolonged tachycardia, renal failure, acute sepsis), and assist in setting of ACS diagnosis only when medical history suggests big probability occurrence of ACS.
- The same applies to their role in predicting the risk of progression of the disease - if the medical history is likely that the patient suffers from ACS's, only then a greater level of troponin should be considered as an indicator of higher risk!
- Kratine kinase (CK) and its CK-MB fraction (specific isoenzyme of the heart muscle) : CK is an enzyme released by damaged heart muscle, but it is released by the skeletal muscles during prolonged physical exertion or after the i.m. injection. Therefore, the key ratio of CK / CK-MB, where, apart from elevated CK, MB fraction should be at least 10%.

- Myoglobin: sensitive but insufficiently specific biochemical indicator of myocardial necrosis. His only advantage that in a case of IM increases before CK-MB and troponin, and sometimes can serve as an early factor in setting up the working diagnosis of IM. As CK, myoglobin may be elevated after prolonged physical exertion or after the i.m. injection. See Table 13-4.

Other useful but not essential laboratory tests in the diagnosis of ACS are:
- CRP: indicates the inflammatory activity in atersclerotic plaque and acute coronary atherothrombotic events
- The brain natriuretic peptide (Brain Natriuretic Peptide - BNP) is the most sensitive indicator of stress or left ventricular dysfunction and can be helpful in identifying patients who will in further develop heart failure.

Lactate dehydrogenase (LDH) and liver transaminases (AST and ALT) are insufficiently sensitive and specific and no longer meets the criteria for contemporary diagnostic protocol of ACS !

It is important to remember that the increase in the concentration of CK and CK-MB can not be expected before 3-4 hours and increased exposure TT and TI before 3-6 hours of onset of the disease. In an ideal scenario, when the patient comes early in a medical institution, we do not have time to wait for these findings to confirm the diagnosis of ACS. In a short period we have to set up a working diagnosis of STEMI, NSTEMI or UA and, depending on the risk, we should hospitalize the patient and start intensive medicament and / or interventional treatment.

Table 13-4. Laboratory tests in ACS

Diagnostic test	Cardiac specificty	Appeerence	Peak concentrations	Duration of elevated values	Advantages	Disadvantages
Myoglobin	+	1-3h	6-7 h	12-24 h	Highly sensitive, early indicator of IM	Indicator IM, Insufficient specific indicator of the muscle damage or kidney failure, rapid normalization
CK-MB	+ + +	3-4 h	24 h	24-36 h	The best alternative to TT and TI, good at detecting reinfarction	Insufficient specific indicator of the muscle damage, late appeearance, required series of repetition when the first record of neat
TI	+ + + +	3-6 h	24 h	5-10 d	The highest sensitivity and specificity, a strong factor risk stratification and selection of treatment, reveals IM and after 10-14 days	Insufficient specific indicator of the muscle damage, late appeerence required series of repetition when the first record of a neat, weaker in detecting reinfarction
TT	+ + + +	3-6 h	24 h	5-14 d		

13.3.4. Echocardiography in the ACS

Echocardiography can detect motion abnormalities of the left ventricle due to IM, and enable assessment of the severity of damage. It can detect a dilated right ventricle in a comprehensive IM and acute complications such as ventricular septal defect or mitral regurgitation. It is sometimes possible to spot and aortic dissection.

13.4. The treatment of acute coronary syndrome

13.4.1. Immediate procedure
A. General measures for all clinical forms of ACS

In the initial treatment of patients with ACS comprises administering therapies that can memorize the following mnemonic abbreviations MONA - Morphine, O2, Nitroglycerin, Aspirin:
1) Morphine administered titrated, in multiple doses, to achieve sufficient analgesia without excessive sedation or respiratory depression,
2) Oxygen is given in a way and at a flow rate that will ensure that the arterial oxygen saturation (SaO2) is 94-98% (88-92% in patients with chronic obstructive pulmonary disease

3) Nitroglycerin in the form of glyceryl trinitrate given sublingual tablets or intrabuccally spray, if the patient is not hypotensive (systolic arterial pressure <90 mm Hg) or if there is not instant right ventricl infarction,

4) Aspirin is administered at the dose of 300 mg by mouth, chewed or crushed, as soon as possible.

For all patients with ACS, we should consider administration of clopidogrel at a dose of 300-600 mg or prasugrel 60 mg, per os, and we should also consider the application of antithrombotic treatment in the form of unfractionated or low molecular weight heparin or fondaparinux.

B. Treatment of STEMI or acute IM with new LBBB

All patients with ACS who come within 12 hours of the occurrence of chest pain and who have:
- ST segment elevation > 0.2 mV in two adjacent precordial leads or > 0.1 mV in two
  or more contiguous standard leads, or
- R-wave and ST segment depression in V1-V3 (posterior MI), or
- newly formed (or possibly newly) LBBB need immediate reperfusion therapy, mechanical or pharmacological. This should reduce the size of infarction, the incidence of complications and mortality from MI.

Coronary reperfusion, in this case, can be achieved in two ways:
1) percutaneous coronary intervention (PCI) - in this case it is called primary PCI, or
2) fibrinolytic therapy, which seeks to dissolve the clot that has clogged coronary artery.

Primary PCI coronary angiography identify occluded coronary artery, through the thrombus is introduced wire guide, and over it a catheter with a balloon. Inflating a balloon at the site of thrombus open the lumen of the occluded artery and restore the flow in the affected part of the heart muscle. Usually artificial stent takes place of a prior occlusion, to prevent reocclusion of coronary arteries. Primary PCI is the most effective method of re-opening the occluded artery and should be applied in all cases where the patient came within 2 hours of the onset of pain and when they can reach values jeme from first medical contact to reperfusion less than 90 minutes.

If this is not possible (eg, because the institution does not have laboratory for heart cateterization) is indicated to apply fibrinolytic therapy because any further delay of reperfusion associated with a higher mortality rate. The advantage of fibrinolytic therapy is that it can be applied outside the laboratory for heart catheterization and the disadvantage is the risk of bleeding, including brain hemorrhage. To avoid such complications, fibrinolytic therapy is contraindicated in some patients (see. Table 13-5.).

Table 13-5. Contraindications for use of fibrinolytic therapy

ABSOLUTE	previous hemorrhagic stroke
	ischemic stroke within 2 months
	damage to the central nervous system or a tumor
	recent major surgery or head injury, or other major injuries
	Indoor active bleeding or bleeding from the GI tract within a month
	known or suspected aortic dissection
	known bleeding disorder
RELATIVE	refractory hypertension (systolic blood pressure > 180 mm Hg)
	TIA in the past 6 months
	taking oral anticoagulant therapy
	pregnancy or immediately postpartum period (first week after birth)
	non-compressible puncture wound blood vessels
	active stomach ulcer
	advanced liver disease
	infective endocarditis
	allergy fibrinolytic to be applied

In 20-30% of patients with STEMI who receive fibrinolytic therapy, the reperfusion is not achieved . In this case the patient should be transported to a facility with a laboratory for cardiac catheterization in order to do saving angioplasty. The practice that right after the initial fibrinolytic therapy, patient perform coronary assisted PCI for now remains a subject of debate.

Noteworthy is that all patients with STEMI undergoing primary PCI should be given at a dose of clopidogrel 600 mg or prasugrel at a dose of 60 mg (not if you have > 75 years, <60 kg or stroke in history)!

All patients with STEMI who receive fibrinolytic should be given aspirin 300 mg, clopidogrel 600 mg and antithrombotic therapy (low molecular weight or unfractionated heparin or fondaparinux)!

C. Treatment of UA and NSTEMI

The immediate goals of treatment UA and NSTEMI are:

1) prevent the formation of a new thrombus, which can in complete grains clog coronary artery,

2) reduce the need of the heart muscle for oxygen

Preventing further thrombus formation involves giving low molecular weight heparin in therapeutic dose (based on body weight, every 12 hours) or fondaksiparinuxa (1x per day, not in kidney disease), aspirin (300 mg loading dose, maintenance dose of 75 mg daily) and clopidogrel (loading dose 300 to 600 mg, a maintenance dose of 75 mg per day).

Reducing the need of the heart muscle for oxygen means giving b-blockers or diltiazem if they are contraindicated, nitroglycerin if the pain persists, and the ACE inhibitor if there is heart failure. Dihydropyridine calcium channel blockers (eg, nifedipine) should be avoided!

13.4.2. Further procedure in patients with ACS

a) Patients with NSTE-ACS

Further treatment strategy in these patients is not identical. In fact, it is a diverse group of patients - those who have relatively mild symptoms and normal ECG or minimal ECG changes, to patients with severe angina of prolonged, extensive ischemic changes in the ECG (eg, depression in all precordial leads) and hemodynamic instability. It is believed that the proven benefits of early coronary angiography (ideally within 72 hours) and early PCI, with only high-risk patients in this group, so it is important to separate those with low risk of those high-risk.

There are several scoring systems with which to stratify the risk of disease progression and the appearance of early death in these patients, for example. TIMI (Thrombolysis in Miacardial Infarction) risk score or GRACE (Global Registry of Acute Cardiac Events) risk score.

Older and simpler TIMI risk score identifies seven independent prognostic risk factors for disease progression and the appearance of early death (Table 13-6.). According to the TACTICS-TIMI 18 study, only patients with a risk score > 3 benefit from an early invasive approach, and need early coronary angiography (ideally within 24 hours) or PCI or coronary artery bypass grafting (CABG). That need all patients with elevated troponins, ST-segment changes on ECG and hemodynamic instability.

Newer and more frequently usable GRACE risk score identifies 8 risk factors for disease progression and death - age of the patients, heart rate, systolic blood pressure, heart failure (Killip classification on), serum creatinine, cardiac arrest on admission to hospital, delevelling ST staples in ECG and elevated cardiac markers. Each factor is assigned a numerical value determined by adding the same, can be obtained GRACE score of 2 to 372. It is considered the only patients with secondary (GRACE score of 109-140) and high risk (GRACE score> 140) can benefit from early coronary angiography revascularization (PCI or CABG).

Table 13-6. TIMI risk score for disease progression or death in patients with NSTE-ACS

Risk factor	Score
1. The age $\geq$65	1
2. $\geq$ than 3 risk factors for CAD	1
3. Coronary artery stenosis $\geq$ 50% on coronary angiography	1
4. ST-segment deviation from the isoelectric line > 0.5 mm	1
5. $\geq$ 2 anginal episodes in the 24 hours beforedmission	1
6. Elevated levels of cardiac biomarkers	1
7. The use of aspirin 7 days before admission	1

b) Patients with STE - ACS

In patients who have had STEMI and were not subjected to reperfusion therapy (eg. Due to the late arrival of the doctor) to do coronary angiography during the same hospital stay. Although we should not expect the benefits of re-opening the occluded coronary artery after long time occlusion, this procedure can detect other vascular desease and indicate PCI in high-risk patients.

14. PULMONARY EMBOLISM

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Despite technological and medical advancements in general, acute pulmonary embolism still results in high mortality and morbidity rates. Quick diagnosis and prompt treatment, though, can lower both mortality and morbidity. Unfortunately, non-specific clinical presentation and various diagnostic guidelines may interfere and even slow down correct and timely diagnosis.

14.1. Definition

Pulmonary embolism (PE) is partial or complete blockage of the lung's main artery or one of its branches by a substance that has migrated from elsewhere in the body through the bloodstream (embolus).

The most common type of pulmonary embolus is a thrombus (or a blood clot) which usually originates from pelvic or lower extremity vein. Once released into venous circulation, blood clots reach lungs in 65%, the right lung only in 25% and the left lung only in 10% cases; lower parts are affected four times more than upper parts. Most emboli lodge themselves within large or midsize pulmonary arteries, with approximately 35% reaching smaller arteries. Emboli made of fat (which may occur after a bone fracture) or amniotic fluid, which cause a small proportion of PE cases, usually affect lung microcirculation. PE and deep vein thrombosis (DVT) are two clinical manifestations of a process termed venous thromboembolism (VTE) and both share the same risk factors. Most commonly, PE results from DVT. Half of patients with proximal DVT suffer from clinically asymptomatic PE; nearly 70% patients with diagnosed PE also have lower extremity DVT.

14.2. Epidemiology

Pulmonary embolism is not rare cardiovascular emergency. Nowadays, it's the third most common cause of mortality related to cardiovascular illnesses, just behind coronary disease and brain stroke in occurrence. Due to occlusion of pulmonary arteries, right heart failure may develop, which is a life threatening state. Non-specific clinical symptoms (or lack of patognomonic symptoms, thereof) hinder PE diagnosis. Still, time is of the essence when trying to ascertain the presence of pulmonary embolism due to dependence of outcome on an expeditious treatment. Research has shown that between 7% and 11% of acute pulmonary embolism cases have fatal outcome. Close to 70% cases of PE is caused by thrombosis of pelvic or lower extremity blood vessels. The incidence of PE is roughly 15 to 20 cases per 100 000 persons, however, exact figure is probably far greater. One third of patients experience spontaneous disappearance of DVT after only a few days. Two thirds of patients with PE experience complete recovery. Fatal outcome in 90% of cases occurs due to misdiagnosed and mistreated PE. Without anticoagulant therapy 50% of patients with proximal DVT or PE suffer repeated thrombosis. Those patients with VTE that received anticoagulant therapy from 3 to 12 months have up to 0.5% risk of fatal pulmonary embolism. As a consequence of PE and DVT two conjoined diseases occur: chronic thromboembolic pulmonary hypertension and post-thrombotic syndrome.

14.3. Risk factors

Up to 20% of patients have idiopathic PE (can't be related to any known risk factor). However, most patients have secondary PE which can be related to at least one risk factor. Known patient-related risk factors are: age; previous occurrence of VTE; malign disease; neurological illness with lower extremity paresis; any medical condition which causes prolonged immobility; congenital or acquired thrombophilia; hormone-replacement therapy; and oral contraceptives. Incidence of DVT rises with patient's age; 65% of those afflicted are persons over 60 years of age. Latest research has shown relation between idiopathic PE and cardiovascular disorders, such are acute myocardial infarction and brain stroke. It is also very likely that obesity, smoking habit, arterial hypertension and metabolic syndrome are in relation with occurrence of arterial thromboembolism and VTE.

14.4. Pathophysiology

Acute pulmonary embolism affects mainly hemodynamic, with effect determined by the size of emboli, pre-existing cardiac or pulmonary disease, and intensity of the pulmonary vasoconstriction. Multiple large clots can rapidly increase pulmonary vascular resistance and cause right-sided heart failure.

The shift of interventricular septum may further compromise cardiac output (CO) due to lower preload of left ventricle. Sudden death usually occurs because of cardiac failure due to decreased perfusi-

on of coronary arteries and the onset of cardiogenic shock with myocardial ischemia. In those patients that survive acute PE despite right-sided heart failure, survival is necessitated by the strong activation of sympathetic nervous system, and increase in chronotropic and inotropic stimulation; with Frank-Sterling mechanism there's increase in pulmonary arterial pressure, which facilitates left ventricle preload and maintains cardiac output. Together with systemic vasoconstriction these compensatory mechanisms work towards stabilisation of arterial pressure. However, additional problem lies in the fact that right ventricle's thin (and un-prepared) wall can't withstand main pulmonary artery pressure higher than 40 mmHg.

Secondary hemodynamic instability develops within 24-48 hrs period usually because of recurrent emboli and/or functional disturbance of the right ventricle. This is especially common in the case of mis-diagnosis or inadequate treatment of PE. At the same time, combination of increased oxygen consumption within right ventricle, with the lower perfusion rate, leads into ischemia and dysfunction. Previous or pre-existing cardiovascular disease may lessen efficiency of the compensatory mechanisms, negatively influencing the final outcome of PE.

Respiratory insufficiency in PE is mainly a consequence of hemodynamic disturbances. Several factors may cause hypoxia during PE: decreased cardiac output leads to desaturation of mixed venous blood which enters pulmonary circulation; also, there are regions within lungs with decreased blood perfusion due to occlusion of the vessels, as well as regions with increased blood perfusion, which leads to disrupted ventilation - perfusion ratio and subsequent hypoxia.

Small and distally-located clots, although they're not disturbing hemodynamic, may cause alveolar bleeding and subsequent hemoptysis, pleuritis and pleural effusion. This manifests clinically as a pulmonary infarction. Effect on alveolar gas exchange isn't pronounced unless the patients suffer from pre-existing cardio-respiratory illness.

14.5. Signs and symptoms

Pulmonary embolism is suspected anytime there is a sudden onset of symptoms including shortness of breath, rapid breathing, chest pain, syncope, and hemoptysis. Unfortunately, those symptoms and signs are not specific, since in differential diagnosis they can be attributed to various other diseases and syndroms. Additional diagnostics tools like chest X-ray, electrocardiography, or blood gas analysis are not suitable for diagnosing PE, but they can be of immense help in differential diagnosis.

14.5.1. Estimation of PE severity

In order to estimate the severity of PE, it is sometimes described as: massive, submassive and non-massive. However, nowadays it is common to classify PE based on factors organised in three groups (*Table 14-1*), which determine the risk level of early fatality. This classification facilitates the choice of optimal diagnostic strategy and adequate treatment.

Still, the simplest division is on the high-risk PE, and the one which is not high-risk, based on the presence of cardiogenic shock and hypotension (systolic arterial pressure <90 mmHg; or a drop of pressure >40 mmHg in 15 min period or longer, if it's not triggered by recent arrhythmia, sepsis or hypovolemia). If the aforem entioned signs are presented, PE is high-risk for early/sudden fatality. This condition demands urgent diagnosis and treatment.

If PE is not high-risk, it can be further classified as either mid- or low-risk PE. Mid-risk PE is determined if there is present at least one indicator of right ventricle dysfunction or myocardial injury. If all indicators of right ventricle or myocardial function are satisfying, we're having a low-risk PE.

Table 14-1. Main indicators of early fatality risk in acute pulmonary embolism

Clinical indicator of shock	Hypotension
Right ventricle dysfunction indicators	Dilatation of the right ventricle coupled with hypokinesis on echocardiography
	Dilatation of the right ventricle on spiral CT
	BNP elevation
	Increase in right heart pressures
Myocardial injury indicators	Positive troponin T or I

14.5.2. Diagnosis

When establishing proper diagnosis, there's 90% increase in likelihood of PE if there exist clinical symptoms like dyspnoea, chest pain and syncope. Syncope is rare, but important symptom which points

towards disturbance of hemodynamic. In the most severe cases arterial hypotension and shock can be observed. Chest pain with or without dyspnoea is one of the most common signs of PE. The pain is caused by distal emboli which irritate pleura by producing alveolar bleeding. Dyspnoea-only with sudden onset is caused by a central PE, usually with already pronounced changes in hemodynamic. In short, clinical signs, symptoms and routine laboratory testing neither confirm nor deny acute PE, but increase suspicion in aforementioned diagnosis.

14.5.3. Imaging

Chest X-ray is not specific. Very often the findings are normal, although it is possible to observe elevated diaphragm, pleural effusion, atelectasis. This diagnostic tool is primarily used to rule-out other causes of dyspnoea and chest pain. PE usually presents with hypoxemia, although 20% of patients have normal partial oxygen pressure in arterial blood and alveo-arterial gradient.

"Multi-slice" CT angiography: this is a quick imaging method. Two large studies showed up to 70% sensitivity rate and up to 90% specificity rate; it replaces ventilation-perfusion scintigraphy and pulmonary angiography as the gold standard method.

Pulmonary angiography: historically, the gold standard method for diagnosis of PE. It enables direct visualisation of thrombi, even those of up to 1 to 2 mm in size, within sub-segmental pulmonary arteries. This is invasive method with mortality rate of up to 0.2%. Fatal outcome during angiography most often occurs when patients already have impaired cardiac and pulmonary function, so hemodynamic monitoring is a necessity during the procedure. Nowadays pulmonary angiography is rarely used as the only method; more often non-invasive or less invasive or combination methods are used: CT angiography, ventilation-perfusion scintigraphy, with compression US of lower extremities and laboratory testing.

Electrocardiography: ECG changes (T wave inversion in V1-V4, typical S1Q3T3, complete or incomplete right bundle branch block) indicate severe case of PE, yet can be present with right heart illnesses of any cause.

Compression US ("leg Doppler"): In 90% of patients the origin of PE is DVT of lower extremities. Compression US has 90% sensitivity rate and 95% specificity rate for proximal DVT. Diagnosis of proximal DVT in patients with PE suspicion is sufficient to apply anti-coagulant treatment without further diagnostic.

Heart US (trans-thoracic and trans-oesophageal): made only in case of significant hemodynamic instability of patient, when other methods would prove too risky to make, and there's urgent need to estimate a necessity of reperfusion therapy. Significant diagnostic parameters are: abnormal mobility of right ventricle wall, dilatation of the right ventricle, paradoxical mobility of the septum, tricuspidal valve insufficiency, increased pressure in pulmonary arteries, congestion of vena cava inferior, dilated pulmonary arteries. Thrombi may be detected via trans-thoracic US, however trans-oesophageal US enables direct observation of thrombus-embolus within pulmonary arteries. It has also been shown that right ventricle dysfunction is coupled with increased mortality in patients with acute PE.

Ventilation-perfusion scintigraphy: Well established and safe method when suspicious of PE, with low rate of allergic reactions. Normal finding definitely rules out PE.

14.5.4. Blood tests

D-dimer: positive predictive value of D-dimer is low. This test has high sensitivity (~95%), but also low specificity (40%). D-dimer is useful in ruling out PE in patients with low to intermediary possibility of pulmonary embolism.

BNP and pro-BNP: increased values indicate negative outcome.

Troponin: prognostic value in patients with PE. It signifies increased possibility of lethal outcome.

14.6. Treatment

14.6.1. Cardiocirculatory and respiratory support

- Moderate application of fluids increases CO, cardiac index and blood pressure in patients with PE, however, one needs to be cautious of possibly causing cardiac decompensation, or worsening thereof.
- Norepinephrine has direct inotropic and vasoconstrictive effect, and thus improves function of the right ventricle; also, stimulation of the peripheral vascular alfa receptors increases perfusion of the right ventricle as well, and increases systemic blood pressure. The usage of norepinephrine is limited to patients with hypotension.
- Dobutamine and dopamine are used in case of low cardiac index.

- Epinephrine combines characteristics of norepinephrine and dobutamine, without systemic vasodilatation effects of dobutamine.
- Vasodilators decrease pulmonary arterial pressure and pulmonary vascular resistance; their main shortcoming is lack of specificity for pulmonary blood vessels after systemic application.
- Preliminary experimental studies indicate that levosimendan could be efficient in acute PE because of simultaneous pulmonary vasodilatation and increase in contractility of the right ventricle, without increase in oxygen consumption.
- Nowadays there's increased interest in the usage of endothelin antagonists and phosphodiesterase inhibitors, which decrease severity of pulmonary hypertension in massive PE. Experimental data shows that infusion of sildenafil could be effective in decreasing of pulmonary arterial pressure.

Hypoxemia and hypocapnia are common in patients with PE. Hypoxemia is usually handled by application of oxygen via facial mask or nasal oxygen catheter; in special cases, mechanical ventilation is applied. Oxygen consumption needs to be reduced, by lowering body temperature and minimising patient's anxiety, and if the breathing frequency is elevated, mechanical ventilation is indicated. However, positive intrathoracic pressure, caused by mechanical ventilation, can decrease venous return and additionally worsen cardiac function.

As a part of the treatment, special consideration needs to be taken when deciding which type of patient monitoring to use. In less severe cases invasive monitoring is not necessary, however highly severe cases are indication for invasive monitoring.

14.6.2. Reperfusion treatment

Trombolysis: Research shows that trombolytic therapy successfully treats thromboembolic obstruction and improves hemodynamic parameters. Direct local infusion of rtPA via pulmonary artery catheter doesn't have advantage over systemic intravenous application. The greatest effect after thrombolytic application is within 48 hrs, however thrombolysis may be useful even in patients with symptoms lasting 6 to 14 days. During administration of thrombolytic agents there is always a risk of bleeding, with fatal intracranial haemorrhage registered in approximately 2% of patients. However, absolute contraindications become relative when patient's life depends on the usage of thrombolytic drugs. In *table 14-2* are shown contraindications for the administration of trombolytic therapy.

Reperfusion treatment with PE catheter: Percutaneous reperfusion treatment with catheter technique is indicated in case of thrombolysis being contraindicated, or if the swift re-canalisation with this treatment is highly probable, in the house with experienced staff in this type of procedures.

Surgical pulmonary embolectomy: If there's definite contraindication for thrombolysis, and cardiopulmonal resuscitation is expected; also, if the patients have foramen ovale aperta and/or intracardiac clots. The mortality in this type of procedures is 6-19%.

Anticoagulant treatment: Maintains central role in the treatment of PE. The goal of initial anticoagulant therapy is to prevent fatal outcome and recurrent episode of PE, with the acceptable risk of bleeding. Swift anticoagulation can be achieved only with parenteral drugs, as noted: intravenous non-fractioned heparin, subcutaneous low-molecular-weight heparin, or subcutaneous fondaparinux. Since the patients receiving no treatment have high mortality rate, anticoagulant therapy should be applied whenever there is suspicion of PE, until such time as definite diagnosis is ascertained. Non-fractioned heparin dose should be adjusted so that value of activated partial thromboplastin time (aPTT) remains elevated roughly 1.5 to 2.5 times more than normal value. Low-molecular-weight heparin should be given cautiously to patient with impaired renal function. Non-fractioned heparin is administered to patients with renal clearance less than 30 mL/min, since it's not secreted via kidneys, as well to patients with high risk of haemorrhage, because of ability to make quick reversion if need arises. In all other cases low-molecular-weight heparin should be administered, it's use not necessary to monitor except in patients with kidney disease or pregnant women. Anticoagulation therapy with non-fractioned heparin and low-molecular-weight heparin or fondaparinux after initial dose should be continued for five days. Oral antagonists of vitamin K should be introduced into therapy as soon as possible, optimally the same day as initial anticoagulant. Administration of parenteral anticoagulants needs to be halted for at least two days when INR reaches value between 2 and 3.

Secondary profilaxis: The goal of long-term anticoagulant therapy in patients with PE is prevention of repeated VTE. Most patients receive coumarin medications, while low-molecular-weight heparin is effective and safe substitute in patients with malignant disease. Active malignant disease presents the greatest risk of repeated VTE which is the reason these patients need to receive anticoagulant profilaxis as long as the disease is active. If the patient had PE during surgery, trauma, estrogen therapy, or pre-

gnancy, anticoagulant therapy lasting at least three months is recommended. Oral anticoagulant medication which doesn't need regular monitoring and whose dosage doesn't need to be adjusted would be an ideal medicine for optimal PE profilaxis. Two such medications are known: selective thrombin inhibitor – dabigatran, and factor Xa inhibitor – rivaroxaban and apixaban. Dabigatran proved to be effective and safe for treatment of VTE.

Table 14-2. Contraindications for the administration of thrombolytic therapy

Absolute contraindications	Relative contraindications
Haemorrhagic CVI or CVI of unknown origin	Transient ischemic brain stroke in past 6 months
Ischemic CVI in the past 6 months	Oral anticoagulant therapy
Injury or tumour of CNS	Pregnancy
Recent head injury or surgery	Refractory hypertension (systolic pressure > 180 mmHg)
Gastrointestinal bleeding in the past month	Severe liver disease
Previously known haemorrhage	Infective endocarditis
	Active peptic ulcer

15. SHOCK

Nenad Karanović*, Toni Lozančić**

Shock is a clinical syndrome whose principal characteristic is the inability to maintain adequate blood flow (perfusion) to tissues and organs with the consequential lack of oxygen, which, if continued, leads to severe disorders of organ function with lethal outcome. This is a condition in which the circulation is not able to supply sufficient oxygen for the tissue demands, resulting in cellular dysfunction. The result is a so-called cellular disoxia (disorder between the delivery of oxygen and its consumption; this is sometimes used to describe the condition between anoxia - scarcity of oxygen, and hypoxia - reduced oxygen concentration). Some clinical syndromes suggest the disorder at the level of microcirculation.

15.1. Pathophysiology

Shock is an acute clinical condition, immediate circulatory failure, which is a result of one or up to four different mechanisms.

The first mechanism is a decrease in venous return of blood due to circulating volume loss (caused by external or internal reasons).

The second mechanism is failing of the heart as a pump, which occurs due to loss of contractile function (resulting from ischemia, infarction, myopathy or myocarditis) or the occurrence of serious arrhythmias (ventricular tachycardia or severe disorders in the vascular system of the heart).

The third mechanism is the occurrence of obstruction (due to pulmonary embolism, pneumothorax or cardiac tamponade).

The fourth mechanism is the loss of vascular tone that results in poor distribution of circulating blood (sepsis, anaphylaxis, spinal injury).

Insufficient/non-efficient oxygen delivery leads to anaerobic metabolism. Prolonged oxygen deficit induces reduction of high-energy phosphates, which leads to breakdown of cellular membrane depolarisation, intracellular oedema, loss of cellular integrity, and ultimately cellular death.

Oxygen delivery (DO_2) = CO x oxygen amount
$$DO_2 = CO \times [(1{,}3 \times Hgb \times SaO_2) + (0{,}003 \times PaO_2)]$$
CO = cardiac output; Hgb = haemoglobin concentration;
SaO_2 = oxygen saturation of peripheral blood

The usual reason for inappropriate oxygen delivery is low cardiac output. Inappropriate oxygen delivery causes the release of inflammation mediators. Further changes on micro-circulatory level additionally compromise cellular hypoperfusion and lead to multiorgan failure.

There are a number of shock classifications, however, none is complete. For the simplicity reasons, a common classification into four basic types is applied nowadays; cardiogenic, distributive, obstructive and hypovolemic shock. Cardiogenic shock is caused by cardiac function failure. Distribution shock is caused by the widening of vascular structures due to various reasons and consequent "reduction" of circulating fluid. Obstructive shock is the result of impediments to the circulation of the blood, for example; pulmonary embolism. Hypovolemic shock arises from the reduction of circulating volume, mostly due to exsanguination.

There are various causes of shock situations involving injuries, external and internal bleeding, various diseases and organ systems failure, allergies, etc. The forms of the above mentioned types of shock are often intertwined, so patients admitted for treatment of one form of shock can develop other forms. For example, the patient that was hospitalized due to hypovolemic or cardiogenic shock may occasionally develop septic shock.

15.2. Epidemiology

Approximately one third of patients admitted to the intensive care unit (ICU) are in a state of circulatory shock. According to recent studies the septic shock is one of the most common in the ICU admissions with approximately 62% of prevalence. Next are cardiogenic and hypovolemic shock with 17% to 16%. The mortality of septic shock is between 40-50%, however, in some studies, it reaches up to 80%. The mortality rate of cardiogenic shock is projected to be 59.4%.

15.3. Diagnosis and clinical presentation

Shock is diagnosed based on a combination of clinical, hemodynamic and biochemical signs.

1) Blood pressure is lowered (systolic pressure less than 95 mmHg or 40 mmHg of the value before deterioration), however hypotension is not always present.
2) Reduction of diuresis up to a standstill.
3) Progressive increase in anaerobic metabolism indicators (lactate) in arterial blood
4) Consciousness disorder: from anxiety, through lethargy to coma.
5) Cardiac arrhythmia: in the early stages of shock heart rate is rapid while in the final stages of shock, especially in the case of severe hypovolemic shock, heart rate is bradycardic. Other arrhythmias also often appear.
6) Peripheral cyanosis
7) Rapid breathing (tachypnea) with shortness of breath (tachydyspnoea)
8) Sweating: skin moist and cold

Table 15-1. Differentiation of various types of shock

Physiol. variable	Preload	Cardiac function	Afterload	Tissue perfusion
clin. measurement	PCWP	CO	SVR	Mixed venous sat./capillary filling
HYPOVOLEMIC	decrease	decrease	increase	decrease/3 sec>
CARDIOGENIC	decrease	decrease	increase	decrease/3 sec>
DISTRIBUTIVE	decr./same	increase	decrease	increase/<3 sec

PCWP – pulmonary wedge pressure; SVR – systemic vascular resistance; CO – cardiac output

Table 15-2. Severity of bleeding, estimate

	stage I	stage II	stage III	stage IV
% of blood loss	<15%	15-30%	30-40%	40%>
pulse/min	<100	100>	120>	140>
arterial pressure	normal	normal/orthostatic decrease more than 10%	decrease	decrease
diuresis	normal	decrease	marked decrease	marked decrease/stop
consciousness	anxious	agitated	confused	letargic

Recommended monitoring during shock:
- ECG
- arterial pressure (non-invasive, invasive if using vasopressors)
- CO
- SVR (systemic vascular resistance) – for cardiogenic shock
- PVR (pulmonary vascular resistance) – for cardiogenic shock
- mixed venous blood saturation – mandatory for cardiogenic shock
- PCWP (pulmonary wedge pressure) – for cardiogenic shock
- CVP (central venous pressure)
- respiration monitoring: speed and volume of breathing, et CO_2
- SaO_2
- body temperature
- diuresis, by hour
- consciousness
- peristalsis and gastrointestinal function
- lab monitoring, depending of etiology – blood gas analysis and ABS mandatory
- routine biochemical monitoring (coagulation, microbiological analysis, etc.)
- radiological and ultrasound diagnostics

15.4. Treatment

Treatment is based on solving the etiology of shock and supporting the organ systems. Treatment of shocked patients is usually maintained in ICU. The shock should be treated ASAP, no matter the etiology, because prolonged state of shock causes irreversible harmful changes to organism, which in the end lead to unsuccessful treatment.

Etiological treatment is of great importance in the treatment of shock. Therefore in the case of, for example, septic shock antibiotics and antifungals should be administered along with other treatment measures. Bleeding must be stopped in hypovolemic shock along with compensation of circulating volume. Causes must be addressed in cases of cardiogenic shock, most commonly acute myocardial infarction, myocarditis and heart failure caused by various diseases.

Hemodynamic support is based on compensation and maintenance of circulating blood volume and maintaining the cardiovascular function with vasoactive drugs and inotropes (drugs that press or expand blood vessels and improve contractility of the heart). However, a strict attention should be paid to fluid intake in cardiogenic shock.

In cardiogenic shock it's sometimes necessary to use intra-aortal balloon pump (IABP) as hemodynamic support, also the use of ECMO (extra-corporeal membraneous oxygenation) should be considered.

Indications for IABP are refractory hypotension, low CO syndrome, detrimental heart function with hemodynamic instability, large area of infarction prior to coronarography.

Contraindications for IABP are aortic regurgitation, aneurysm or dissection of aorta, uncontrolled sepsis, uncontrolled coagulation disorder, severe bilateral vascular disease.

Indications for ECMO are failure of heart, lung or both organs at the same time, whose function can't be improved by any other means of treatment.

Crystalloid solutions are most frequently administered, then the colloids and blood derivatives. It should be noted that all drugs used in resuscitation also are applicable during the shock states.

Table 15-3. Treatment of hemodynamic disorders

arterial pressure	PCWP	CO	SVR	Treatment
decrease	decrease	decrease	decrease	volume
normal	increase	normal	increase	venodilator, diuretic
decrease	increase	decrease	increase	inotrope
increase	increase	decrease	increase	vasodilator
unchanged	increase	decrease	increase	inotrope, vasodilator
decrease	normal	normal	decrease	⬚ blocker

Respiratory support: Delivery of oxygen is decreased in these patients, so the oxygen must be administered in high flow through a mask or nasal cannula. The goal is to reduce oxygen consumption by lowering body temperature and (possible) anxiety. However, if satisfactory needs of ventilation are not met or breathing is increased in frequency, it is necessary to use machine-controlled ventilation using special devices (respirators) with different modes of ventilation, from controlled to assisted.

Other measures of treatment are based on the maintenance of homeostasis of the organism using different drugs and procedures. This includes measures to prevent various complications and control of metabolic status and hydration. Kidney insufficiency is common occurrence, so renal support treatment is often used. In septic shock special filters are used, which remove inflammation mediators. Surgical complications may also occur during shock. Compensatory treatment of amino-acids and other nutrition agents is mandatory (either enteral, or parenteral), however care needs to be taken when implementing enteral diet. In case of worsening of patient's condition (for example, need for vasopressor dosage increase), enteral diet should be discontinued, however that depends of specialist's estimation.

15.5. Anaphylactic shock (see also Chapter 16!)

This is the most severe form of acute allergic reactions. It most frequently occurs very quickly, within a few minutes after exposure to an allergen, but it can also be delayed for several hours. It is caused by different drugs or medical devices (radiological contrasts, latex). However it can be caused by food, different insects and solutions used in the household. Mortality remains high even with measures of treatment and according to some data reaches up to 5%.

15.5.1. Clinical presentation

Cardiocirculatory system: hypotension and tachycardia.

Skin manifestations (including mucosal): urticaria, generalized oedema, localized Quincke's oedema, itch.

Respiratory system: laryngospasm, bronchospasm, difficult and rapid breathing

Gastrointestinal system: vomiting, diarrhoea

Nervous system: disorder and loss of consciousness

It is important to emphasize that the clinical presentation does not have to develop fully and that sometimes it is difficult to assess in the early stages whether the symptoms are caused by an allergic reaction or other events.

Differential diagnosis it could be vasovagal syncope, acute bronchospasm, airway obstruction with foreign body, pneumotorax, acute pulmonary oedema, pulmonary embolism, medication poisoning, heart infarction, or heart arrhythmia.

Anaphylactoid reaction manifests by severe reaction very similar to allergic reaction, but without definite proof of immune system involvement. Clinically it manifests identically to anaphylaxis, however the presence of IgE antibodies can't detected like in anaphylactic shock.

15.5.2. Treatment

1) Ensure patency of the airway (chin lift, deflection of the head - head tilt, oropharyngeal, endotracheal tube)
2) Adrenaline 0.5-1 mL i.m. or in severe cases 0.2 mL i.v. (not recommended for those who have no experience in the intravenous administration of these types of drugs) repeated if necessary every 10-15 minutes
3) Oxygen at high concentration
4) Administration of fluids, usually with crystalloid solution.
5) Antihistaminic drugs
6) Aminophilin if there is bronchospasm
7) Corticosteroids (however, they act with a delay)
8) Support of the cardiocirculatory system; vasoactive drugs, if necessary, inotropes.

16. ANAPHYLAXIS AND ANAPHYLACTIC SHOCK

Božena Ivančev**, Mladen Carev*

16.1. Introduction

Anaphylaxis is a medical emergency. Knowing the accurate definition and pathophysiology of anaphylaxis is not as important as its emergency treatment.

Therefore, it's very important to recognize anaphylaxis and to prepare adequately. Today, it's recommended for all medical practice to have written protocol for anaphylaxis emergency as well as all needed drugs available.

16.2. Definition

Anaphylaxis is a severe, potentially life-threatening, generalized or systemic hypersensitive reaction characterized by fast developing symptoms including:
- **Airway** - throat and tongue swelling
- **Breathing** - shortness of breath, bronchospasm, hypoxia, loss of consciousness, respiratory arrest
- **Circulation** – hypotension, tachycardia, loss of consciousness, cardiac arrest

These are usually associated with skin and mucous membrane changes after exposure to allergens.

The simplest definition would be: anaphylaxis is a serious allergic reaction that is rapid in onset and may cause death.

Anaphylactic shock is a type of distributive shock caused by allergic reaction, characterized with serious systemic vasodilatation and a capillary leakage, but also includes direct myocardial depression.

16.3. Pathophysiology

Anaphylaxis occurs in an individual after exposure to an antigen to which that person has produced a specific IgE antibody. The antigen to which the person produces the IgE antibody response that leads to an allergic reaction is called the allergen. The IgE antibodies produced may recognize various epitopes of the allergen. These IgE antibodies then bind to the high-affinity IgE receptor on the surface of mast cells and basophiles. Upon re-exposure to the sensitized allergen, the allergen may cross-link the mast cell or basophile surface-bound allergen-specific IgE resulting in cellular degranulation as well as de novo synthesis of mediators. Histamine is thought to be the primary mediator of anaphylactic shock. Many of the signs and symptoms of anaphylaxis are attributable to binding of histamine to its receptors; binding to H1 receptors mediates itching (pruritus), rhinorrhea, tachycardia, and bronchospasm. On the other hand, both H1 and H2 receptors participate in producing headache, flushing, and hypotension.

Anaphylaxis is typically triggered by drugs (β-lactam antibiotics, insulin, streptokinase, allergen extracts), foods (nuts, eggs, seafood), proteins (tetanus antitoxin, blood transfusions), animal venoms and latex. On the other hand, there are anaphylactoid reactions defined as those reactions that produce the same clinical picture with anaphylaxis but are not IgE mediated, characterized by symptoms of histamine release.

The most frequent allergens in anaphylaxis are:
- medications
- intravenous radiocontrast media
- blood products
- insect bites and stings
- food

Alimentary allergens are the most often cause of anaphylaxis in childhood, as opposed to adults where medications (especially muscle relaxants, antibiotics and NSAIDs) are frequently causes of anaphylactic reaction.

16.4. Prognosis

According to literature, the mortality in anaphylaxis is <1%. An average onset of symptoms is 30-35 minutes after food intake and 10-15 minutes after insect bite or sting. The fastest onset is after intravenous administration of allergen - up to 5 minutes. Death never occurred if more than 6 hours elapsed after exposure to allergen.

16.5. Clinical symptoms

As in other conditions and diseases, here it is also recommended to follow ABCDE protocol (A - airway, B - breathing, C- circulation, D - disability, E - exposition).

Airway - swelling of the throat and tongue, wheezing, stridor. Stridor is an abnormal, high-pitched, musical breathing sound. It is caused by a blockage in the throat or voice box (larynx) in inspiration. Bronchospasm, confusion caused by hypoxia and respiratory arrest are serious respiratory symptoms of anaphylaxis.

Circulation – hypotension, pale and cold skin, tachycardia. The most serious cases (anaphylactic shock) are manifested by loss of consciousness, ischemic changes in ECG and heart arrest.

Glasgow Coma Score is used to determine the state of consciousness.

In patient with anaphylaxis urticaria, rashes and angioedema are common findings. Sometimes neurological (tinnitus) and gastrointestinal symptoms are expressed (vomiting, diarrhea).

16.6. Diagnosis

According to the WHO guidelines anaphylaxis is probable if <u>any of 3 criteria</u> are satisfied:

1) Rapid onset of symptoms (minutes to hours) with cutaneous and mucose membranes changes (generalized urticaria, rush, flushing, lip, tongue and uvula edema) + <u>at least one of 2 following</u> symptoms: a) rapid onset of respiratory symptoms (cough, dyspnea, stridor, hypoxemia), b) rapid onset of hypotension or organ dysfunction (syncope, incontinence)

   or

2) <u>2 or more following symptoms</u>, which develop fast after exposure to allergen:
   a) Sudden respiratory symptoms (dyspnea, cough, stridor, hypoxemia)
   b) Sudden hypotension or organ dysfunction (syncope, incontinence)
   c) Sudden abdominal symptoms (pain, vomiting)

   or

3) Decrease of arterial pressure after exposure to known allergen to the individual patient (in adults decrease of systolic pressure <90mmHg or decrease of 30% of basal values).

16.7. Treatment

The most important step is stopping the cause of anaphylaxis e.g. the contact with allergen. Assessment of airway, breathing, circulation and skin changes is necessary. The patient position has to be comfortable and efficient - sitting position for respiratory symptoms, Trendelenburg position for circulatory symptoms (head down, legs up).

Epinephrine (adrenaline) is the primary treatment for anaphylaxis with no absolute contraindication to its use. According to European Resuscitation Council (ERC) guidelines epinephrine is given intramusculary 0.5mg (in children 6-12 yrs 0.3mg, <6 yrs 0.15 mg). The additional dose can be given after 5-15 minutes. Subcutaneous and inhalational administration of epinephrine is no longer recommended. Intravenous administration of epinephrine is the most efficient, but it is mostly used by anesthesiologists or other educated professionals with experience. In adults 50μg boluses and 1μg/kg in children are recommended. In some cases continuous epinephrine infusion may be considered. Patients on β-blockers may be resistant to the effects of epinephrine. In this situation if epinephrine is not effective intravenous glucagon can be administered.

Supplemental oxygen via face mask and large intravenous access are mandatory.

It is recommended that in adults 1-2 liters of crystalloids are administered (in children 10 mL/kg for 5-10 minutes). There is no evidence to support colloid or crystalloid resuscitation in anaphylaxis. However, it should be counted that the colloid alone can also be a frequent cause of anaphylaxis, especially if the patient is just receiving it. If iv. access is difficult or impossible, intraosseous route of administration of drugs should be considered.

There are numerous possibly useful, although second-line drugs in anaphylaxis. Antihistamines (both H1 and H2) while commonly used and assumed effective based on theoretical reasoning, are poorly supported by evidence. Antihistamines H1 oppose vasodilation and bronchoconstriction mediated by histamine. On the other hand, there is very little evidence to support routine use of H2-antihistamines (eg. ranitidine) in the initial treatment of anaphylaxis. Corticosteroids are also used in the treatment, for example hydrocortisone 200mg iv. (children 6-12-yrs 100mg; 6mo-6yrs 50mg; <6mo 25mg). To note is that

steroids are effective, but act with a certain latency. Their prophylactic effectiveness in these situations is uncertain. Nebulized salbutamol and ipratropium may be effective for bronchospasm that does not resolve with epinephrine. Aminophyllin iv. can be used in bronchospasm. Norepinephrine is applied in the most serious cases of vasodilatation.

16.8. Prevention of allergic reactions

Prevention of allergic reactions (premedication) is usually performed before application of iodine radiocontrast media in patients with a history of a significant prior contrast reaction.

Prevention includes:

a) Premedication. Adults, standard procedure
- Prednisone 50mg per os
  - 13,7 and 1 hour before procedure
- chloropyramine 20mg (Synopen) -1hour before procedure
  - ev. ranitidine

b) Premedication. Adults who can't take medications by mouth
- Hydrocortisone iv. 200mg
  - 13,7 and 1 hour before intervention +
- Antihistamines

c) Premedication –adults, emergency intervention
- Hydrocortisone 200mg 4 hours before

d) Premedication- children
- Prednisone 0,7mg/kg (max 50mg) per os
  - 13,7 and 1 hour before +
- Dimidril (Diphenhydramine)
  - 1mg/kg iv/per os (max 50mg) 1 hour before

16.9. Anti-shock therapy medications

It is inevitable to have on hospital wards, operating theatres, and general practitioner offices all necessary medications in case of anaphylaxis. This anti-shock therapy set includes:

1) Epinephrine – the first choice (ampoules 1 mg/mL)
2) Antihistamines (chloropyramine, ranitidine)
3) Corticosteroids (methylprednisolone, hydrocortisone)
4) Aminophyllin (ampoules 250 mg/10 mL)
5) Atropine (ampoules 0.5 or 1 mg)
6) Normal saline or Ringer solution
7) Oxygen
8) Other:
   - Norepinephrine
   - Dopamine
   - Dobutamine

Accompanied by medications, necessary equipment has to be obtained:
   - pressure gauge, stethoscope
   - pulse oxymeter
   - oxygen catheter
   - equipment for mechanical ventilation (face mask, Ambu)
   - equipment for endotracheal intubation
   - Intravenous cannula (different sizes), infusion systems

17. POISONING

Nenad Karanović*, Igor Vuković**

17.1. Introduction and epidemiology

Acute poisoning is one of the major reasons for hospital admission. It is estimated that the different intoxications are the reason for intervention in emergency receptions in 5-10% of cases. 12 million agents are now known to lead to poisoning.

The intoxication can be intentional or accidental. According to data from the US there are 2,168.248 poisoning cases reported annually. Adults account for one third of the cases. About 71% were accidental poisonings and in 92% of the events the intoxication was caused by a single agent. Oral intake was present in the majority of cases. According to British intentional poisoning in adults data, most of the cases younger than 35 are of female gender, of otherwise good health and in who attempt to intake harmful substance in order to make a "call for help" and they usually want to be found. In contrast, in the group of adults older than 55 years, male persons are most often represented, who attempt to poison themselves due to depression or untreatable diseases.

According to some research intrahospital general mortality at various poisoning cases is around 0.5%.

Substances that cause the greatest number of death cases were analgesics, antidepressants, sedatives / hypnotics / antipsychotics, then different stimulants, "street drugs", medicines for the treatment of cardiovascular disorders and alcohol. In developed countries means that very often cause poisoning are paracetamol, benzodiazepines, antidepressants and NSAIDs, while in developing countries the most common cause of poisoning are pesticides.

Iatrogenic caused intoxications caused by errors in the instructions or unrecognized drug interactions recently become a significant problem, and according to some estimates amount to about 1% of cases.

A very important issue that has an impact on the treatment of poisoned patients is related to the current recommendations for the treatment of such cases. One should be aware that all information are obtained on the basis of very limited studies conducted on animals, people, the individual case reports and on the pharmacokinetics of drugs, known pathophysiology and usually on agreed conclusions.

Studies on animals and healthy volunteers can not be adequately extrapolated to the clinical situation, therefore, therapeutic guidelines only suggest appropriate actions, but do not have to be supported by final evidence.

Furthermore, we should not forget that the operating instructions supplied with the different drugs or agents used in households are most often outdated and do not provide sufficient information. The same goes for textbooks, especially the older ones. It is therefore recommended to consult the relevant sites on the internet such as Toxbase (http://www.spib.axl.co.uk) or Isabel (http://www.isabel.org.uk) or to consult the Poisoning Control Center at the Institute for medical Research and Occupational Health, Zagreb, Ksaverska 2. Information is available 24 hours a day on the emergency phone 01 234 83 42.

17.2. General guidelines for the treatment of poisoned before hospital admission

It is necessary to quickly and systematically examine the intoxicated patient. The assessment is carried out with the help of mnemotechnic principle ABCD. Assessment is repeated at certain intervals as significant changes in the conditions of a poisoned patient can quickly develop.

Emergency measures- ABC reanimation measures:

- Assess and ensure adequate airway and enable or improve ventilation.
- Stabilize the cardiovascular system. Various toxins cause vasodilation, hypotension and arrhythmia.
- Pay attention to the potential seizures and treat them.

The objectives of hospital treatment after emergency resuscitation measures and stabilization of the condition are:

- To prevent further absorption,
- Speed up elimination,
- Administer antidote, if it exists,
- Organ systems support

After the primary treatment and assessment of the poisoned patient, a decision on admission is made. A fraction of the poisoned patients does not need admission to hospital, but only an observation lasting for several hours, while a smaller part will have to be admitted to an intensive care unit.

Table 17-1. Emergency measures immediately upon hospital admission

Airway assessment	Breathing sufficiency (fast, slow, shallow, deep, stridorous etc.) and oxygenation estimation with the help of pulse oximetry monitoring and GCS
	Oxygen insufflation
	Securing the airway
	Intubation if necessary, especially if GCS ☐ 8 (does not completely exclude the possibility of aspiration) and mechanical ventilation
	Pulmonary hygiene (including bronchoscopic)
Hemodynamic status asse-ssment	Monitoring: EKG, BP, CVP
	Reanimation procedure if needed
	Hypotension – isotonic solutions, antidotes, careful use of vasopressive drugs
	Dose titration
	Arrhyithmia – Primarily treat precipitating factors (acidosis, hypokalemia, hypomagnesemia, hypoxia). Antiarrhythmic drugs are prone to provoke arrhythmias themselves
	Specific measures recommended: digoxin specific AT, cardiac electrostimulation
State of consciousness asse-ssment and neur ologic status	Verbal response, external stimuli response, GCS, photoreaction and pupillary diameter, presence/absence of reflexes, con-vulsions, epileptic seizures, agitation, hypoglycemia
	If necessary, administer: 50% glucose solution iv (25-50 g), Tiamin 100 mg iv, Naloxone 0,4-2 mg iv, im, Flumazenil iv
	Benzodiazepine if convulsions are present
Initial clinical assessment	Clinical interview: Type and quantity of substance, time and duration of poisoning, possible abuse of some other substan-ces, background (self-destruction or homicide)
	Physical examination: Complete examination (head trauma is frequent complication of poisonings), vital signs (including temperature), neurological status, response to early resuscitation measures
Radiological diagnostics	Chest Rtg (possible aspiration prior to hospital admission)
	Brain CT is routine at comatose patients, MRI if needed
	Further diagnostics if needed
Laboratory analyses	Depending on initial examination, follow up with blood tests, glucose, electrolytes, renal and liver test, CL, carboxyhemo-globin, methaemoglobin, acid-base status with blood gas analysis, plasma osmolarity
	Urine – complete analysis
	Toxicological analyses, blood, urine, gastric content if needed
	Further examination if needed (cholinesterase, thyroid hormone levels, coagulogram…)
	Remark: some authors suggest routine plasma paracetamol concentration analysis
Skin, eye and GI decontamination (if no contraindications are present)	Skin washing with non-abrasive soap and water. Drop clothes into special containers
	Eye decontamination: water or saline irrigation
	Gastric lavage: perform within one hour from ingestion (depending on state of consciousness). Ipekakua syrup is obsolete
	Poison absorption: *carbo medicinalis* 1g/kg initially, then 0,5 – 1 g / 4g or continuously via NG probe > 12,5 g/ h
	Intestinal passage acceleration: cathartics (dubious), complete intestinal irrigation (not routinely used)

17.3. Diagnosis of poisoning cases

History and physical examination: Because the medical history data obtained from the poisoned per-son is often insufficient or not credible, it is always prudent to approach the family members or friends.

17.4. Antidotes

Antidotes are substances which increase the mean lethal dose of toxin or have a favorable impact on the toxic effects. Unfortunately, they are available only for a limited number of drugs and poisons. They can be administered at any time of treatment if it is deemed that the effects of poisonous agents are sti-ll present. Some are used in continuous infusion or in successive boluses. Table 17-2 shows antidotes for some poisonous substances or drugs.

17.5. Specific intoxications

Since poisonings with different toxins surpass the boundaries of this text, we will focus on the most important and most frequent. Some means of addiction and abuse from narco-millieur are specially men-

Table 17-2. Antidotes for some toxic substances

The drug / poison	Antidote
Acetaminophen	N-acetylcysteine
anticholinergics	physostigmine
Anticholinesterase agents	Atropine
Arsenic	dimercaprol (BAL)
Copper	D-penicillamine, N-acetyl cysteine
Benzodiazepines	Flumazenil
⬜ - blockers	atropine, glucagon
Carbon monoxide	Oxygen (including hyperbaric)
Cyanides	Amyl nitrite, sodium nitrite, sodium thiosulfate, hydroxicobalamin
Digoxin	Digoxin specific antibody
Ethylene glycol (antifreeze)	Ethanol / Fomepizole, thiamine, pyridoxine
Heavy metals (arsenic, copper,gold, lead, mercury)	dimercaprol (BAL), EDTA, penicillamine
Hypoglycemics	Dextrose, glucagon, octreotide
Iron	Deferraxomine, mesylate
isoniazid	Pyridoxine
Methanol	Ethanol or Fomepizole, folic acid
Opioids	Naloxone
Organophosphates	Atropine, pralidoxime

tioned, are the so-called recreational means or drugs and their symptomatology and treatment since abuse cases are in increase and their peak is still not apparent. Digoxin poisonings, β-blocker and calcium blocker poisonings are not mentioned since those recommendations are easily accessible in textbooks and manuals due to frequent use of those medicaments in everyday hospital and out-hospital use.

Paracetamol (acetaminophen) is the most frequent substance reported as the overdose or poisoning intoxication. Out of 110000 reported cases of overdose or intoxication with paracetamol in the US in year 2000, 580 patients had severe liver damage and 210 of them died. According to British data, acute liver failure occurs in 0,6% patients overdosed with paracetamol.

After oral intake paracetamol is quickly absorbed and reaches its peak plasma concentration in <1h. Paracetamol is primarily metabolized by liver, but its metabolism differentiates depending on age and blood concentration. Half-life within therapeutic range is 2-4 h. 95% of metabolites is nontoxic, but 5% consists of n-acetyl-p-benzokinomine (NAPQI), an especially toxic metabolite produced by cytochrome P-450 oxidase system.

Liver is the primary organ which manifests paracetamol intoxication, although other organs can be affected as well. Toxicity threshold which leads to liver damage is 150 mg/kg BM in adults, while in children it is somewhat higher, 200 mg/kg BM. However, even lower doses are able to cause severe damage in certain circumstances and patients at risk. Doses from 75 mg/kg are considered dangerous in these patients. Kidney damage is probable caused by the same mechanism as liver damage.

Clinical presentation: Paracetamol overdose consists of four stages. First stage is developed within 24 h and it presents with anorexia, nausea, vomiting, fatigue, paleness, diaphoresis, although it may be asymptomatic. Elevated levels of liver enzymes can be detected only 18h after ingestion. Second stage develops within 24-48 h after non-treated intoxication and it presents with pain situated in upper right stomach quadrant and with elevated liver enzymes, even if stage one symptoms fade away. If the clinical presentation progresses into stage three, 48-96 h after ingestion, encephalopathy, coagulopathy and hypoglycemia occur. Liver enzymes reach extremely high levels. Stage four takes place four days after the ingestion which will end with recovery, or in most severe cases, lethal outcome.

Consequences: Stage three – hemorrhagic pancreatitis, myocardial necrosis and acute kidney failure rarely occurs without fulminant liver failure. Stage four – patient may start to recover without any sequelae at all or he can die or be indicated for urgent liver transplant. Decrease in plasma lever enzyme concentrations can mark the onset of recovery or massive hepatocellular necrosis accompanied by increased prothrombin time, increased ammonium and bilirubin levels. If patient starts to recover, significant progress becomes visible between 5 and 7 days since ingestion.

Treatment: Gastric lavage is mandatory within 60 minutes since ingestion. Active *carbo medicinalis* is administered mandatory. It interferes with peroral N- acetylcysteine (NAC) only in a small portion, so the dosage does not need corrections. Paracetamol concentration in blood is determined four hours after ingestions, and compared usually with two types of nomogram: Rumack – Matthew or Prescott's. These nomograms allow for more convenient estimation of need for N- acetylcysteine. If indicated, it is applied perorally (it can iduce vomiting) at dose of 140 mg/kg BM, and then continued with 70 mg/kg BM every four hours for 72 h, so that complete dose does not surpass 1330 mg/ kg BM. N- acetylcysteine is perorally administered by diluting the 10% or 20% solution with juice to produce a 5% solution. If nausea interferes with intake, metoclopramide or ondansetron can be used. Intravenous N-acetylcysteine is preferred. It starts with dose of 150 mg/kg BM in 200 mL of 5% glucose within 15 min. It is continued at 50 mg/kg in 500 mL for the next four hours, and after that 100 mg/kg in 1000 mL of 5% glucose through 16 hours. The whole dosage should not surpass 300 mg/kg BM under 20 h 15 min.

However, Rumack-Matthew nomogram has its limitations and imprecisions. Bond and Lite reported that this nomogram cannot be used in almost 50% of paracetamol intoxication cases, and even in higher percentage in those with bad outcome. Therefore routine N-acetylcysteine at all at-risk patients (alcoholics, fatigued, malnourished, bulimic, older, HIV-positive, patients that use drugs with enzyme induction; karbamazepine, phenobarbital, phenytoine, rifampicin, alcohol or those suffering from cystic fibrosis), even if paracetamol levels in blood are within non-toxic range. Also, use at all patients with signs of hepatotoxicity is suggested, as in those patients at whom it is not possible to determine the concentration of paracetamol in plasma.

In case that anaphylactoid reactions occur (5-15%), which are short-termed and dose-dependent with the most frequent onset of within 15 min of administration, it is recommended to stop the infusion through 30 min. Antihistamine drugs can be given if needed. Methionin is an oral antidote which is used in cases of severe allergy on NAC, but it has significant drawbacks.

Liver transplant is one way to treat severe, futile cases of paracetamol intoxication.

Prognosis: NAC application within 8 h from ingestion most often leads to favorable outcome. Treatment or admission delay, stage three or four with encephalopathy, elongated prothrombin time, acidosis, kidney failure, brain edema and sepsis announce possible bad outcome.

Salicylates: Intoxication with these drugs is less present then 20 years ago. After ingestion, acetylsalicylate acid is quickly converted into salicylate acid by hydrolysis, and then into salicyluric acid and salicyl glucuronid phenol. It is rapidly absorbed from stomach and intestine and metabolized in liver and eliminated within 2-3 hours. Therapeutic plasma levels are 100-300 mg/L. Chronic ingestion may elongate half-life to <20 h. Clinical signs of intoxication present in most people at serum levels >400 mg/L. At this point salicylates become metabolic toxin affecting numerous organs and systems by disrupting the oxidative phosphorylation and Krebs cycle. Salicylates cause respiratory alkalosis due to direct stimulation of respiratory center. However, disrupted oxidative phosphorylation causes metabolic acidosis, which then enhances the salicylate entry into CNS and decreases the salicylate renal elimination.

Clinical presentation: Mild intoxication or overdose occurs after 150 mg/kg BM. It presents with nausea, vomiting, tinnitus and deafness.

Moderate intoxication occurs after ingestion of >20 mg/kg BM and causes peripheral vasodilation, sweating, agitation, tachypnea and hyperpyrexia. Disordered thrombocyte function can result in petechial and subconjunctival hemorrhage.

Severe intoxication occurs at >300-500 mg/kg BM with onset of hypotension, severe metabolic acidosis, kidney failure, coma and convulsions. Lung edema, liver failure and hypoglycemia can also occur. Cardiac workload disorders, tachycardia, arrhythmia and asystole are possible. Plasma levels over 500 mg/kg BM are potentially lethal, although lower concentrations can also result with lethal outcome.

Treatment: Gastric lavage within 60 minutes from ingestion. Active *carbo medicinalis*, multidose regime, urine alkalization, hemodialysis and respiratory and cardiovascular support measures if needed.

Alcohols (ethylene glycol and methanol): Ethylene glycol and methanol poisonings are rare nowadays, but can result with significant morbidity and mortality.

Ethylene glycol and methanol are weak toxins, however their metabolites are significantly toxic.

Alcohol dehydrogenase metabolizes ethylene glycol into glycoaldehyde and glycol acid, and into glyoxal and oxal acid with further metabolism. Methanol is also metabolized by alcohol dehydrogenase into formaldehyde, which is then converted into formic acid by aldehyde dehydrogenase. Formic acid is primary toxin causing metabolic and eyesight disorders. Only 30 mL of methanol can cause severe mor-

bidity at adult person. Approximately 150-240 mL of 40% solution can be lethal. Ingestion of 100 mL of ethylene glycol can be lethal at adults.

Poisoning symptoms may be delayed if person simultaneously consumes ethanol.

Clinical presentation: Nausea, vomiting and abdominal pains are frequent. Eyesight disorders including blindness are frequent in cases of methanol poisoning. Hypotension, pulmonary edema, ataxia, CNS depression, convulsions and coma occur. Metabolic acidosis is significant. Hypoglycemia occurs.

Treatment: Aggressive support measures. Gastric lavage within an hour from ingestion. Active coal does not absorb alcohols, but can be useful if other types of poisonings are suspected. Maintain diuresis. Treatment is based on interfering with metabolism of these substances with alcohol dehydrogenase. Ethanol and fomepizole are used.

Ethanol can be given parenterally or perorally with target plasma concentration of about 1000-1500 mg/L.

Fomepizole is an alcohol dehydrogenase inhibitor which also prevents decomposition unto acid metabolites. It is more convenient than ethanol since it does not cause a CNS depression and does not need monitoring of its plasma concentration. However, high price is limiting factor. In cases when alcohols degrade into acids neither ethanol nor fomepizole are of any use. Hemodialysis may be necessary to eliminate alcohols themselves and toxic metabolites. It is indicated in cases of severe or refractory acidosis, eyesight disorders, kidney failure or pulmonary edema. It is indicated in cases of ethylene glycol poisonings at levels of >500 mg/; same value goes for methanol. Treatment is conducted until blood levels of both substances are decreased to <200 mg/L. Hemodialysis is conducted independently of fomepizole usage, if indicated.

Opioids: Acute opioid intoxication is, unfortunately, frequent cause of hospital admission.

Securing the adequate means of ventilation and oxygenation with antidote administration – naloxone is the most important aspect of treatment.

Clinical presentation: Narrow pupils, respiratory depression and consciousness disorders are typical signs. However, combination of opioids and stimulating substances (cocaine and heroin) or so called "Speedball" may alter clinical presentation.

Naloxone has a brief half-life, 30-100 min. It is recommended to use it In small successive doses of 100 mcg to evade withdrawal syndrome in addicts. In some cases it is necessary to give it in continuous infusion even longer than 72 h (methadone intoxication – half-life 24 h).

Amphetamine: Use of these toxins has increased during the last decade in Europe and USA. These substances are used to treat narcolepsy, attention disorders and for body mass control. Methamphetamine ("crank", "ice") and 3,4 methylendioxy-methamphetamine (MDMA, commonly known as "ecstasy") are among illegal substances.

Amphetamine toxicity presents as CNS stimulation, cathecholamines peripheral release or reuptake inhibition and monoamino oxidase inhibition, leading to increase of central and peripheral cathecholamine concentration. As a rule, the therapeutic index is low.

Clinical presentation:

CNS – confusion, tremor, anxiety, agitation, irritability, convulsions, hyperreflexia, hallucinations, acute psychosis.

CV – tachyarrhythmia, myocardial ischemia, hypertension

Other: mydriasis, hyperthermia

Complications: Rhabdomyalysis, kidney failure, coagulopathies, hyponatremia. Severe liver failure is reported after MDMA usage with need for transplant. Intracranial hemorrhage, CVI, necrotic vasculitis and lethal outcomes are also reported.

Treatment: Support measures. Gastric lavage has little value since toxin is already absorbed at time of hospital admission. Active coal has its place as treatment option. Hypertension is usually treated with vasodilators. Tachyarrhythmia are treated with esmolol or propranolol. Agitation, violent behavior and psychosis react well to butyrophenone drugs (haloperidol and DHBP), benzodiazepines and phenothiazines. Active cooling is indicated if rectal temperature is $> 40^0$ C. Fluid compensation and diuresis maintaining has significant role in prevention of possible rhabdomyalysis, especially at elevated levels of creatinine-kinase (CK).

Dialysis and hemoperfusion have no effect.

Phencyclidine: Also called "Angelic dust", it possesses various anticholinergic, opioid, dopaminergic, alpha-adrenergic and stimulating effects on CNS. It can be smoked, sniffed, taken perorally or by iv route. It is often combined with alcohol, marihuana or LSD.

Clinical presentation: Violent or bizarre behavior, agitation, altered state of consciousness in more than 50% of cases, from lethargy to coma. Nistagmus, hypertension, muscle rigidity, dystonic reactions, convulsion. Diaphoresis, hypersalivation and urine retention occur in smaller portion of cases. Respiratory and cardiac arrests are possible (0,3-2,8%). Cases of rhabdomyalysis, kidney failure, intracerebral and subarachnoid hemorrhage are reported. In all cases of unusual behavior and sympaticomimetic stimulation with narrow pupils, phencyclidine intoxication should be considered.

Treatment: Support therapy. Gastric lavage is usually unhelpful since toxin is already absorbed. Active coal has proven to be useful. Hemodialysis is not useful due to large distribution volume. Benzodiazepines are also used, especially in combination with haloperidol. Severe hypertension is treated with nitropruside or labetalol. Beta-blockers should not be used alone due to risk of uncontrolled alpha-stimulation and danger of intracranial bleeding.

Intoxication is proved by presence of toxin in urine.

Cocaine: Another addictive substance that can be used by sniffing, breathing or by iv route. Raw cocaine or "crack" is more potent ant absorbs faster.

Toxic effects of cocaine are caused by CNS stimulation and inhibition of neuronal catecholamine uptake. Cocaine half-life is about 60 min. However, its metabolites can be discovered in blood and urine even 24-46 h after use. It is often mixed with heroin ("speedball) and phencyclidine, and very often it is combined with ethanol. In presence of ethanol it is esterificated in liver into cocaethilen, a compound similar to cocaine, but more toxic and with longer duration of effects.

Clinical presentation: Onset and duration of symptoms depend upon the type of intake. Smoking and iv route cause symptoms within 1-2 min. When taken orally, symptoms occur within 20-30 min.

CNS: euphoria, anxiety, agitation, psychotic reactions, delirium, convulsions

CVS: vasospasm, heart attack, CVI, vasculitis, heart arrhythmia, heart failure, pulmonary edema, hypertension with cases of aortic dissection reported.

Cocaine-induced coronary syndrome: it occurs in 6% of patients with presternal pain. Diagnosing a heart attack caused by cocaine abuse may go with certain difficulties. Abnormal ECG occurs in 84% of cocaine users with presternal chest pain. Troponin is important for discovery of infarction.

Respiratory: bronchospasam, asthmatic status, pulmonary hypertension, alveolar hemorrhage, barotrauma. Inhalation of "crack" cocaine may cause acute pulmonary syndrome characterized by dyspnea, diffuse pulmonary infiltration and hemoptysis. Symptomatology ranges from mild respiratory distress to respiratory failure.

Other: Widened pupils, rhabdomyolysis (direct toxic effect on muscles), DIC, increased thrombocyte aggregation, hepatal and renal dysfunction, hyperthermia, intestinal ischemia.

Treatment: Reanimation if necessary. Altered mental status is treated with benzodiazepines or haloperidol. Convulsions are treated with benzodiazepines. Gastric lavage is not recommended due to possible convulsion induction, but the use of active coal is obligatory in case of peroral abuse of cocaine. Fast treatment of agitation and hyperthermia are of most importance.

Ischemic cardiac pain is controlled with nitroglycerin with sedatives. Alpha-adrenergic drugs and calcium channel blockers are second therapeutic line. Beta-blockers should not be used alone and are even contraindicated in some cases. Hypertension is treated with nitropruside or labetalol. Aspirin is advisable due to prevention of possible thrombocyte aggregation. Thrombolysis is performed in cases of myocardial infarction or if invasive reperfusion is unavailable. Maintain diuresis, especially in cases of rhabdomyolysis. Bronchodilator inhalation and corticosteroids in general beneficially affect the cocaine-induced bronchospasm.

Neither hemodialysis nor hemoperfusion can eliminate cocaine significantly.

Gama-hydroxybuthyrate (GHB): Also known as liquid ecstasy, G-liquid, fantasy and rape-drug becomes more popular means of abuse among youth population all the time. During the eighties this substance started as means to increase muscular mass and as growth hormone stimulator and it was declared illegal a decade later. GHB is derived from GABA and it is considered to act as inhibition transmitter through specific cerebral receptors, possibly even through GABA receptors. Constant use causes tolerance and addiction. Sudden cessation of use may cause withdrawal symptomatology, delirium and psychosis. This substance is often used combined with alcohol and amphetamines.

Clinical presentation: Low doses cause euphoria. Nausea, vomiting, hypothermia, bradycardia, hypotension and respiratory acidosis occur at high doses. Even higher doses lead to coma and potential lethal outcome.

Treatment: Mostly supportive. Consider the possibility of poisoning or a different substance abuse. Comatose patients most often return to consciousness within several hours. Several case reports of physostigmine use to treat comatose patients are published. However, this way of treatment is controversial, since consciousness returns all the same with support therapy. A risk of asystole and convulsions exist when administering physostigmine if GHB is combined with cyclic antidepressants.

Toxicological proving of GHB is difficult. Only specialized laboratories are able to detect this substance in blood or urine. It can also be detected by hair analysis.

Selective serotonin reuptake inhibitors (SSRI): Usage of these antidepressants is in gradual increase because they are significantly less toxic than tricyclic antidepressants and MAO inhibitors. However, the combination of these drugs with MAO inhibitors, tricyclic antidepressants with serotomimetic effects or MDMA can result in serotonin syndrome and death. Pathophysiological mechanism is probably caused by activation of 1A serotonin receptors in brain stem and medulla oblongata.

Serotonin syndrome: Altered mental state – agitation, confusion, coma. Autonomic instability – diaphoresis, hyperpyrexia, tachycardia, hypertension. Neuromuscular dysfunction – myoclonus, hyperreflexion, muscle rigidity, tremor. Rhabdomyolysis and DIC can occur in severe cases. Hyponatremia and syndrome of inappropriate antidiuretic hormone can also develop.

Clinical presentation: Most frequently nausea, vomiting, unconsciousness, diarrhea. However, coma, hypotension and convulsion can also appear.

Treatment: Supportive measures. Gastric lavage is most often meaningless due to time lost (over one hour). Active coal is indicated. Dialysis and hemoperfusioon are uneffective. There are anectodal reports about successful use of serotonin antagonists (cyproheptadine, chlorpromazine, diphenhydramine and benzodiazepines) used in intoxication cases. Cooling measures are recommended in hyperpyretic patients.

Tricyclic antidepressants (TCA): Tricyclic antidepressant intoxication is relatively common in developed countries. Ingestion of >10 mg/kg BM causes a severe intoxication while doses of 20-30 mg/kg are considered potentially lethal. Symptoms most often appear within one hour after ingestion, and they cease within 24-48 hours. Mortality cause is most often cardiological, and is developed within 24 h. Anticholinergic effects and inhibition of neuronal reuptake norepinephrine and/or serotonin are cause CNS manifestations. CVS manifestations are caused by anticholinergic effects, peripheral alpha-adrenergic blockade and blockade of sodium-dependent channels on cardiac cellular membranes which induces abnormal conduction of impulses through the heart. Alpha-receptor blockade worsens cardiac function due to hypotension.

Clinical presentation:

Anticholinergic effects – mydriasis with weak photoreaction, tachycardia, dry and hot skin, sedation, increased reflexes – myoclonus, delirium, lethargy, ileus, urine retention.

CVS effects: sinus tachycardia with extended QRS complex, QTc and PR interval. It is sometimes difficult to differentiate sinus tachycardia from ventricular. Appearance of different degrees of AV blocks is usual. Right branch block is frequent. QRS elongation of >100 ms is often paired with convulsions, while elongation of >160 ms is conjoined with appearance of malignant arrhythmia. Heart failure and pulmonary edema can occur.

CNS effects: convulsions

Treatment: Gastric lavage is recommended (within 2 hours of ingestion) and one-time giving of active coal also. Support measures are most important. Sodium bicarbonate is drug of choice for cardiac dysfunction. It is recommended to patients with arrhythmia, QRS extension of >120 ms or hypotension, but without acidosis. In cases of severe CVS instability inotropic and vasopressive drugs may be indicated, but they should be given with extreme care, only after reaching pH 7,5-7,55. All antiarrhythmic drugs should be avoided, except lidocaine which is a drug of choice in indicated cases. AV block refractory to bicarbonate should be treated with temporary electrostimulation (pacemaker). Besides lidocaine, ventricular tachyarrhythmia can be treated with cardioversion or electrostimulation.

Convulsions are treated with sedatives and barbiturates (benzodiazepines, phenobarbiton). Bicarbonates can be administered to further prevent the possibility of transfer of TCA into CNS. According to

some authors it is recommended to reach arterial blood pH range 7,5-7,55. Monoclone antibody therapy is in research.

Physostigmine is not recommended due to possible occurrence of convulsions and arrhythmia.

Discharge from ICU is allowed only after cessation of arrhythmia and normalization of ECG and normalization of acidosis in arterial blood, and minimally 12 hours after cessation of all means of treatment.

Carbon monoxide: This toxin is frequent cause of poisoning both here and abroad. Due to its affinity to hemoglobin (240 times than that of oxygen) it results in decrease of hemoglobin oxygen saturation, causing a cellular hypoxia by blockade of cytochrome oxidase. The gas is without color, smell and taste.

Clinical presentation: Depends od concentration, time of expore and minute ventilation. Concentrations up to 5% are generally well tolerated. Slight exposure (carboxyhemoglobin 5-10%) results with headache and mild dyspnea. Carboxyhemoglobin concentration 10-30% causes headache, vertigo, unconsciousness, weakness, dyspnea, irritability, nausea and vomiting so it is often misinterpreted as commond cold or food poisoning. Patients with coronary artery disease have risk of cardiac ischemia and myocardial infarction at these concentrations. Concentrations of >50% result in coma, convulsions, CV collapse and death. However, it should be stressed out that carboxyhemoglobin concentrations do not always correlate with severity of clinical presentation.

Late consequences: 10-30% of those survived have so called delayed neuropsychiatric sequelae (DNS). They occur 3-240 days after intoxication. Symptomatology includes permanent vegetative state, parkinsonism, short-term memory loss, behavioral changes, deafness, incontinence and psychosis. For now there is no way to predict these phenomena. 50-75% of these patients recovers completely within one year.

Diagnostics: Carboxyhemoglobin is determined by cooximetry. Pulse oximetry is unable to resolute carboxi- from oxihemoglobin, and may report normal values when patient is severely intoxicated. In smokers and residents of urban polluted environments 10% values may be found. Furthermore, low carboxyhemoglobin values do not need to reflect previous exposition. ACB status, ECG monitoring and antero-posterior (a-p) x-ray are useful. Metabolic acidosis marks a severe cellular hypoxia.

Treatment: 100% high flow oxygen should be given as soon as possible. It shortens the carboxyhemoglobin half-life from 5-6 h to 40-90 min. If possible (Zagreb, Osijek, Pula, Split) hyperbaric oxygen (2,8 atm) is treatment of choice within 6 h of exposition and it further reduces the carboxyhemoglobin half-life to 15-30 min. Newer data point out the fact that hyperbaric oxygenation lower the occurrence of cognitive deficits after intoxication and DNS also.

Organophosphates/carbamates and nerve agent chemical weapons: Most insecticides are organophosphates and carbamates by chemical structure. Their use is in increase due to fast decomposition. Both types of compounds demonstrate toxicity through inhibition of acetylcholinesterase. However, organophosphates are irreversible while carbamates are reversible inhibitors. Most intoxications occur due to peroral use, however absorption can also happen through skin, conjunctives and respiratory system.

Intoxication systems occur within 12-24 h of toxin exposure.

Clinical presentation: Symptoms may be nonspecific, but most frequently include weakness, disordered, blurred vision, nausea, vomiting, vertigo, stomach pain. Occuring signs are myosis in 85% of cases, salivation (>50%), respiratory distress (48% - bronchospasm, bronchorrhea, insufficiency), altered mental state (42%) and muscle fasciculation (40%) which can progress into pareses or paralyses (nicotine stimulation). Bradycardia occurs, but rarely also tachycardia. Onion-like odor in breath or sweat of poisoned patients can frequently be spotted. Organophosphates may pass the blood-brain barrier and cause stimulation of central receptors including aniety, confusion, convulsions, psychosis and ataxia.

Diagnosis: Based on clinical presentation and most often on determining the pseudocholinesterase activity in blood. Pseudocholinesterase levels can be falsely low in genetic disorders, liver disease, anemia or malnutrition. Acetylcholinesterase is therefore better to estimate poisoning, however it is located in erythrocytes and neuron endings and is determined with more difficulty. It should be pointed out that acetylcholinesterase concentration does not correlate with clinical symptomatology, so diagnosis is based on the grounds of clinical presentation and medical history data.

Treatment: Secure airway and ventilate adequately, skin decontamination, active coal. Intravenous administration of atropine or glycopyrrolate has no centreal effects (glycopyrrolate does not cross the blood-brain barrier). Atropine is given in dose of >40 mg/day for extended period of time. After initial 2-6 mg iv bolus dose iv it is given every 15 min in further 2 mg boluses until atropinization effects occur, after which it is recommended to use in continuous infusion of 0.05 mg/kg/h. CNS toxicity is possible. Atropine blocks muscarinic but not nicotine stimulation. To block nicotine stimulation, primary muscle weakness, pralidoxime is used, initialy 30 mg/kg iv through 15 min, than 8 mg/kg/h iv until muscle wea-

kness improves. Benzodiazepines are used to treat convulsions. Pralidoxime is often unnecessary in carbamate poisonings.

Prognosis: Intoxicated patient demands 5-14 days of intensive care, depending on toxin. Mechanical ventilation is needed in 60-70% cases, and mortality rate is 15-36%. Delayed neuropathies occur 1-3 weeks after exposure, and recovery is variable. The emergence of so called intermediary syndrome is possible 24-96 h after cholinergic crisis; respiratory insufficiency with muscular weakness and weakened reflexes are developed. Treatment is primary supportive, and recovery occurs in 1-3 weeks.

Notion: Some of the most potent nerve agent weapons are classified as organophosphates. Sarin and VH toxins are among them, and may be used with unforeseen consequences in potential terrorist attacks.

Corrosive agents: acids and bases: Corrosive agent injuries and poisonings are relatively frequent. They are most often caused accidentaly, but in psychiatric patients even intentionally in suicide attempts.

Alkali ingestion causes tissue liquefaction necrosis (saponification of fats and solubilization of proteins). Injuries caused by acids occur due to coagulation necrosis.

Besides esophagus, stomach and intestines can also be affected and perforations and bleedings also appear.

Ingested quantity, concentration and agent pH are important for severity of injuries. Severe injuries are possible if pH is <2 or >12,5.

Clinical presentation: Besides laboratory analysis of blood and urine, a-p x-ray p/s and native abdomen are obligatory. CT if needed.

Procedures: Esophagoscopy within 24 h of ingestion.

Treatment: As a rule, diluents are not given due to possibility of vomiting and repeated exposure to corrosive agent, however, they may be considered during ingestion of solid alkali to prevent adhesion to oral or esophageal wall. Water and milk in small quantities are used. NG probe placement may be useful during large quantity ingestions, especially with acids. However, the possibility of further injuries needs to be evaluated, even with the fact that iatrogenic esophageal perforation is very rare. It is useful to consult otorhinolaryngologist and gastroenterologist. Under no circumstances should acids be neutralized with bases and vice versa due to further injury due to heat generated by chemical reaction.

Generally, support measures, volume compensation and analgetics are used.

Complications: Airway edema or obstruction can appear immediately or within 48 h of ingestion. Gastroesophageal perforation may develop promptly. Secondary complications include mediastinitis, pericarditis, pleuritis, tracheoesophageal fistulae, esophageal-aortic fistula and peritonitis. Delayed perforation can occur even 4 days after ingestion. Strictures appear in more than 70% of patients within 2-4 weeks. GI hemorrhage may appear even after 3-4 days. Carcinoma is a long-term risk in 1-4% of exposed and may appear after many years.

Psychological and psychiatric approach: All patients who have been treated for selfintoxication or suspected selfpoisoning should be examined by a psychiatrist in order to assess the possibility of a future self-destructive episode. The risk group includes older men, especially if they have recently become widowed, then unemployed, those who left a suicide note in the self-destructive attempt, then patients with severe terminal illness, patients who suffer from depression and those who were found in isolated locations after self-destructive attempt.

Conclusion: Clinicians should be aware that serious poisonings do not have to be caused by well-known toxins and means, but can also be caused by non-licensed pharmacological products, alternative medicine products, various herbal preparations and common means from the environment. Therefore, identifying and treating the cases of poisonings can be a challenging task for the clinician.

Most of acutely intoxicated persons are treated only by supportive measures. The assessment on the use of gastrointestinal decontamination and measures to increase the removal of toxins is on an individual basis. The use of antidotes, if they are existing is recommended, but the approach is also individual here.

18. RESPIRATORY FAILURE AND BASIC OF TRANSPORT MECHANICAL VENTILATION

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18.1. Physiology of breathing

The task of breathing is to ensure the delivery of oxygen to tissues and remove carbon dioxide from the body. This is achieved by:

- pulmonary ventilation - air flow in both directions between the atmosphere and the alveoli
- diffusion of oxygen and carbon dioxide between the alveoli and blood
- the transfer of oxygen and carbon dioxide in blood and body fluids to the cells and tissues and back

18.1.1. Lung ventilation –inhalation and exhalation exchange

Inhalation and exhalation exchange is a complex process that requires the integration of the functions of the central nervous system (CNS) and respiratory muscles. When we talk about the role of the CNS in breathing should be noted that it is mainly controlled involuntarily, ie. is fully automatic, rhythmic act, but it is to some extent be willing to manage, for example, the voluntary retention of breathing (apnea) or in carrying out some, non-respirating activities, such as singing.

Involuntary breathing control performs network of nerve cells in medulla oblongata and brain bridge. Nerve cells of the network (ie, respiratory neurons) via the spinal motor neurons rhythmically stimulate ie. trigger respiratory muscles, thus creating a pressure gradient required for the movement of air into the lungs (breath or inspiration) and outside it (gasp or expiratory). During normal breaths increases the volume of the chest due to the contraction of inspirational muscles: diaphragm, whose contraction extends the chest cavity, and external intercostal muscles, whose contraction increases the anteroposterior diameter of the chest cavity. Normally calm breathing occurs almost completely thanks to the contraction and relaxation of the diaphragm, while the role of external intercostal muscles of less importance. However, the increased breathing (eg. in the effort), obstructive and restrictive breathing difficulties, for inhalation and exhalation are used and so-called auxiliary respiratory muscles, inspiratory and expiratory. The lungs following dissemination of the chest cavity due to the negative intrapleural pressure (PPL) - the fluid pressure in the narrow space between the lung pleura and chest pleura. Thanks to the expansion of the lungs, the pressure in the alveoli become slightly negative but sufficient for inhalation of about 0.5 L of air for 1.5-2 seconds, as long as normaly lasts, quiet breath. Exhalation is normally, at rest, completely passive process. Diaphragm and intercostal muscles relax and the elastic forces in the lungs and chest cavity lead to reduced chest wall and the lung volume reduction. Reducing the volume of the lungs increases alveolar pressure to approximately + 0.1 kPa, and this leads to the displacement of air inhaled during the 2-3 seconds as normally lasts exhalation.

A normal relationship between breaths (I: E) is 1: 2

Negative pressure in the pleural space is the reason why the lungs at the end of exhalation still contain a certain volume of air (about 2200 mL in adults) who are called functional residual capacity (FRC) . Normally, each breath restores about 1/7 FRC. This enables a uniform and steady transfer of oxygen into the blood and the issuing of CO_2 in the environment, were prevented by sudden fluctuations in the concentration of O_2 and CO_2 levels and ensured stable operation of the mechanisms that control breathing.

Airways creates a certain resistance to the passage of air breathing. In a healthy person, during normal breathing this resistance is minimal, and is mainly produced in the bronchi and biger bronchioles, because their overall diameter is much smaller than the total diameter of 65 000 final bronchioles. In obstructive pulmonary disease (e.g., in asthma), the situation is reversed. Airflow resistance is created in small bronchioles due to their small individual diameters and wall material (absence of cartilage plates, reactive layer of smooth muscle).

For small airways obstruction characteristic is that it is much more difficult to exhale than inhale air. The reason lies in the fact that additional positive pressure, required chest for breath, not only pushes the air out of the alveoli, but at the same time seeks to collapse bronchioles. In contrast, additional negative pleural pressure generated during breathing "stretching" the airways and keep them open, at the same time as expanding the alveoli. Therefore, the air easily enters the lungs during inhalation and during exhalation becomes trapped in them. (ie. Auto - PEEP).

18.1.2. Ventilatory gas exchange membrane

Due to the difference in pressure gas on both sides of respiratory membranes, at the level of the alveoli leads to diffusion of gases, and O_2 diffuses from the alveolar air into the blood pulmonary capillaries, and CO_2 from the blood pulmonary capillaries into the alveoli. The ability to perform respiratory membrane gas exchange is expressed in membrane diffusing capacity, ie. the volume of gas that diffuses through the membrane in 1 minute, under a pressure difference of 1 mm Hg. Respiratory membranes diffusing capacity is about 20 times more for CO_2 than for O2! Because of this, in pulmonary diseases with impaired respiratory membranes, such as pulmonary emphysema, interstitial lung disease, pulmonary vascular disease or a disease of the left ventricle with pulmonary stasis, the diffusion of CO_2 will be held in situations where the transport of oxygen in blood is so low that it threatens the death of the patient!

Gas exchange on respiratory membrane depends not only on the diffusion capacity, but also the mutual consistency of pulmonary ventilation (V) and perfusion - pulmonary capillary blood flow (Q). When we talk about the relationship between ventilation and perfusion in the lungs, it is possible that there are three situations:

- If the V / Q ratio in the lungs = 1, the ratio of ventilation and perfusion is ideal, ie. optimal oxygenation and very efficiently removal of CO_2
- If V / Q ratio in the lung < 1, perfusion is better than ventilation (for example, atelectasis or pulmonary edema). Therefore, part of the venous blood remains non-oxygenated and we call it right-left shunt ($\downarrow PaO_2$, normal or $\downarrow Pa\,CO_2$)
- If the V / Q ratio in parts of the lungs > 1, the ventilation is better than perfusion (eg. in pulmonary

Normally 97% of the oxygen is transferred from the lungs to the tissues chemically related to hemoglobin, and only 3% are dissolved in water and plasma cells. It is obvious that the amount of O_2 that is carried by the blood to the tissue almost entirely determined by the amount of oxyhemoglobin (HBO_2), or the oxygen saturation of hemoglobin in arterial blood (SaO_2).

Carbon dioxide occurs in the cells of the organism as a product of aerobic digestion. It diffuses into the intracellular fluid and then into the capillary tissue, react with water in erythrocytes forming a volatile carbonic acid (H_2CO_3), which dissociates into hydrogen ions and bicarbonate ($CO_2 + H_2O \leftrightarrow H_2CO_3 \leftrightarrow H\,CO_3^- + H\,+$). Most of produced H - ions bind to the hemoglobin in red blood cells (hemoglobin is the protein strong acid-base buffer), and HCO_3^- ions getting out of the erythrocytes in exchange for chloride ions (Cl). In this way, transmits about 70% of CO_2. The remaining CO_2 is transported dissolved in the plasma, or as a compound with hemoglobin and proteins.

18.2. Respiratory failure

Respiratory failure is the most commonly define as a syndrome in which the respiratory system fails delivering in one or both of its essential function of gas exchange:

- in oxygenation (enrichment in oxygen) = **hypoxemia or respiratory failure type I**
- in ventilation (elimination of CO_2) = **hypercapnic respiratory failure or type II**

Causes of respiratory failure may provide general disease of the lungs, heart, chest wall or respiratory muscles and / or loss of central control of breathing. The common causes of type 1 respiratory failure were cardiogenic or non-cardiac edema, pneumonia, ALI (Acute Lung Injury - ALI) / ARDS (Acute Respiratory Distress Syndrome - ARDS). The common causes of type 2 respiratory failure are serious diseases with increased airway resistance in them (asthma, COPD), neuromuscular diseases (Guillain-Barre syndrome, myasthenia gravis, motor neuron disease), abnormal chest wall (such as kyphoscoliosis deformity, injury such as "flail chest"), drug overdose ...

Respiratory failure could be classified as acute or chronic. While acute respiratory failure is often a disease that threatens the life of patients and which is characterized by severe disturbances in blood gas analysis and the ABS, the manifestations of chronic respiratory failure are generally less dramatic and often unrecognized. For example, the hypercapnic acute respiratory failure (type 2) usually develop over a few minutes or hours and the pH is typically < 7.3. Occasionally the failure develops days (or longer), and the body has enough time to develop renal compensation and an increase in the concentration of bicarbonate in the blood, so that the pH is only slightly reduced. It is worth mentioning that distinguish acute from chronic hipoxemic failure is not possible on the basis of the analysis of gases in arterial blood; polycythemia or cor-pulmonale may suggest that it is a condition that lasts for a long time!

18.2.1. Acute hypoxemic respiratory failure

Acute hypoxemic respiratory failure is characterized by $PaO_2 < 60$ mmHg and normal or low $PaCO_2$.

Pathophysiologicaly, it primarily occurs due to the right-left shunting of blood at the level of the lungs (V / Q <1), caused by alveoli flooded with liquid or their collapse, eg. in the presence of atelectasis, in severe pneumonia or cardiac or non cardiac pulmonary edema, but diffusion problems on swollen alveocapillary membrane should not be neglected . It is most common in acute heart failure (or in acute exacerbation of chronic heart failure), in severe pneumonia or with acute lung injury (ALI / ARDS), a major pathophysiological mechanism is the formation of pulmonary edema that develops due to an increase in pulmonary capillary hydrostatic pressure, eg . in the scheduling of the left ventricle or the overload of patients with liquids (so-called, high-pressure hypoxemia respiratory failure) or due to increased capillary permeability of lung capillaries, eg in acute lung injury (ie. low pressure hypoxemia respiratory failure). Lung injury may be direct (eg. In the aspirator pneumonia) or indirect (for example, in sepsis, acute inflammation of the pancreas, with massive blood transfusions), but in all cases the alveoli are flooded with proteinaceous fluid. Fluid-filled alveoli and alveolar swollen membranes do not allow the exchange of gases, primarily oxygen, and oxygenation of blood that washes such alveoli remains at the level of the mixed venous blood regardless of the amount of inhaled O2. So deoxygenated blood constantly enters the pulmonary veins and the left heart (RL shunt) and causes arterial hypoxemia.

Acute hypoxemia causes shortness of breath, restlessness and anxiety. Patients are confused, narrowed consciousness, cyanotic, tahipnoic, tachycardic and sweating. There may be a cardiac arrhythmia with severe heart failure occurs, and distension of the neck veins. By lungs auscultation we can hear fine rattle, which are typically distributed diffusely and harsher the bases. Pulse oximetry reveals low levels of oxyhemoglobin saturation of oxygen in arterial blood (SaO_2).

All patients with low SaO_2 should determine the acid-base status (ABS) and record the X-ray of the chest, and the search for the cause of acute respiratory hypoxemic failure, taking into account the pulmonary and extrapulmonary disease. Sometimes it is clear what it is because it is a known disease or the existing state (eg, acute MI, acute pancreatitis, sepsis) which are characterized by this type of respiratory failure and in other cases it is crucial history eg. pneumonia should be suspected in immunocompromised individuals, the alveolar hemorrhage in patients with collagenosis or after bone marrow transplantation, the fluid overload in critically ill patients, as they often receive significant amounts of IV fluids during resuscitation.

On high pressure edema indicates protodiastolic gallop, engorged neck veins and peripheral edema in physical examination, and diffuse central infiltrates, cardiomegaly and thicker wire drawing on the chest radiograph. Diffuse infiltrates within ARDS usually lie distal. Focal infiltrates primarily speak in favor for pneumonia, atelectasis or lung contusion.

Although controversial, setting pulmonary catheter may help lead to the correct diagnosis, especially in the potential overlaps several states.

18.2.2. Hypercapnic respiratory failure

Hypercapnic respiratory failure is characterized by the $PaCO_2 > 50$ mm Hg, and pH < 7.35 (depending on the duration and development of compensatory mechanisms). Usually hypoxemia is present when patients breathe room air

Hypercapnia in this case is usually a consequence of reduction of minute ventilation, increased less dead space ventilation. Elevated CO_2 that occurs with a fever, sepsis, with extensive trauma and burns, and the increased work of breathing, usually does not contribute to a significant failure of ventilation.

The consequence is hypercapnia respiratory acidosis. Severe acidemia (pH < 7.2) induces arteriolar vasoconstriction in the lung with systemic vasodilation, decreased myocardial contractility, and increased irritability of the heart with a penchant malignant arrhythmias. Acute hypercapnia causes cerebral vasodilation and subsequent increase in intracranial pressure, which can be a serious problem in patients with head injury. Tissue buffers and renal compensation can significantly correct the acidemia if it occurs gradually. However, the sharp rise in $PaCO_2$ (eg. in apnoic people in that $PaCO_2$ growing at a rate of 3-6 mm Hg / min) compensatory changes are too slow to come to the fore.

On the failure of ventilation to be thought in patients with shortness of breath, a visible effort of breathing or cyanosis and changes in sensorium, as in those whose disease can cause neuromuscular weakness.

Patients who are suspected to hypercapnic respiratory failure should be determined ABS, monitor pulse oximetry and chest X-ray. Respiratory acidosis in the ABS (eg. pH < 7.35 with $PaCO_2 > 50$) can confirm the diagnosis. However, one should remember that in people with chronic ventilation failure is often found extremely high value of the resulting $PaCO_2$ (60-90 mmHg) and pH that is only slightly reduced.

As in the initial failure of ventilation ABS may be neat, some simple tests of lung function can be useful, especially in patients with neuromuscular diseases who are prone to failure of ventilation without signs of respiratory distress. For example, vital capacity < 10-15 mL / kg and maximum power breaths ≤ 15 cm H2O speak for impending failure. When the failure of ventilation is diagnosed, the cause should be determinated. Sometimes it is obvious underlying disease (e.g., acute asthma, COPD, myasthenia). In other cases helps history - for example, the sudden appearance of tachypnea and hypotension after surgery leads to pulmonary embolism, focal neurologic deficit mostly for stroke or neuromuscular cause. Neuromuscular appropriateness estimated by measuring the strength of the respiratory muscles (negative pressure on inspiration, positive pressure during exhalation), neuromuscular transmission (nerve conduction tests, electromyography) and the search for the causes of weakened incentives of breathing (toxicological screening, brain scans, thyroid function tests, ...) .

18.3. Respiratory failure treatment

In general we can say that the treatment of respiratory failure includes the following measures:
1) Treatment of the underlying disease
2) Supportive oxygenation and ventilation measures, ie:
3) the implementation of oxygen
   a) establish adequate and effective airway:
   b) content aspiration of airway (sputum, blood, secretions) endotracheal intubation, tracheostomy
4) Machine ventilation (noninvasive or invasive) to increase the PaO2 and PaCO2 up or rest respiratory muscles.

Below we are called to deal with invasive mechanical ventilation in prehospital conditions (ie. transport mechanical ventilation)

18.4. Transport mechanical ventilation

18.4.1. Indications

Transport mechanical ventilation in prehospital conditions has its place:
1) During the resuscitation
2) During the pre-hospital care of patients with predominantly respiratory problems such as:
- **Gas exchange abnormalities in ventilatory membrane:** ARDS, pulmonary contusions, massive consolidation of lung parenchyma any other etiology, alveolar edema of any etiology
- **Mechanics of respiratory disorders:** chronic lung disease exacerbation (COPD, asthma, ...), trauma to the chest (serial rib fractures, Flail chest)
- **Respiratory misfire induced by CNS disorder** (high spinal cord injury, multiple sclerosis, amyotrophic lataralna sclerosis, ...) or neuromuscular diseases (myasthenia gravis, ...)
3) In prevention of secondary injury (brain injury with GCS ≤ 8)

18.4.2. Machines for mechanical lung ventilation

Machines for mechanical lung ventilation (ventilators) are devices intended to replace or assist the natural function of breathing. Classified depending on:
- how to create a force breaths
- the control variables and
- the characteristics of the so-called. phase variables

18.4.2.1. Inhalation forces

Mechanical ventilators must produce inhalation force that normally produces by respiratory muscles. This is done mainly in two ways:
1) by applying negative pressure outside the chest
2) application of positive pressure within the lungs

Accordingly distinguish ventilators of negative and positive pressure:
1) *negative pressure ventilators* rhytmically create a negative pressure around the chest, and in this way expanding chest cavity. It creates in the alveoli subatmospheric pressure which allows breathing the air. In this way it is possible to ventilate patients with generally healthy lungs, such as, for example, have been suffering from the polio.

2) *positive pressure ventilators* produced inhalation force through the piston, bellows or by high pressure. Those needs pressurized inhalation (Supply air) oxygen or mixtures of oxygen and air into the lungs via the airway of the patient. Due to the use of multiple microprocessors that control the operation of these ventilators, increased speed of all processes relevant to their functions and enables the use of various modes of mechanical ventilation. Because these ventilators are applicable in the most diverse demands of patients, even in those situations when the lungs of patients are not healthy.

Modern methods of artificial ventilation are based on the positive pressure ventilator, and will hereinafter be discussed solely on them!

18.4.2.2. Control variables

There are three primary variables that controls ventilators:
- pressure in the airways
- inhalation volume, and
- inspiratory flow

Accordingly, we distinguish between:

1) **Pressure controlled ventilator** – which provides breaths by periodic application of oxygen or a mixture of oxygen and air under constant pressure peaks, the volume and flow are variable because they depend on the laxity of the lungs and chest and airway resistance.

2) **Volume controlled ventilator** – which provides breaths by periodic application of a fixed volume of oxygen or a mixture of oxygen and air. In this flow remains constant and the pressure is changed depending on the state of patients' lungs and airways.

3) **Flow controlled ventilator** – which provides breaths by periodic application of a constant flow of oxygen or a mixture of oxygen and air. In doing so constant is volume, but it is measured indirectly through the flow meter (measured flow and volume is calculated as a function of time). Thanks to microprocessor-controlled valves, oxygen or mixtures of oxygen and air is brought into the lungs different curve shapes such as rectangular, sinusoidal, accelerating or decelerating, and it is possible to satisfy the needs of more patients.

18.4.2.3. Phase variables

Respiratory cycle can be divided into four different stages:
1) The transition from the exhalation to inhalation
2) Inhalation
3) The transition from inhalation to exhalation
4) Exhalation

On the transition from exhalation to inhalation trigger that initiates inhalation (variable shutter, eng. trigger) can be pressure, flow, or time:
- When using time, starting inhalation depends on the set breathing frequency, regardless of the patient's attempts.
- When using a pressure, inhalation begins when the main pressure drops (eg. when the patient tries to breathe), regardless of the given frequency.
- When using the inhalation, flow begins when it falls below a given flow.

During inhalation (limit variable) pressure, flow and volume growth above basal values. Inhalation will not end as long as the default variable reaches the set (limit) value. The transition from inhalation to exhalation (cyclical variable) happens when the variable set reaches a predetermined value. For example, on the flow controlled ventilator inhalation will end when achieve a predetermined volume, on the volume controlled ventilators when it is achived default volume, etc.

Exalationis also called the initial or baseline variable, since all variables measured in relation to the baseline value - those at the end of exhalation. It can last as long as some of the variables (pressure, flow or volume) does not fall to the basal value. Today, the most commonly used basal variable is pressure, because in this way it is possible to control the pressure in the airways at the end of exhalation.

18.4.3. Basic types of mechanical ventilation

There are three main types of breathing machine:
1) **Controlled breathing** - in which the ventilator delivers breaths to the defined variables, and a specific fixed frequency, regardless of the patient's possible breathing efforts.

2) **Assisted breathing** - in which the ventilator begins assisted breath when the patient attempt to produce breaths sufficient that trigger fit into the set sensitivity . This type of breathing ensures patient cast the breath given by predetermined variables, and it ends when it reaches the default cyclical variable.

3) **Spontaneous breathing** - in which ventilator produce flow that helps the patient's spontaneous inspiratory efforts. The flow is controlled by the patient, ie, it is higher when the patients inspiratory effort is greater. A spontaneous breath ends when the patient needs fall below the basic incentive value.

18.4.4. Special features of the transport mechanical ventilation

Transport ventilators must be small, compact, have an independent source of energy (compressed oxygen), spend little oxygen for the drive (on most ventilators there is switch which selects ventilation with 100% oxygen, or a mixture of oxygen and air), and be simple to use. They thurn on simply (open bottles with compressed oxygen, pressing the on / off), and usually offer the option of adjusting the respiratory or cardiac volume of breathing, respiratory rate, gas flow, duration of breath or relations I: E, peak pressure in the airways , PEEP, ...

It is clear that they can not offer all modes of mechanical ventilation devices offered in intensive care units. In transport mechanical ventilation method is usualy used standard mechanical ventilation, which include controlled mechanical ventilation and various types of assisted ventilation, for which is characteristic that in part or the initiation of breathing patient participates. Some devices even have the option of using PEEP. Therefore, we will hereafter devote upward mechanical ventilation and synchronized interrmitent mandatory ventilation (a type of assisted ventilation), which are mostly represented in the transport mechanical ventilation.

Controlled Mechanical Ventilation – CMV

During CMV inhalation starts automatically according to pre-set parameters and repeat periodically according to a given frequency, regardless of the patient's spontaneous breathing attempts. If the CMV does not apply positive pressure at the end of exhalation (PEEP), then it is called intermittent positive pressure ventilation – IPPV. If the controlled ventilation is applied PEEP then it is called continuous positive pressure ventilation – CPPV.

According to the control variables, CMV can be:

a) **Volume controlled mechanical ventilation** - in which the predetermined volume of breathing is rhythmically insert into the lungs of patient. The ventilator ends breath when predetermined volume is delivered to the lungs.

In doing so it is necessary to limit the inspiratory pressure (in the beginning usually at 35 cm H2O) to allow ventilator to interrupted breath when inspiratory pressure reaches a preset value (even if did not put the default volume), because in this way protects patients from possible barotrauma.

b) **Pressure controlled mechanical ventilation** - at which the inspiratory gases are insert into the lungs under constant pressure, and for the duration of inhalation is responsible predetermined maximum pressure (Pmax). As the pressure is constant, the flow is greatest at the beginning of breaths, and then gradually decreases depending on the fulfillment of lung with inspiratory gases.

In this type CMV limiting factor is the ventilator respiratory volume. During ventilation, if there is a decrease in pulmonary compliance or increase in airway resistance, the patient will be hipoventilated, as it will not receive sufficient inspiratory volume. This is why patients who are ventilated with pressure controlled ventilation system should be strictly supervised!

Synchonized Intermitent Mandatory Ventilation – SIMV

SIMV is one way of assisted mechanical ventilation. The ventilators delivers a certain number of compulsory (set) of breaths and between them the patient can breathe spontaneously. The default breaths are delivered in the form of a volume or a pressure, and for which it is characteristic that it can be synchronized with the patient's spontaneous breaths (SIMV) or independent (Intermitent Mandatory Ventilation - IMV) if there is no spontaneous respiratory attempts when the ventilator needs to deliver the next breath. Patients spontaneous breaths can be backed by pressure (at the beginning of breath pressure which produces ventilator, rapidly reaches the value required for the entire breath).

Benefits from SIMV-are as follows:

- The patient can use a variable amount of own respiratory work, and at the same time secure the given level of ventilation that ventilator will accomplish

- Variabilityof ventilation is moving in a wide range of almost complete mechanical ventilation to almost complete spontaneous breathing so SIMV is very effective in the process of separating the patient from the ventilator

18.4.5. Securing the airway for transport mechanical ventilation application

In prehospital conditions of the transport mechanical ventilation can be perform on non-invasive (no ET intubation) and invasive wy (with ET intubation).

Noninvasive Positive Pressure Ventilation – NIPPV is a very attractive method of mechanical ventilation for prehospital personnel (it does not require ET intubation for which they are often not skilled), but also is much less applied in daily practice because it is relatively contraindicated in the following situations:

- in respiratory arrest (NIPPV is a type of assisted ventilation)
- in hemodinamicly unstable patients (hypotension that does not respond to the compensation volume of circulating blood, ischemia, arrhythmias)
- in patients who can not maintain open airway (disturbed by coughing, swallowing problems)
- in patients with a marked secretion in trehaobronhal tree
- in an agitated and noncompliant patients and
- in patients with surgery, injury or facial burns

Because of all these, ET intubation and invasive ventilation remain the gold standard of prehospital transport machine ventilation.

Endotracheal intubation

ET Intubation is the process of setting plastic or rubber hose (tube) into the trachea for the sake of securing the airway and artificial ventilation. It has many advantages over other methods of ensuring the airway:

- preventing inflation of the stomach and reduces the risk of vomiting and regurgitation,
- ensures the airway from aspiration of foreign content,
- to clean the tracheobronchial tree

More over intubation:

- facilitates resuscitation measures (artificial ventilation independent of external compressions),
- provides for the application of controlled mechanical ventilation, and various types of assisted ventilation as well as the application of PEEP (opens and stabilizes collapsed and fluid-filled alveoli, increases FRC),
- provides for the application of high concentrations of oxygen and respiratory delivery of the desired volume (TV),
- to the endotracheal administration of drugs.

For ET intubation is required accessories:

- laryngoscope with spatulas of various sizes and layouts (curved on the Macintosh, which have fallen into disuse and flat at Magill used in intubation of infants and young children),
- tube of appropriate size (according to the age of the patient),
- syringe for balloon,
- anesthetic agent in a spray or gel
- rails for tube (or stiletto mendren - coated wire that is inserted into the tube so that it is strengthen and shape, and thus easier to be placed in the trachea)
- Magill forceps (curved pliers that are used for the extraction of foreign bodies in the intubation or to guide tube at nasotracheal intubation),
- accessories for fixing the tube (leucoplast, strips of bandages)
- probe for position determination of ET tube, and
- protective gloves

Before intubation is well (if possible) pre-oxygenate the patient with 100% oxygen during 2-3 minutes (use ambu with a mask using oxygen tanks!).

Intubation may be performed orotracheal or nasally. Nasal intubation has many advantages (the patient is easier to bear, is more suitable for longer transport, etc.), but is more difficult to perform and often accompanied by severe epistaxis. So it is rarely recommended for a less experienced person. Nevertheless, there are patients where it is preferably, for example, in severe injuries to the mouth and

oral cavity, or in patients with trismus. Orotracheal intubation is performed so that a savior is placed over the head of the patient, extend patient's head with his right hand. Then the thumb of his right hand pushes the patient's chin down and open patient's mouth. He holds laryngoscope in his left hand. Spatula enters from the right side of the patient's tongue and the tongue is pushed to the left and then the spatula is pushed further into the depths until you see the epiglottis. While it works, right hand hold head position.

Table 18-1. Choice of endotracheal tube

Age of the patient (weight)	The inner diameter of the tube (mm)	Size of the aspiration catheter (F)
0-1 year (3 – 10 kg)	3,5 – 4,5	8
1 year/ little child (10 – 13 kg)	4,0	8
3 years (14 – 16 kg)	4,5	8 - 10
5 years (16 – 20 kg)	5,0	10
6 years (18 – 25 kg)	5,5	10
8 years – 11 years (24 – 32 kg)	6,0 cuffed	10 - 12
12 years – adolescent (32 – 54 kg)	6,5 cuffed	12
16 years – adult (50 + kg)	7,0 cuffed	12 - 14
Adult women	7,0 – 8,0 cuffed	
Adult men	8,0 – 8,0 cuffed	14

* For children older than 1 year the size of the tube (mm) can be calculated by the formula:

age in years / 4 + 4 for tube without balloon (cuff)

and

age in years / 4 + 3 for tube with a balloon.

** As children of the same age can vary a great, in the selection of the tube we can also use the following comparison: the corresponding tube is approximately the width of a little finger on the child's hand.

When using a curved spatula, its top line up in vallecula above the epiglottis and lifted it upwards, while the epiglottis indirectly raise because of withdrawing glossoepioglottic frenulum. When using a flat spatula, it is placed under the epiglottis and then it is picked up directly. In both cases reveals the entrance to the larynx, but the curved spatula does not touch it, and therefore is less risk of injury and at the same time will leave more space for the insertion tube. No matter which spatula is used for lifting epiglottis, it is prohibited to use upper jaw teeth as a stronghold spatula.

Sometimes intubation is difficult, so it is good to have an assistant to help visualize the entrance to the larynx (eg. move away corner of the mouth or change the position of the larynx from the outside, through the neck).

Besides, assistant should at all time during performing of the so-called crush intubation (intubation in patients with a full stomach) suppress patient's cricoid cartilage backward (Selik grip). In that way esophagus remains closed and the possibility of regurgitation of gastric contents is smaller.

The presence of an assistant is required during intubation of patients with suspected cervical spine injury. In this case, with both hands he is holding the head of the injured person in the center line and does not allow excessive extension of the head during intubation.

When he finally managed to show the entrance to the larynx, the tube should be push on the right side of the mouth so that at no time does not lose of sight of the entrance to the larynx. Tube is in place when the label gets in the position of the vocal cords, ie. when the cuff is finished directly below them. Only then can inflate the cuff.

Before fixation is necessary to check position of the tube. It should first be switched off inadvertently introducing tube into the esophagus. This can be checked by monitoring CO_2 in exhaled air (so-called End-Tidel CO_2), but only when a person has a heartbeat. A simpler method, which does not limit the use of so-called ET tubeposition test . After that still need to check that the position of the ET ensures the ventilation of both lungs. This is done by auscultation hemithorax and with simultaneous ventilation of patients with ambu.

At the end, with the tube set oropharyngeal airway (bite prevention of tube or its refraction), and both are fixed in place by a bandage.

Complications ET intubation are:
1) esophageal intubation,
2) injury to the lips, teeth, tongue, larynx or trachea,

3) epistaxis (with nasotracheal intubation),
4) bronchial intubation (only one lungventilation).

Medicines for ET intubation

Unlike patient / injured that are in heart failure, many other patients are conscious and / or have defense reflex. ET intubation then should be performed with sedation or anesthesia, and possibly neuromuscular blockade.

Sedative of choice is **midazolam** (Dormicum, amp a 15 mg / 3 mL), short-acting benzodiazepine withpotent amnestic effect. Its activity is reversible with flumezanil (Anexate amp. À 5 mL / 0.5 mg).

Of all anestheticspriority is given to three anesthetics:

- **Thiopental** (Nesdonal, bottle à 500 or 1000 mg) - it's ultra-short acting barbiturate with quick early onset and duration of action for about 10 minutes. It is particularly indicated in patients with elevated intracranial pressure (eg. in head injuries), and should not be used in hypotensive patients and those with bronchospasm.
- **Propofol** (Diprivan, Amp A 20 mL / 200mg) - it is a newer anesthetic very rapid and short-acting, which, unlike thiopentala, leaves preserved spontaneous breathing when not administered too quickly. This allows its use for continuous sedation.
- **Etomidate** (Hypnomidate, amp ± 10 mL / 20mg) - it is the ultra-short actingnon -barbiturate hypnotic which has minimal hemodynamic effects. Tthat is why it is an anesthetic of choice in hypotensive and injured patients.
- Between neuromuscular blockers priority is given to non-depolarising agents, as follows:
- **Rocuronium** (Esmeron, vials and 5 mL / 50mg) - it is a neuromuscular blocker with rapid onset of action, which enables ET intubation within 60 seconds after IV drug administration. Depending on the applied dose effect is 25-30 minutes.
- **Vecuronium** (Norcuron, amp. A 4 mg) - is neuromuscular blocker of medium duration of action, without any hemodynamic effects.

18.4.6. Monitoring of breathing in patients on mechanical ventilation

Monitoring of breathing in patients on the transport mechanical ventilation is reduced version of monitoring patients in intensive care units. Transport ventilators in fact do not have all the features that have freestanding ventilators.

Basically are followed:

1) Mechanics of breathing - most often:
   a) The value of peak positive pressure Ppeak or PIP (Picture 18-1): ↑PIP = ET tube obstruction, bronchospasm, wrap ventilator pipe , pneumothorax, ... ↓PIP = "leakage" emissions from the system, bursting of ET tube cuff..
   b) The volume of exhaled gases (TVE or MVE)
2) Oxygenation - ie. SaO_2 and
3) Ventilation - ie. the partial pressure of exhaled carbon dioxide ($ETCO_2$)

Monitoring oxygenation

Hypoxemia is a common etiologic factor of morbidity and mortality in patients on mechanical ventilation, and require its early detection in order to promptly respond. Clinical signs of hypoxemia (tachycardia, tachypnea, change in mental status and / or cyanosis) often are masked or hardly visible. However, we can use a good non-invasive monitor oxygenation - Pulse Oximeter - who in most situations is giveing enough information to safely manage our patients.

Pulse oximeter measures the pulse rate and saturation of hemoglobin with oxygen (ie. SpO_2) at the level of arterioles, on a non-invasive, continuous way. Hemoglobin saturation with O_2 is defined as the ratio of the concentration of oxyhemoglobin and total hemoglobin:

$$SaO_2 = (cHbO_2 / cHBO_2 + CHB) \times 100$$

The amount of O_2 that is carried by the blood is almost completely determined by the amount HBO_2, and SaO_2. And if we know oxygen saturation of hemoglobin, we also know the partial pressure of O_2, because their relationship is defined by dissociation curve of oxyhemoglobin.

Pulse oximeter combines two methods to determine SaO_2 :

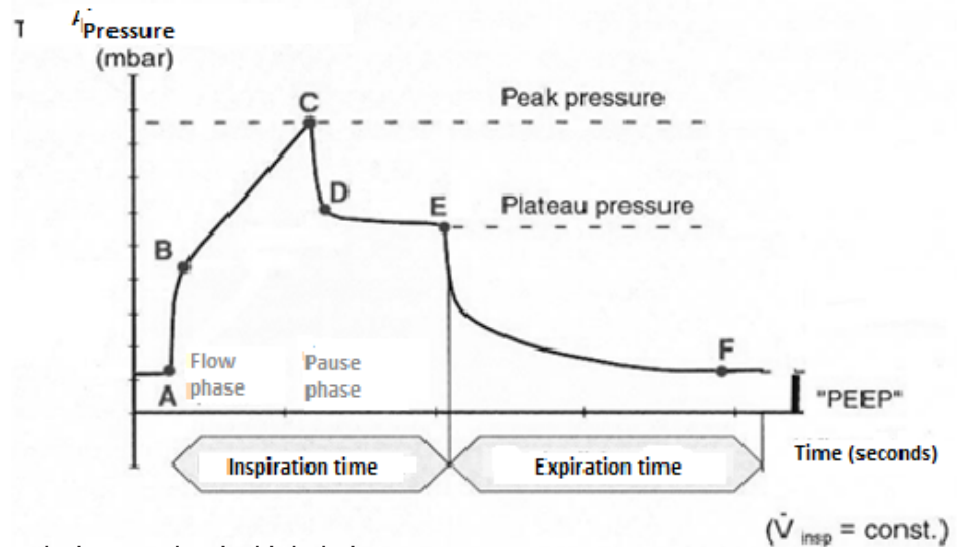- spectrophotometry - which allows the photometric determination of the concentration HBO_2 and reduced Hb, and

Figure 18-1. Airway pressures during mechanical inhalation.

- plethysmography - providing analysis only on pulsatil arterial blood, not on the surrounding venous blood and tissues.

A spectrophotometric method for determining SaO_2 is based on the Beer - Lambert law which states that the intensity of light transmission through a blood sample, with constant light intensity and the concentration of hemoglobin, is logarithmic function of hemoglobin oxygen saturation.

Table 18-2. Medications for ET intubation

Medicine	Dose	Onset of action	Duration of action
A Sedatives			
Midazolam	0,1–0,3 mg/kgTT	1–2 min.	30–60 min
Diazepam	0,25–0,4 mg/kgTT	2–4 min.	30–90 min.
B Anesthetics			
Thiopental	3–5 mg/kgTT	10– 20 sec.	10 min.
Propofol	1,5–2 ,5 mg /kgTT	< 1 min.	10 min.
Etomidat	0,2–0,3 mg/kgTT	< 1 min.	1 min.
C Neuro-muscular blcators			
Rocuronium	0,45–0,9 mg/kgTT	oko 60 sec	25–35 min
Vecuronium	0,1–0,2 mg/kgTT	1–4 min.	oko 30 min.

Pulse Oximeter uses light at two wavelengths - red, wavelengths of 660 nm, and infrared, wavelengths of 920-940 nm (1, 2, 3). The light beams of these wavelengths produce the greatest difference in the absorption of light between HBO_2 and reduced Hb, because HBO_2 absorbs most infrared and reduced Hb red light.

The light beams are emitted from the two light-diodos (LED - light emitting diodes), one that gives the red and the other which provides infrared light, passed through the tissue and captured by photo detector on the opposite side.

There are photodetectors that read SaO_2 with ear, nose, children's feet. The photodetector detects the absorption of both types of light, ie, converts the received light into an electrical signal. Since the passage of light is determined by interplay between HgO_2 and reduced Hb, so the electrical signal is different. Determination of SaO_2 base on it.

Plethysmography allows the received light reading only in pulsatil, arterial blood, and not in non-pulsatil tissue - venous blood and other tissues (nails, bones, muscles). This is accomplished by pulse oximeter first determining the absorption of light during diastole, when there is no pulsating blood. The resulting value, which is generally not changed, is the reference value for determining the "pulsatile absorption". When the systolic pulse wave appears, previous, reference value is subtracted from the value of the measured light absorption. This gave the extent of absorption of the two wavelengths of the rays, only from pulsating blood.
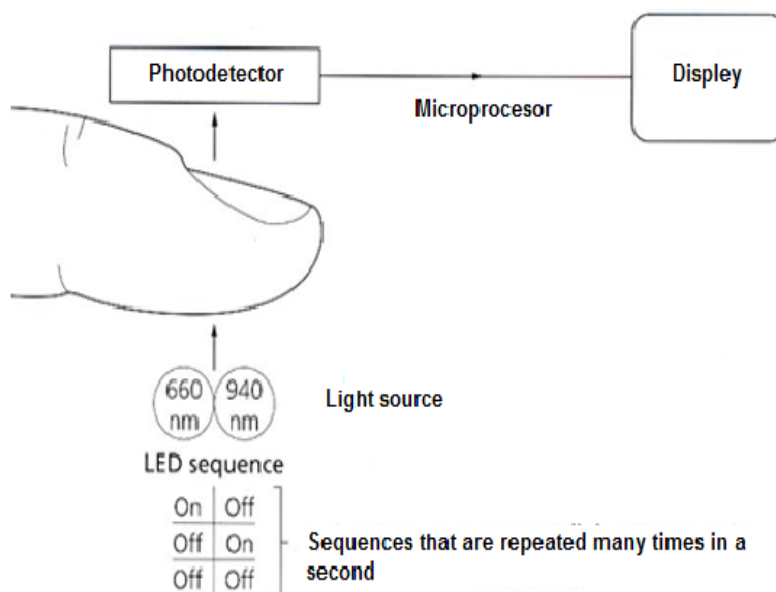
Figure 18-2. The transmission of light through the hand finger.

All measurements that photodetector do are processed in microprocessor and the value displayed SaO_2 is synthesis of all obtained data. As for the analysis of obtained data time is necessary, displayed values are not current, but rather those before 10 to 60 seconds. This will show desaturation on the display after 60 seconds if the photodetector is on the finger, and after 10-15 seconds if it is on the ear. The accuracy of this method of measurement of SaO_2 is between ± 2-3%, for a wide range of SaO_2 of 70 to 100%.

18.4.6.2. Ventilation monitoring

Capnometry and capnography

Carbon dioxide (CO_2) is produced in the cells of the organism as a product of anaerobic digestion. The quantity of CO_2 depends on the person's metabolism and its elimination depends on the pulmonary blood circulation and alveolar ventilation. At rest state, in the body is generated about 200 mL CO_2 per minute or 13000-15000 mmol in 24 hours. From the cells CO_2 diffuses into the extracellular fluid, from there into the blood and from the blood to the lungs.

Diffusion of CO_2 from venous blood in alveolar capillaries goes in the direction of the alveoli, and increases $PACO_2$ (partial pressure of CO_2 in the alveolar air). Normally, the CO_2 so effectively removes from the lung capillaries that $PACO_2$ and $PaCO_2$ not differ more from 0.3 to 0.6 kPa (2-5 mmHg). This difference (ΔCO_2 or alveolar - arterial CO_2 difference) is formed thanks to the blood, which is in the lungs suffered changes of O_2 and CO_2, adds blood from the pulmonary parenchyma (so called venous tinge) and the blood that has passed through unvented alveoli.

So, we can say that:

$$PaCO_2 = \Delta CO_2 + PACO_2$$

or, if we ignore the small value ΔCO_2, that is

$$PaCO_2 \approx PACO_2$$

The highest value of CO_2 in exhaled air is achieved at the end of exhalation. This value is called the CO2 at the end of exhalation (end-Tidel CO_2 or ET CO_2) and best reflects the alveolar CO_2. That's why we can say that:

$$ETCO_2 \approx PACO_2 \approx PaCO_2$$

The concentration or the partial pressure of exhaled CO_2 can be measured in several ways. Today, as the method of choice we use method of infrared absorption. It is based on the fact that CO_2 absorbs infrared light, depending on the concentration (Lambert - Beer's law). Devices that operate on this principle have a pump that takes samples of exhaled air in the measuring chamber illuminated by infrared light of a specific wavelength. In addition to this chamber, infrared light also illuminates control chamber which is filled with room air. The absorption of infrared light in the measuring chamber is proportional to the partial pressure of CO_2 in the chamber. Photodetector reads absortion and converts the light signal into
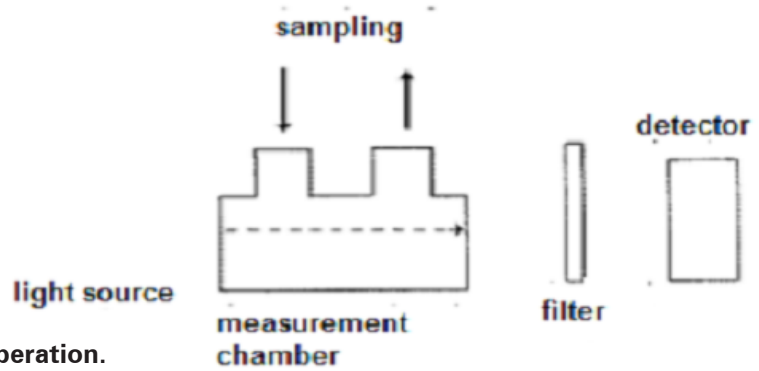
Figure 18-3. The principle of capnogram operation.

electrical. Microprocessor processed obtained data and compare it with those coming from the control chamber. This allows calculation of the partial pressure of CO_2 (Figure 3).

Depending on the method of sampling of exhaled air, we distinguish:
- devices with sideways by taking a sample ("side stream") and
- devices that analysis is performed in the respiratory circuit ("mainstream" or "flow-through")

Methods of displaying measured values

Under **capnometry** we mean a numerical expression of the measured concentration or partial pressure of CO_2 during inhalation and exhalation and under **capnography** graphical representation of concentration or partial pressure of CO_2 during respitaration cycle. Graphical representation may be variant:
- Small recording speed (25 mm / min) gaves the so-called. trend curve (Figure 18-4):

On this curve can be read only concentration or partial pressure of CO_2.
- If the speed is 12.5 m / s obtained capnography curve in real time showing all phases of breathing from the respiratory cycle to cycle (Figure 18-5):

On this curve can be seen four phases:
1) Phase A - B, which is the initial phase of exhalation, there is no CO_2 in sample, because it is an air of anatomic dead space.
2) Phase B - C, where there was a sudden jump in the partial pressure of CO_2, because at the point of sampling starts appearing alveolar air.
3) Phase C - D, called alveolar or expiratory plateau. In this phase pure alveolar air is sampled . The highest value of the partial pressure of CO_2 (point D) called $ETCO_2$. The value of the partial pressure of CO_2 best reflects $PaCO_2$.
4) Phase D - E, in which begins inhalation and the partial pressure of CO_2 decreases rapidly to zero if there is no re-inhalation of exhaled gases (rebreathing).

Capnography curve in real time giving the most information and maximum benefit.

Figure 18-4. Capnography trend curve.

Figure 18-5. Capnography curve in real time

19. OXYGEN THERAPY

Mladen Carev*

19.1. Introductory remarks

The respiratory failure therapy consists of the treatment of the cause, as well as of additional important supporting measures:

- increase of the concentration of inhaled oxygen - FiO_2,
- artificial airway,
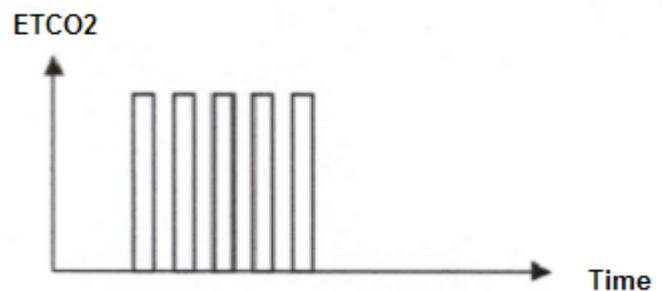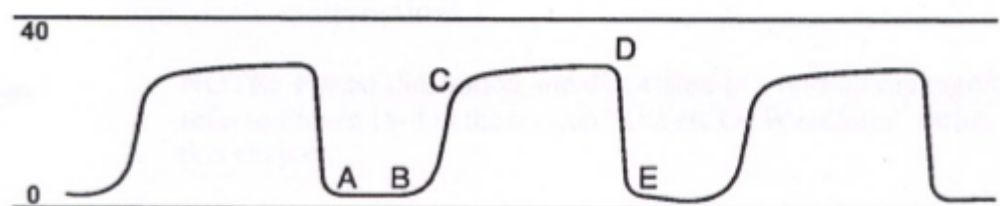- mechanical ventilation.

Administration of higher concentration of oxygen is necessary in most cases. In some cases alveolar ventilation may be remarkably improved by establishing adequate and effective airway, as well as by aspiration of airway contents (sputum, blood, secretions), and endotracheal intubation. Mechanical ventilation is required for the most difficult cases. Here it will be discussed about the technical aspects of application of oxygen and oxygen treatment in the strict sense. The establishment of airway and mechanical ventilation are discussed elsewhere.

Oxygen therapy is the use of oxygen at a concentration greater than environmental ($FiO_2 = 21\%$). Indications for treatment with oxygen can be:

- Conditions of hypoxia and hypoxemia
  - Insufficient oxygenation of the lungs due to external reasons
  - Pulmonary disease
  - Insufficient transport and delivery of oxygen
- Shock
- Decompression Sickness
- Anesthesia
- In a mixture with anesthetics

19.2. Oxygen therapy – basics

19.2.1. The technical aspects of oxygen application

Medical oxygen can be stored and supplied in several ways.

a) a) The gaseous oxygen in steel cylinders under pressure. The pressure and flow regulator may be mounted on such a cylinder (Figures 19-1.)

b) b) The gaseous oxygen delivered via pipelines to the place of application (operating rooms, wards, intensive care units) (Figure 19-2.). In addition to oxygen and other gases can be delivered in this way (air, nitrous oxide), but the wall outlet is strictly specific to a particular gas, in order to prevent error (so-called Diameter Index Safety System).

Proper use of oxygen cylinder is a very important procedure, especially in emergencies. Most often the cylinders are made of stainless steel, but can also be of aluminum and kevlar. Depending on the material from which they are made they are filled differently depending on their certificate. Usually the charging is carried up to half of the value at which they are approved. The cylinders come in different volumes. Aluminum cylinders are lightweight and suitable for emergency medical care. Before using the cylinder, the entire system should be inspected and tested. After filling, the cylinder is usually labeled with tape of the company that filled and tested it, and this tape should be removed before use.

There have been differences among regions of the world in the color of cylinders, but lately it has been standardized. The body of the cylinder is always white, while the color of the cover-up depends on a particular gas. For example, oxygen has a white cap, nitrous oxide blue, carbon dioxide gray, nitrogen black, etc. Furthermore, they come in various volumes and are filled under different pressures. As a reminder, 1 atm = 101.325 kPa = 1.01325 bar = 760 mmHg. Anglo-American unit is psi (pounds-force per square inch); 1 atm ≈ 14.7 psi. In Croatia the pressure in the cylinders is most often expressed in bar or kPa.

The oxygen cylinders of 10 liters are usually fixed systems and are used in hospital emergency rooms and in ambulance cars (important for the long transports because small portable cylinders would not be sufficient). Cylinders of less volume, i.e. 3 liters, are usually portable. The quantity of oxygen in liters in each tank can be calculated by multiplying the pressure (bar) x volume of cylinder (L). For example, the pressure gauge on the cylinder reads 150 bar, the volume is 10 liters; the amount of oxygen in the bottle is

1,500 L (with a given flow rate of oxygen, for example, 5 L/min, the bottle can last approximately 5 hours). In addition to oxygen cylinder, very important parts of the system are pressure reducing valve (pressure drops to approximately 5 bar) with pressure gauge, flow regulator, and more recently with cylinders coming also the pin code as a security system (Figures 19-3a., 19-3b, and 19-3c.). There are two types of oxygen flow-meters. Thorpe's system is used in fixed systems as it must be vertical; flow-meter contains a ball located in a plastic cylinder. Bourdon system is usually used for the transport because it can operate in any position (even when the cylinder is in lying position).

When using medical oxygen it is necessary to implement certain safety measures. Oxygen is a flammable gas, and improper use may cause an explosion. When using oxygen one should not smoke and also the cylinders should be kept away from open flames and sources of ignition. Besides, the cylinders should not be handled with dirty and greasy hands, and metal keys should not be used when opening the cylinder because it can cause sparks. Do not use cylinders, if you notice damage to the cylinder itself and/or valves. Furthermore, the cylinder should not fall and become damaged during the transport (then it becomes a projectile!!). Therefore, it is advisable to use a trolley to transport cylinders.

If you hear the rustling during the cylinder opening, you should close the cylinder and check the flow regulator well fitting. It is recommended that you do not empty cylinders to less than 15 bar (security pressure). When connecting the system it is also vital to follow the security measures. When placing the system on a cylinder one should be very careful and tighten the screw. The amount of oxygen is checked when you open the main valve on the cylinder. Then the desired flow rate and method of administration of oxygen are chosen.

19.2.2. Methods of delivery of oxygen to the patient

In many cases of respiratory failure medical oxygen at a concentration higher than in the atmosphere ($FiO_2 = 0.21$ or 21%) must be delivered to the patient breathing spontaneously. Oxygen can be delivered to the patient either from the oxygen cylinders or from the hospital delivery system. In both cases it is necessary to know the systems of oxygen delivery to patients and the percentage of oxygen delivered (Table 19-1).

This can be achieved in several ways:

a) Through nasal catheter (cannula) - flow of oxygen is 1-6 L/min, resulting in a FiO_2 of 0.24 to 0.44 (each increase in the flow of 1 liter/minute causes subsequent increase of FiO_2 of about 0.04). In this manner, oxygen is administered to patients having a subjective feeling of suffocation if they breathe through the face mask. This mode can also be indicated if the patient has nausea or vomiting, and in patients with chronic obstructive pulmonary disease. Both nasal catheter ends are placed in the nose of patients (each in one nostril). Catheter tubing is going around the ears of patients and the part of the catheter under the chin is tightened with the sliding loop in order to be fixed. Of course, this method is effective only if the patient breathes through the nose.

b) by a simple mask - flow rates of 6 L/min and more are required, resulting in a FiO_2 0.5-0.6

c) through a mask with a reservoir ("non-rebreathing") - this mask has additional oxygen reservoir as well as special valves that prevent the entry of atmospheric air. With a flow of 6-10 L/min, and good adhesion to the face of the patient, it may be possible in some cases to achieve FiO2 of 1 (100%) in spontaneously breathing patients

d) by so-called Venturi masks - they bring very precise oxygen concentration in certain patients. Oxygen at high flow rates is passing through the narrow openings that also have an entry for atmospheric air on both sides. With changes in oxygen flow and the size of inlet for atmospheric air it is possible to achieve precise FiO_2 of 0.24, 0.28, 0.31, 0.35, 0.40 and 0.50 (each different concentration is launched with a mask and connector in a different color).

e) In a patient who is endotracheally intubated and mechanically ventilated, it is possible to obtain very precise inhaled oxygen concentrations. They are set up on the ventilator and can vary from 0.21 to 1.0.

Table 19-1. Methods of delivery of oxygen to the patient

Method	Oxygen flow (L/min)	Achieved FiO_2
Nasal cannula	1-6	0.24-0.45
Face mask	6-10	0.35-0.6
Mask with oxygen reservoir bag	5-15	0.5 – 1

19.3. The use of oxygen in anesthesia

Oxygen is used during anesthesia in following situations:
- mandatory in general anesthesia
  - in combination with nitrous oxide
  - in combination with air
- in regional anesthesia with sedation
- for surgery with intravenous sedation (monitored anesthesia care)

19.4 Complications of oxygen application

They can be divided into:
1) Oxygen toxicity
2) Depression of ventilation
3) Retinopathy of prematurity
4) Absorption atelectasis
5) Risk of fire

Oxygen toxicity occurs when there is more oxygen in the body than can be metabolized and/or eliminated. Toxic oxygen species are superoxide (O_2^-), hydrogen peroxide (H_2O_2), hydroperoxide (ROOH) and hydroxyl radical (OH). In normal conditions these oxygen free radicals are removed by various protective mechanisms of the organism, but otherwise the lipid peroxidation of cell membranes with a loss of cellular integrity, alteration of enzyme systems and damage of the structure of proteins can occur. Oxygen toxicity primarily affects the lungs and central nervous system. There are two important factors: PaO_2 and the exposure time.

Pulmonary toxicity is manifested as acute tracheobronchitis, cough, substernal pain, and a condition similar to acute respiratory distress syndrome (ARDS). Lung injury due to hyperoxia includes a cascade of intracellular events beginning with the formation of free radicals, followed by reaction with cellular DNA and damage to endothelial cells and alveoli. Next the interstitial edema and alveolar membrane thickening occur. Blood is directed out of areas with poorer lung oxygenation and there is ventilation-perfusion mismatch. In the later stages of lung damage epithelial alveolar type II cells and fibroblasts proliferate resulting in pulmonary fibrosis and pulmonary hypertension.

Regarding CNS oxygen toxicity (here it is called the Paul Bert effect), it occurs when breathing oxygen at pressures >1 atm, and it is manifested by tremor, twitching, and convulsions. The goal should be to use the lowest possible FiO_2 compatible with adequate tissue oxygenation. This is the maximum allowed time for each value of FiO_2:
1) 100% - no more than 12 hours
2) 80% - no more than 24 hours
3) 60% - no more than 36 hours.

The only indications for 70-100% FiO_2 would be:
1) cardiopulmonary resuscitation (CPR)
2) the periods of acute cardiorespiratory instability
3) during transport of patients

Depression of ventilation by oxygen is important in patients with chronic obstructive pulmonary disease (COPD). In this group of patients there is chronic carbon dioxide retention, and hypoxemia is the main stimulus for ventilation. Increased PaO_2 suppresses peripheral chemoreceptors, and decreases ventilation stimulus.

In premature infants hyperoxia leads to retinopathy of prematurity (ROP), which can leave permanent damage to vision. The mechanism is increased PaO_2 that causes retinal vasoconstriction, followed not only by the necrosis of blood vessels, but also by the creation of new blood vessels. There is bleeding with retinal detachment and blindness. To reduce the risk of ROP PaO_2 should be kept <80 mmHg in this population.

"Denitrogenation" absorption atelectasis is actually the collapse of poorly ventilated alveoli. They are dependent on the volume of nitrogen in order to remain above the critical volume. Nitrogen is a gas that is poorly soluble in plasma, and remains in a high concentration in the alveolar gas mixture. If the proximal airways is obstructed (purulent plugs or similar), the gas is gradually absorbed through the alveoli

into the blood due to the concentration gradient, but it is not regenerated (the airway is blocked). Due to all this there is a resulting collapse of the alveoli, i.e. atelectasis. Slow diffusion of nitrogen slows down the appearance of atelectasis. However, if the nitrogen is replaced with another gas, e.g. oxygen the process of absorption atelectasis is significantly accelerated.

The risk of fire is discussed in the previous chapter. Increased FiO_2 increases the risk of fire. Very important are preventive measures, and that is:

- Use the lowest effective FiO2
- Use the system for gas scavenging
- Avoid using outdated equipment

19.5. Hyperbaric oxygen therapy

This is a treatment in which the patient breathes 100% O_2 at a pressure higher than 1 atm (1 atm = 760 mm Hg at sea level). The basis of this treatment is to increase the concentration of dissolved O_2 (Henry's law - the concentration of any gas is proportional to the partial pressure).

If a healthy person breathes air, PaO_2 is about 100 mm Hg, and the amount of dissolved oxygen is about 0.3 mL/100 mL of blood. If he/she breathes 100% O_2, PaO_2 is then 600 mm Hg, and the amount of dissolved oxygen is 1.8 mL/100 mL of blood. If, however, he/she breathes 100% O_2, but under pressure of 3 atm (2000 mm Hg PO2), the amount of dissolved oxygen will be as high as 6 mL/100 mL of blood.

Physiological effects of hyperbaric oxygenation are:
- Reduction of bubbles (Boyle's law)
- Hypoxia
- Improving immune function
- Neovascularization
- Vasoconstriction

Indications for use of hyperbaric oxygenation can be acute and chronic.

Acute conditions are:
- Decompression sickness (divers' disease, the bends)
- Air embolism
- Carbon monoxide poisoning
- Crush syndrome
- Burns
- Acute arterial insufficiency
- Gangrene (Clostridium)
- Necrotizing soft tissue infections

Chronic conditions that may respond to the application of this treatment are:
- Radiation necrosis
- Diabetic wounds of the lower limbs
- Refractory osteomyelitis.

20. PARENTERAL AND ENTERAL NUTRITION

Mladen Carev*

20.1. Introductory remarks

The proper nutrition and adequate absorption of ingredients from the intestine are a prerequisite for the maintenance of homeostasis in the body. Nowadays there has been a substantial change of clinical thinking with regard to the importance of clinical nutrition. In the past it was considered only an additional, supportive treatment. According to today's concepts, nutritional support is one of the basic measures to treat the critical patients. Adequate nutrition in critically ill may improve wound healing, stimulate immune response, and reduce hospital stay, morbidity and mortality.

20.2. Definition

The clinical nutrition is defined as the intake of three types of basic nutritional compounds (carbohydrates, fats, proteins), as well as water, electrolytes, vitamins and trace elements, that can be delivered either via enteral or parenteral route. Clinical nutrition in the narrower sense can be divided into parenteral and enteral. Parenteral nutrition is a nutrition bypassing the intestines. Enteral nutrition uses intestines and is divided into the oral food intake (*per os*) and the intake of food or commercial nutrient solutions with the use of the feeding tubes. These tubes can be placed in the stomach, duodenum and jejunum. In addition, nutritional support can be complete or partial, depending on the patient's condition.

20.3. Clinical Nutrition – Energy Sources

The three main sources of energy in people are carbohydrates, fats and proteins. It is estimated that 1 gram of carbohydrate (glucose) and protein bring about 4 kcal of energy, while 1 gram of fat brings up to 10 kcal of energy.

Calculation of the energy needs at rest (REE - resting energy expenditure) can be made as follows:

a) precisely using indirect calorimetry (measured by oxygen consumption and carbon dioxide VO_2 and VCO_2; rarely used)
b) empirically approximately 25 kcal / kg (usually imprecise method, but often used)
c) Harris-Benedict formula - calculating the basic energy needs (BEE - basal energy expenditure); it is necessary to know the patient's gender, age, weight, and height:

MALE: BEE = 66 + (13.7 x kg) + (5 x cm) - (6.8 x age)

FEMALE: BEE = 655 + (9.6 x kg) + (1.8 x cm) - (4.7 x age).

Then one should calculate REE; REE = BEE x 1.2.

However, in the clinic Long correction factors linked to activity of patients and various clinical conditions are used (Table 20-1.).

Also, it is very important to calculate the input of nitrogen into the body. The nitrogen balance is obtained when the input is equal to the loss. Nitrogen losses can be quite accurately calculated by measuring the loss in the urine (measuring the urea in the urine); however, this is rarely used in practice. Empirically, there is a routine daily intake of 1-1.5 g protein/kg (it should be known that 1 g N_2 corresponds to 6.25 grams of protein). The objective of maintaining the nitrogen balance is to prevent the endogenous protein catabolism, which, in turn, mobilizes amino acids for energy production and for the production of acute phase reactants in the liver. This catabolism further leads to increased urinary excretion of nitrogen and consequently negative nitrogen balance.

In clinical nutrition there are also some other compounds to be included, such as vitamins (12 vitamins - A, B, C, D, E, K, B1, B2, B6, pantothenic acid, biotin, folate), and the essential trace elements (chromium, iodine, copper, manganese , iron, selenium, zinc).

20.4. What kind of nutrition?

The basic postulate of clinical nutrition is: "If the gut works, use it". Gastrointestinal tract is the route of choice for nutritional support, if its functional integrity is preserved. Maintaining the integrity of the mucous membranes of small and large intestines becomes a priority. Therefore, one should always encourage the feeding of patients with normal food or with enteral formulas whenever possible, i.e. when there is no absolute contraindication. Full rest of the intestines is clearly accompanied by the progressi-

Table 20-1. Correction factors for calculating resting energy expenditure

Physical Activity	Factor	Clinical Condition	Factor
Bed rest	1.2	Fever	1+0.13/°C
Rising from Bed	1.3	Elective Surgery	1.0 – 1.1
Shivering	1.3	Peritonitis	1.2 – 1.5
Quadruparesis	0.8	Multiple fractures	1.2 – 1.4
Hemiparesis	1.2-1.3	Craniotrauma	1.5 – 1.8
		Severe infection/sepsis	1.4 – 1.8
		Severe Burns	1.5 – 2.0
		Cancer	1.1 – 1.3
		AIDS	1.5 – 1.8

ve atrophy and disorder of intestinal mucosa. It appears that only small amounts of food in the intestinal lumen (100-200 mL) can prevent atrophy of the intestinal villi, and substantially influence on reducing the consequent bacterial translocation and other potentially fatal complications. In conclusion, enteral nutrition keeps the integrity of the intestinal mucosa, maintains mucosal immunity, and prevents increased permeability of the mucous membranes, thereby reducing the bacterial translocation. Enteral nutrition is cheaper, and easier compared to parenteral, and it appears that enteral nutrition better preserves structure and function of the GI tract with regard to parenteral. Furthermore, enteral nutrition improves nitrogen balance, increases the secretion of bile, protects the normal intestinal flora, protects against fatty infiltration of liver and gastrointestinal bleeding. There are also reports of reduced stay in the ICU.

Therefore, the fundamental question that the clinician must ask himself is whether there is any contraindication for enteral feeding, either absolute: shock, intestinal ischemia, ileus, intestinal perforation, peritonitis, or relative: partial mechanical bowel obstruction, severe diarrhea and vomiting, enterocutaneous fistula (> 500 mL / 24 h), short bowel syndrome (<60 cm), intensive chemotherapy, active gastrointestinal bleeding. If there is not any contraindication, enteral nutrition should be used exclusively because of all aforementioned reasons.

20.5. Parenteral nutrition

Parenteral nutrition (PN) is the method that allows the patient to sustain good physical condition for a longer period of time, without any oral and enteral feeding. It can be complete or partial, peripheral or central (depending on the venous route), as well as continuous or cyclic.

Indications for the PN are: 1) afunction of larger parts of the intestines, 2) in malnourished patients who can not take and absorb food, 3) in the preoperative preparation of cachectic patients, 4) in conditions needing to be treated with resting of GI tract (pancreatic, enterocutaneous fistulas). Furthermore, all patients who are presumed not to be able to feed normally within 3 days of admission should be given PN within 24-48 hours, if enteral nutrition is contraindicated or patients can not tolerate it.

The central venous catheter is often needed for the implementation of PN; the parenteral nutrition mixtures, which completely cover the energy needs are almost always hyperosmolar. Peripheral venous access can be considered for formulations with a low osmolality (<850 mOsmol/L).

Solutions for parenteral nutrition provide the required amount of energy and nutritional substances, micro- and macroelements and vitamins in a tolerant volume. Today, a very popular solution is "all in one bag", meaning that all main ingredients are in one bag (glucose, amino acids and fats).

Glucose in parenteral nutrition can be used by tissues can not use other energy sources. Furthermore, it is a low-cost, compatible with drugs, and its utilization in the periphery is the most optimal and fastest. The minimum amount of carbohydrates is 2 g/kg glucose/day.

Lipid emulsions should be an integral part of the PN. They provide not only energy but also essential fatty acids in the critically ill. There are three generations of lipid emulsion: 1) soybean or safflower oil with long-chain triglycerides (LCT), 2) a mixture of LCT, medium chain triglycerides (MCT) and olive oil, and 3) SMOF lipids (abbreviation of **S**oybean-LCT, **M**CT, **O**live oil, **F**ish oil). Today the administration of lipid emulsion with olive oil and fish oil with added omega-3 fatty acids has been more and more advocated.

Amino acids are administered at a daily dose of 1-1.5 g/kg, in order to prevent the catabolism of endogenous proteins. Amino acids are mixed or co-administered with glucose solutions (today usually "all

in one bag"). Standard solutions of amino acids are comprised of approximately 50% the essential (n = 9) and 50% non-essential (n = 10) and semi-esssential (n = 4) amino acids. The amino acid solution for patients in the ICU should contain about 0.2-0.4 g/kg/day of L-glutamine.

Complications of PN may include:

a) those from a central venous catheter (pneumothorax, hematothorax, puncture of the artery, infectious complications, air embolism, rupture of the veins, etc.),

b) from the carbohydrates (hyperglycemia, hypoglycemia, hypophosphatemia, hypercapnia)

c) from lipids (fatty liver, cholestasis, nonalcoholic steatohepatitis), and

d) other complications (atrophy of the intestinal mucosa, acalculous cholecystitis).

Regarding the technical implementation, intravenous system for PN should never be used to measure central venous pressure, for blood sampling, and also for administration of additional drugs. Usually it is performed with multi-lumen catheters, and one "port" must be exclusively intended for infusion of parenteral nutrition!

20.6. Enteral nutrition

The oral route is the only way of enteral nutrition, which stimulates the secretion of saliva. The basic requirement for the implementation of this method is the preserved act of swallowing and passability of the esophagus and stomach. However, in critically ill this type of diet is usually not possible.

More often enteral nutrition is carried out by stomach and enteral tubes (duodenal, jejunal), as well as by gastrostomy (surgical, percutaneous endoscopic, laparoscopic), and jejunostomy (surgical, percutaneous endoscopic, laparoscopic).

Enteral tube is usually placed with transnasal access, and regarding tip position we distinguish, nasogastric, nasoduodenal and nazojejunal tube. The technique of inserting a tube is usually blind, but they can also be placed with radiological and endoscopic support. Complications associated with insertion of tubes are relatively common, but usually of mild character (clogging of the tube, the nasopharyngeal erosion, esophageal reflux, esophagitis, etc.). Orogastric route is rarely used, but is indicated with of the skull base fractures.

Endoscopic methods are much simpler and less aggressive than surgical, and are applicable when enteral nutrition is carried out for more than 4 weeks. These include percutaneous endoscopic gastrostomy (PEG) and percutaneous endoscopic jejunostomy (PEJ).

Surgical gastrostomy and jejunostomy is performed when endoscopic approach is impossible.

20.6.1. The enteral formulas

There may be several types: 1) "homemade", 2) the polymer, 3) oligomeric (semi-elemental) and 4) mononomeric (elemental) formulas.

The so-called "homemade" preparations include natural foods triturated with mixer. Possible disadvantages are that it is not always known the exact type or quantity of ingredients, as well as possible bacterial contamination. They may be sometimes too dense for use.

The polymeric formulas are basic commercial preparation in hospitals. They include intact proteins, lipids (LCT or LCT + MCT), which constitute>20% of calories, and polymers of glucose (without lactose and gluten). They are of low osmolality, acceptable taste, and price. The side effects are tolerable.

Oligomeric (semielemental) formulations contain hydrolyzed protein (in the form of di-, tri-peptides, and free aminoacids), fats (LCT or LCT + MCT, but only 5-20% of calories), carbohydrates- partially hydrolyzed starch and polymers of glucose. The good side is that they can be administered in the cases of food allergy, maldigestion, inflammatory bowel disease, and pancreatic failure. The drawback is that they are considerably more expensive.

Monomeric (elemental) formulations contain amino acids, monosaccharides, and disaccharides, and very little fat (essential fatty acids, MCT, which make up <3% of caloric intake). Their advantage is that theoretically they do not require any enzymes for their absorption; therefore they are suitable for chronic pancreatitis and short bowel syndrome. The disadvantages are their organoleptic properties (for amino acids), and diarrhea (hyperosmolality).

Otherwise, many products on the market differ in the energy composition (usually 1-2 Kcal/mL), osmolality (280-1100 mOsm/kg - the main determinant being carbohydrates), and the amount of prote-

in (usually 30-40 g/L, if it is more, then they are named HN - "high nitrogen"). There are also specialized formulations for patients with diabetes mellitus, burns, end-stage renal disease, pulmonary disease, etc.

Today there are also marketed many immunomodulating formulations enriched with arginine, nucleotides and ω-fatty acids. They are recommended for elective surgery of the upper GI tract, in trauma patients, and in patients with mild sepsis.

20.6.2. The technique of enteral feeding

There are two methods of enteral feeding: 1) bolus administration - 6 to 10 daily doses, each dose is 50 to 200 (max 400) mL, administered over 5 to 30 minutes, and 2) a continuous administration - 20 to 150 mL/hour for 16-18 hours. Continuous administration can be carried out either with the help of gravity or an electrically driven pump.

The bolus enteral feeding is only valid for a stomach tube. The advantages are that it is more physiological, less expensive, and there is less chance of bacterial growth and contamination. Possible disadvantages are that it takes more nursing time, there is the greater chance of pulmonary aspiration, and is also associated with many complications, such as diarrhea, cramps, nausea, bloating and a feeling of abdominal discomfort.

In continuous enteral feeding giving via enteral pump the possible advantages are that it can be very precisely controlled, with reduced retention, risk of aspiration, and fluctuations in blood glucose levels. They can also be used with very narrow tubes and viscous preparations. Furthermore, enteral pumps are equipped with various alarms and automatic flushing saving about 30 minutes nursing time per patient per hospital day. For intragastric feeding the starting regime is usually not necessary - the stomach is a huge reservoir of diluted ingredients. For other forms of enteral nutrition the patient's nutritional needs should be gradually increased over 3 days with regard to amount and/or flow.

The possible complications of enteral feeding are tube shift, tube clogging, cramps, nausea, bloating, regurgitation, aspiration, and metabolic abnormalities (hyperglycemia, hyperkalemia, hypophosphatemia, hypomagnesemia, etc.). Furthermore, other possible complications are erosions of the nostrils and the GI mucosa, sinusitis, bacterial contamination of the preparation, and the accidental connection of enteral nutrition to an intravenous line. Possible aspiration of gastric contents can be prevented by raising the head of bed for 30-45 degrees and by using of jejunal tubes. Diarrhea is by far the most common complication of enteral nutrition (>30%). It is caused by sorbitol in preparations, osmolarity of formulas, speed of infusion, bacterial contamination, as well as the patient's condition. The measures for the prevention of diarrhea are salting of food, the use of the pump, the regular changing of sets for the purpose of preventing bacterial contamination, heating the preparation at room temperature and avoiding broad-spectrum antibiotics.

21. STRUCTURED APPROACH TO THE SERIOUSLY INJURED

Antonela Bunoza**, Mihajlo Lojpur*

21.1. Introduction

The severity of injuries can range from minor to life-threatening. Nemely,they may affect many parts of the body, including the brain, the extremities and internal organs. Injuries of vital organs are still serious than injuries of limbs, although the injuries of the limbs can also be the cause of serious morbidity and mortality.

The multitude of possible injuries to various organ systems make major trauma a complex problem. A systematic, organized approach to each patient, following International Trauma Life Support **(ITLS)** guidelines, is necessary to determine the patient's condition and appropriate interventions. This, as well as rapid transport will have the greatest impact on trauma survival in pre-hospital setting.

21.2. Epidemiology

In developed countries, every year a serious trauma experiences about 3% of the total population. Of the total number of injured 4% of them being permanently disabled and 1.5% die. It is important to note that death and disability due to trauma affecting mostly young adult segment of the population (people ages 1-45).

21.3. Structured approach to the seriously injured

Whether you are a bystander when an accident occurs, or working in the ED when a Trauma Alert is called, a quick, thorough ITLS patient assessment is the essential first step in effective patient management. It is important to have a systematic way to approach trauma patients, to ensure that nothing is missed.

Steps of ITLS Patient Assessment are:

1) Primary Survey
2) Secondary Survey, and
3) Ongoing Exam

21.3.1. Primary survey

The **ITLS primary survey** is a rapid examination used to identify and intervene in other life-threatening conditions and injuries and to make transport decisions. It is divided into 3 parts:

1) TheScene Survey,
2) The Initial Assessment, and
3) The Rapid Trauma Survey or Focused Exam.

The primary survey should take no more than 1.5-2 minutes and should be interrupted only for safety, airway obstruction and/or cardiac arrest.

Scene survey includes 5 components:

1) **Personal Protective Equipment** - Keeping yourself protected is the first priority of any first aider. The key skill for this is awareness of your surroundings and the changing situation. Once you are aware of the hazards, you can then take steps to minimize the risk to oneself. One of the key dangers to a first aider is bodily fluids, such as blood, vomit, urine and feces, which pose a risk of cross contamination. Body fluids can carry infections and diseases, including, but not limited to, HIV and hepatitis.

The main tool of the first aider to avoid this risk is a pair of impermeable gloves. Gloves protect the key contact point with the victim (i.e. the hands) and allow you to work in increased safety. They protect not only from bodily fluids, but from any dermatological infections or parasites that the victim may have.

The other key piece of protective equipment that should be in every first aid kit is an adjunct for helping to perform safe mouth-to-mouth resuscitation. With mouth-to-mouth resuscitation, there is a high probability of bodily fluid contact, especially with regurgitated stomach contents and mouth borne infections. A suitable mask will protect the rescuer from infections the victim may carry (and to some extent, protect the victim from the rescuer). It also makes the performance of CPR less onerous (not wishing to perform mouth to mouth is a key reason cited for bystanders not attempting CPR).
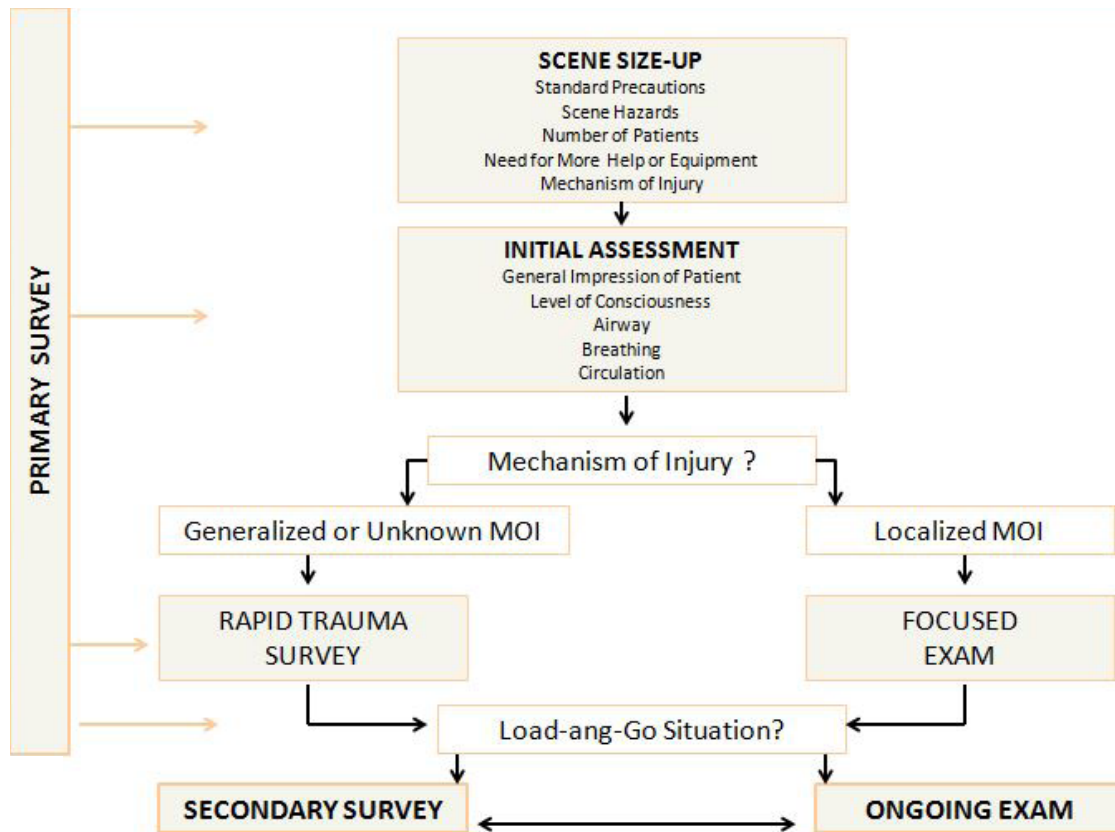
Figure 21.1. ITLS patients assessment.

CPR adjuncts come in a variety of forms, from small keyrings with a nitrile plastic shield, up to a fitted rescue 'pocket mask' such as the one pictured.

Larger first aid kits, or those in high risk areas could contain additional equipment such as:

- **Safety glasses** - Prevents spurting or pooled fluid which could splay from coming in contact with the eyes.
- **Apron or gown** - Disposable aprons are common items in larger kits, and help protect the rescuers clothing from contamination.
- **Filter breathing mask** - Some large kits, especially in high risk areas such as chemical plants, may contain breathing masks which filter out harmful chemicals or pathogens. These can be useful in normal first aid kits for dealing with victim who are suffering from communicable respiratory infections such as tuberculosis.

Often times, all of these will be included as a part of a larger kit. The kit should have a list of instructions on how to properly don/don off the equipment. Follow these instructions to prevent an accidental exposure.

1) **Scene hazards** - As you approach a scene, you need to be aware of the dangers which might be posed to you as a first aider, or to the victim. These can include obviously dangerous factors such as traffic, gas or chemical leaks, live electrical items, buildings on fire or falling objects.

There are also human factors, such as bystanders in the way, victim not being co-operative, or an aggressor in the vicinity who may have inflicted the injuries on the victim. If these factors are present, have the police called to control the situation.

If there are dangers which you cannot mitigate by your actions (such as falling masonry), then STAY CLEAR and call the emergency services. Remember to **never put yourself inharms way**.

1) **Number of patients** - Determine the total number of patients
2) **Need for more help or equipment** – If there are more patients than the responding unit can effectively handle, initiate a mass casualty plan. Begin triage.
3) **Mechanisms of injury (Generalized or focused? Potentially life – threatening?)** - determine from the patient, family, or bystanders and inspection of the scene (Examples: Vehicle Crash – Speed at impact? Rollover /Head-on, Reae end ?; Fall – How high and onto what ?; Stabbing – What caliber gun?)

INITIAL ASSESSMENT AND RESUSCITATION OF THE INJURED PATIENT

In severe trauma, assessment and resuscitation should be performed simultaneously. The purpose of the initial evaluation and management is to diagnose and address life-threatening problems, which can cause death or serious morbidity if not treated early.

The initial assessment includes 5 components, which should always be followed in strict order.

1) **General impression of the patient** – The general impression will help you decide the seriousness of the patient's condition based on his level of distress and mental status.

The general impression contains the following elements: approximate age, sex, and level of distress or responsiveness.

Examples of a typical general impression may look something like the following: I have an approximately 30-year-old male in moderate distress. Or I have an approximately 60-year-old female who appears to be unresponsive.

Emergency Medical Responders have always formed a general impression when they first see a patient, even if they are not immediately aware of doing so. With experience, you may form one on intuition alone. You may notice if the patient looks very ill, pale, or cyanotic. You may notice unusual details such as odors, temperature, and living conditions. You may immediately see serious injuries or that the patient looks stable.

This impression forms an early opinion of how seriously ill or injured the patient is. Your decision to request immediate transport or to continue assessing the patient may be based solely on your general impression.

2) **Level of consciousness (LOC)** – our actual assessment of a patient begins by determining the patient's level of responsiveness. You must quickly determine if he is responsive or unresponsive. A responsive patient may be obviously awake and interacting with those around him. An unresponsive person may not be so obvious.

You must kneel beside the patient, tap his shoulder, and state loudly something like, "Are you okay?" or "Can you hear me?" If he responds, you know he is not totally unresponsive. You will then categorize his level of responsiveness based on the AVPU scale, the letters of which stand for alert, verbal, painful, and unresponsive.

A — Alert. The alert patient will be awake, responsive, oriented, and talking with you.

V — Verbal. This is a patient who appears to be unresponsive at first but will respond to a loud verbal stimulus from you.

P — Painful. If the patient does not respond to verbal stimuli, he may respond to painful stimuli, such as a sternal (breastbone) rub or a gentle pinch to the shoulder.

U — Unresponsive. If the patient does not respond to either verbal or painful stimuli, he is said to be unresponsive.

1) **Airway assessment and protection** (maintain cervical spine stabilization when appropriate)
2) **Breathing and ventilation assessment** (maintain adequate oxygenation)
3) If the patient is unresponsive, check for adequate breathing by observing the chest rise and fall. The patient is not breathing if there is no chest movement. Gasping respirations are called *agonal respirations*. They should not be considered normal respirations.
4) **Circulation assessment** (control hemorrhage and maintain adequate end-organ perfusion)
    a) Check for a Pulse

If the patient is not breathing, check for a **carotid pulse** at the neck to determine if blood is circulating. The pulse at the neck is considered more reliable than the pulse at the wrist. A pulse at the wrist (the **radial pulse**) may not be present if the patient is in shock.

Check for a carotid pulse for 5 to 10 seconds. It is not important during the primary assessment to count the exact rate of the pulse. You only want to confirm the presence of a pulse.

• If the pulse is very rapid or weak, the patient may be in shock.
• If there is no pulse, alert dispatch and begin CPR.
• If the patient is not breathing but does have a pulse, the patient may have an airway obstruction or he may be in respiratory arrest. You must take immediate action to ventilate the patient before the heart stops.
    b) Check for Serious Bleeding

The next step in the primary assessment is checking for serious bleeding. While any uncontrolled bleeding may eventually become life threatening, you will only be concerned with profuse bleeding

during the primary assessment. Blood that is bright red and spurting may be coming from an *artery.* Because blood in arteries is under a great deal of pressure, large amounts of blood may be lost in a short period of time. Flowing blood that is darker in color is most likely coming from a *vein.* Even if the bleeding is slow, it may be life threatening if the patient has been bleeding for a long period of time.

Look at the amount of blood that has been lost on the ground, in clothing, and in the hair. Your concern is for the total amount of blood that has been lost, not just how fast or slow thebleeding is.

Assessment of circulation may be altered slightly when you immediately see profuse bleeding. In this case, attempt to control the bleeding as soon as it is discovered. Do what you can to control it, but never neglect the patient's airway and breathing status.

After initial assessment you will continuewith a rapid trauma surveyorfocusedexamdepends on themechanism of injuryandthe results of theinitial assessmentof the injured.

The trauma patient is classified as either having no significant mechanism of injury (probably not causing a serious injury) or having a significant mechanism of injury (probablycausing a serious injury).

- To assess a trauma patient with no significant mechanism of injury, begin by performing a focused assessment on the area that the patient tells you is injured
- To detect and care for serious injuries in a patient with a significant mechanism of injury, perform a rapid trauma assessment looking for obvious injuries

Table 21-1. Significant mechanism of injuri for adults and childs

Signs of significant mechanisms of injury for an adult include:	Significant mechanisms of injury for a child include:
Ejection from a vehicle	Falls of more than 10 feet
Death of one or more passengers in a motor-vehicle crash	Bicycle collision
Falls greater than 15 feet	Medium-speed vehicle collision
Rollover vehicle collision	
High-speed vehicle collision	
Vehicle-pedestrian collision	
Motorcycle crash	
Unresponsiveness or altered mental status	
Penetrations of the head, neck, chest, or abdomen	

Rapid trauma survey

It is a quick method (should take no more than two to three minutes), to identify hidden and obvious injuries in a trauma victim. The goal is to identify and treat immediate threats to life that may not have been obvious during an initial assessment.

Rapid trauma survey is quick and systematic (from head to toe) exam of these body sections: Head and Neck, Chest, Abdomen, Pelvis, Extremities and Back :

- **Head**: DCAP-BLS-TIC (Deformity, Contusions, Abrasions, Puncture/Penetration - Burns, Tenderness, Laceration, Swelling - Trauma, Instability, Crepitus)
- **Neck**: DCAP-BLS-TIC, Tracheal Deviation, Neck veins
- **Chest**: DCAP-BLS-TIC, Look (equal rise and fall), Listen (auscultate) and Feel (crepitus, subcutaneous emphysema, fractures, flail segment), Percuss, Heart Sounds
- **Abdomen**: DCAP-BLS, Penetrating wounds, Flaccid, rigid, pain, tender
- **Pelvis**: DCAP-BLS-TIC
- **Extremities:** crepitus, pain, exposed bone ends
- **Back**: Examine posterior during roll and placement on backboard- DCAP-BLS-TIC

Finally take initial vital sign (blood pressure, pulse and breathing rate) and collect details of the history according to the form designated by the acronym SAMPLE

- The first set of *vital signs* is called *baseline vital signs.* Compare all other vital sign readings to the baseline vital signs. This comparison helps determine if the patient is stable or unstable, improving or growing worse, and benefiting or not benefiting from care procedures.

For an adult, a continuous pulse rate of less than 60 beats per minute or above 100 beats per minute is considered abnormal. Likewise, a respiratory rate above 26 breaths per minute or below 10 breaths per minute is considered serious. You should be concerned about these vital signs because they indicate unstable situations that could become life threatening, and the patient could worsen quickly.

- *SAMPLE history* is an <u>mnemonicacronym</u> to remember key questions for a person's <u>assessment</u>. It is used for alert people, but often much of this information can also be obtained from the family or friend of an unresponsive person. The parts of the mnemonic are:

1) **S**igns and Symptoms
2) **A**llergies
3) **M**edications
4) **P**ast medical history, injuries, illnesses
5) **L**ast meal/intake
6) **E**vents leading up to the injury and/or illness

If the patient has impaired consciousness make a brief neurological examination (perform this exam now if there is altered mental status; otherwise, perform it during the detailed secondary survey).

This mini neurological assessment is made to establish:

- Level of consciousness, using GCS.

Table 21-2. Glasgow coma scale.

Glasgow Coma Scale					
	1	2	3	4	5	6
Eye	Does not open eyes	Opens eyes in response to painful stimuli	Opens eyes in response to voice	Opens eyes spontaneously	N/A	N/A
Verbal	Makes no sounds	Incomprehensible sounds	Utters inappropriate words	Confused, disoriented	Oriented, converses normally	N/A
Motor	Makes no movements	Extension to painful stimuli (decerebrate response)	Abnormal flexion to painful stimuli (decorticate response)	Flexion / Withdrawal to painful stimuli	Localizes painful stimuli	Obeys commands

The scale is composed of three tests: eye, verbal and motor responses. The three values separately as well as their sum are considered. The lowest possible GCS (the sum) is 3 (deep coma or death), while the highest is 15 (fully awake person). Generally, brain injury is classified as Severe, with GCS < 8-9, Moderate, GCS 8 or 9–12 (controversial), Minor, GCS ≥ 13.

- Pupils: size, symmetry and reaction.
- Any lateralising signs or signs of cerebral herniation (unconscious, dilated pupil(s), hypertension, bradycardia, posturing)?

Uneven pupils (suspected head injury)

Figure 21-3 . Pupil abnormalities in head trauma (eg one pupil may be dilated and the other may be constricted or pupil reaction may be sluggish to light)
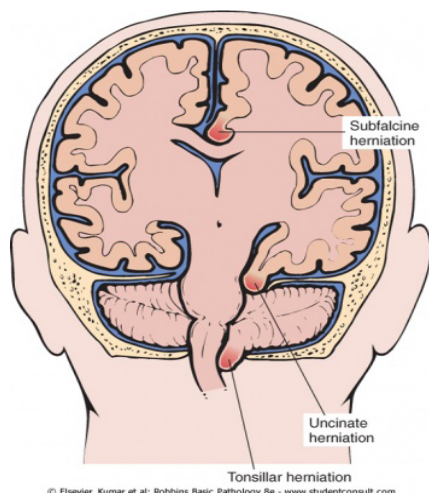

Figure 21-4. Brain herniation – it occurs when something inside the skull produces pressure that moves brain tissues. This is most often the result of brain swelling from a head injury. Herniation compresses brain tissue and thus damages it.

Focused exam

When your trauma patient has no significant mechanism of injury, the steps of the further assessment are appropriately simplified. Instead of examining the patient from head to toe (rapid trauma survey), focus your assessment on just the areas that the patient tells you are painful or that you suspect may be injured because of the mechanism of injury. The assessment includes a physical exam, a baseline set of vital signs, and a patient SAMPLE history.

This is used for patients with a medical complaint who are conscious, able to adequately relate their chief complaint to you, and have no life-threatening conditions.

Load and go situation

In some situations, the nature or severity of a patient's illness or injury may exceed the EMS personnel's ability to effectively manage the patient. Lifesaving treatments may need to be initiated within a short time frame (minutes to hours) if the patient is to have any chance for survival. These critically ill or injured patients require immediate transport for appropriate, specialized lifesaving techniques and therapies available in a hospital setting.

Life-threatening conditions for load and go situation may be identified during initial assessement or during rapid trauma survey/focused exam of primary survey, or at any point during the response.

Table 21-3. Life-threatening conditions for load and go situation

Initial assessement	Decreased LOC or altered mental status
	Abnormal respirations
	Abnormal circulation (shock or uncontrolled hemorrhage)
	Abnormal Chest Exam
	Tender, distended abdomen
Rapid Trauma Survey	Pelvic instability
	Bilateral femur fractures
	Significant mechanism of injury or poor general impression

***LOC** – level of consciousness

21.3.2. Secondary survey

When the primary survey is completed, resuscitation efforts are well established, and the vital signs are normalizing, the secondary survey can begin.

It includes 2 components :

1) Repeated initial assessment, and

2) Detailed exam

The detailed exam includes a detailed history, repeat vital signs and thorough but efficient physical examination.

In detailed, head to toe physical exam, you will examine the same body areas that you examined during your rapid assessment but you will look more closely at each area to search for findings of lesser priority than life threats and/or signs of injury that have worsened.

You should look for abnormality. This can take the form of asymmetry, deformity, bruising, point tenderness, minor bleeding and medic alert bracelets or necklaces.

The injured should be reviewed in the following order :

• **Head** - Check the scalp for cuts, bruises, swellings, and other signs of injury. Examine the skull for deformities, depressions, and other signs of injury. Inspect the eyelids/eyes for impaled objects or other injury. Determine pupil size, equality, and reactions to light. Note the color of the inner of the inner surface of the eyelids. Look for blood, clear fluids, or bloody fluids in the nose and ears. Examine the mouth for airway obstructions, blood, and any odd odors.

• **Neck** - Examine the patient for point tenderness or deformity of the cervical spine. Any tenderness or deformity should be an indication of a possible spine injury. If the patient's C-spine has not been immobilized immobilize now prior to moving on with the rest of the exam. Check to see if the patient is a neck breather, check for tracheal deviation

• **Chest** - Examine the chest for cuts, bruises, penetrations, and impaled objects. Check for fractures. Note chest movements a look for equal expansion.

• **Abdomen** - Examine the abdomen for cuts bruises, penetrations, and impaled objects. Feel the abdomen for tenderness. Gently press on the abdomen with the palm side of the fingers, noting
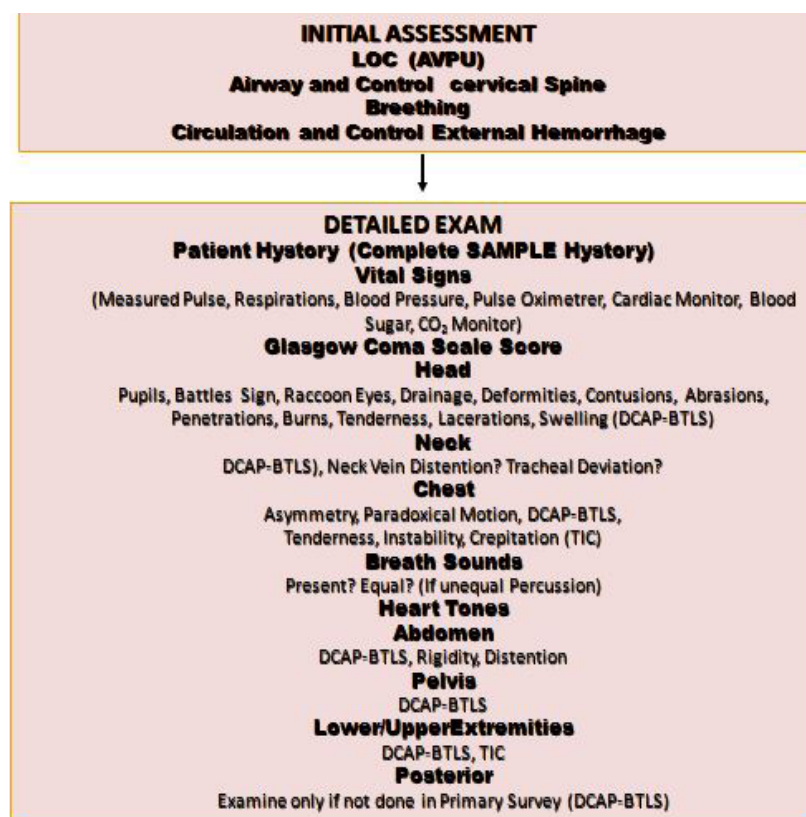
Figure 21.6. Secondary survey

any areas that are rigid, swollen, or painful. Note if the pain is in one spot or generalized. Check by quadrants and document any problems in a specific quadrant.

- **Lower Back** - Feel for point tenderness, deformity, and other signs of injury
- **Pelvis** - Feel the pelvis for injuries and possible fractures. After checking the lower back, slide your hands from the small of the back to the lateral wings of the pelvis. Press in and down at the same time noting the presence of pain and/ or deformity
- **Genital Region** - Look for wetness caused by incontinence or bleeding or impaled objects. In male patients check for priapism (persistent erection of the penis). This is an important indication of spinal injury
- **Lower Extremities** - Examine for deformities, swellings, bleedings, discolorations, bone protrusions and obvious fractures. Check for a distal pulse. The most useful is the posterior tibial pulse which is felt behind the medial ankle. If a patient is wearing boots and has indications of a crush injury do not remove them. Check the feet for motor function and sensation.
- **Upper Extremities** - Examine for deformities, swellings, bleedings, discolorations, bone protrusions and obvious fractures. Check for the radial pulse (wrist). In children check for capillary refill. Check for motor function and strength.

Do not delay transport to perform a detailed physical exam; it is only performed while enroute to the hospital orwhile waiting for transport to arrive.

The secondary survey plays a crucial role in avoiding missed injuries.

Table 21-4. Commonly missed injuries

Blunt abdominal trauma: Hollow viscus injury, pancreatoduodenal injuries, diaphragmatic rupture
Penetrating abdominal trauma: Rectal and ureteral injuries
Thoracic trauma: Aortic injuries, pericardial tamponade, esophageal perforation
Extremity trauma: Fractures (especially in distal extremities), vascular disruption, compartment syndrome

21.3.3. Ongoing exam

The ongoing assessmentwill be performed on all patients while the patient is being transported to the hospital. It is designed to reassess the patient for changes that may require new intervention. You will also evaluate the effectiveness of earlier interventions, and reassess earlier significant findings.

Table 21-5. Ongoing exam

ITLS Ongoing Exam
Subjective Changes – "How do you feel?
Reassess Mental Status – LOC, Pupils, GCS
Reassess ABCs – Patency, Vital Signs, Color, Skin Condition, Temperature, JVD, Tracheal Deviation, Breath Sounds, Heart Tones
Reassess Abdomen – Development of Tenderness, Distention, Rigidity
Check Each Identified Injury – Change in Status, PMS
Check Interventions – Patency, Position, Flow Rate, Security

*PMS – pulse, motor, and sensory

You should be prepared to modify treatment as appropriate and begin new treatment on the basis of your findings during the ongoing assessment.

Seriously ill or injured patients should be reassessed every five minutes. A good rule to follow is that by the time you finish a reassessment from start to finish, it is time to start over with the beginning of the next reassessment. Patients who are not seriously ill or injured should be reassessed every 15 minutes.

21.4. "ABC" assessment and immediate resuscitation measures

21.4.1. Airway (A - airway)

As stated above, the control of the airway should be performed under the assumption that for each of the injured there is an unstable fracture of the cervical spine, therefore, with protection of the cervical spine from excessive manipulation. Head and neck of injured patient may not be hiperextended or hiperflexioned, or rotate, so it is best to set on the injured immobilizing agent (soft or hard collar) and the assessment and the establishment of the airway done while it is at the place. If immobilizing means to be temporarily removed, the establishment of the airway should be performed by manual, "in-line" immobilization.

At the start of the evaluation of the airway attention should be focused on the search for signs of obstruction:

1) **Look**:
   a) if the patient is agitated (hypoxia) or sleepy (hypercapnia),
   b) whether it is cyanotic (conc.of hemoglobin reduced ≥ 5 g%),
   c) if the accessory respiratory muscles are used in breathing (dyspnea),
   d) if trachea is in the midline (valve pneumothorax?).
2) **Listen** are there any sound phenomena during speech or breathing:
   a) hoarseness and pain in his speech speaks for injury to the trachea,
   b) stridor breathing speaks in favor of mechanical obstruction with vomiting content, blood or secretions.
3) **Feel** the flow of air that comes out of the patient's mouth if breathing is uncertain.

The examination should include inspection of injuries because some injuries often result in obstruction of the airway.

- Fractures of facial bones do not require immediate treatment, except in cases of uncontrolled bleeding or secretion.
- Fractures of the lower jaw are often associated with soft tissue injuries, and can easily compromise the airway (early intubation?)
- Injuries of larynx and pharynx on the other hand seldom require emergency tracheotomy. For them to be doubted if the present hoarseness, if one notes the neck hematoma or edema or feel a subcutaneous emphysema.

The method of disposal of the airway (ET intubation, use of other means, the establishment of a surgical airway) will depend on the experience of the team, tools at our disposal and the factors related to the injured and his injuries.

Airway can be cared for temporarily (raising the chin and jaw thrust, the use of oro- or naso-pharyngeal "airway") or definitely (ET intubation, tracheotomy or conicotomy). The decision of definitive airway should be based on the clinical situation.

Definitive airway is required:

- in the case of injuries or conditions that directly or potentially threaten airway (inhalation injuries, fractures of the lower jaw, injuries to the larynx or trachea, retropharyngeal hematoma, head injury with GCS < 8 or epi seizures),
- if the airway is difficult to ensure from aspiration of blood or vomit, if it is impossible to maintain adequate ventilation and oxygenation with ambu, using the mask and the oxygen,

- if there is a wish to apply transport mechanical ventilation
- if it is impossible to secure the airway in any other way

ET intubation remains the gold standard for airway management in injured, but it requires skill and carries the risk of further injury. Usually the ET tube is introduced orotracheal, through the mouth. However, orotracheal intubation usually requires some degree of cervical hyperextension and the injured should always be carried out with the use of in-line stabilization of the head and neck by an assistant.

Blind nasotracheal intubation (without the use of a laryngoscope) is applicability of orotracheal in situations with a prospect or confirmed fracture of the cervical spine. It is performed on injured who are still breathing, but not enough, because the air flow when breathing facilitates blindly introducing tube into the trachea. It is contraindicated on any injuried that are apnoic, who have severe bone fractures or facia bone or skull base fracture .

A tracheotomy is rarely possible to do it in field conditions, even when we have the knowledge and skill of performing it. It does not apply to conicotomy , which is a very simple method when it is performed with the use of ready-made kits.

21.4.2. Breathing (B – Breathing)

Assessment of breathing includes:

1) Assess the depth and frequency of breathing
2) Inspection mobility of both chest sides during breathing (symmetry?) and mutual auscultation:
   a) Silenced breathing sound usually speaks in favor of significant damage to the lungs,
   b) Asymmetric mobility of the chest wall during breathing speasks in favor of the loss of chest muscles ability to shrink properly,
   c) Paradoxical movement of the chest wall during breathing speech in favor of the injured skeletal ribcage.
3) Inspection and palpation of the neck to detect injuries or possible deviation of the trachea
4) Palpation of the chest in order to perceive or crepitus felt the strain of the wall.
5) Percussion of the chest to detect pneumothorax (hyper- resonance sound) or haematothorax (dullness)

There are four types of injuries that can acutely endanger ventilation of injured, and should be familiar with. These are flail chest, open or tension pneumothorax and massive haematothorax.

Flail Chest occurs when part of the chest wall becomes unstable due to multiple fractures of the ribs. During inspiration negative pressure sucks this segment of the chest wall and during exhalation positive pressure bulge it, so it always moves in the opposite direction from the rest of the thoracic wall, disrupting the mechanics of breathing. It is important to know that lung below that segment of the wall is usually damage and does not participate in oxygenation. In addition, injured is holding breath because of extreme pain, which further contributes to hypoxemia.

These patients need:

1) Oxygen
2) Analgesia, which may be of importance to ensure adequate spontaneous ventilation in the injured with a small segment of the flail chest. High-risk patients (the elderly or those with COPD) may require an epidural analgesia to avoid the detrimental effects of systemic narcotics to their marginal ventilation,
3) Airway toilet because they can not cough up,
4) Intubation and ventilatory support in the injured with large flail chest segment (greater than 6-9 cm in diameter) but also those with a smaller segment of flail chest and the accompanying acute or chronic pulmonary disease.

Open pneumothorax is open communication between chest and external environment. Identified as wheezy chest wound and characterized by the rapid onset of hypoxia, because it interferes with the mechanics of breathing.

Requires urgent covering of chest wall defect with occlusive bandage, after which occurs a dramatic recovery of respiratory function.

Tension pneumothorax is a severe version of pneumothorax. It occurs in situations where the air with every exalation goes out in interpleural space and have no place to get out of it. Thus, the air pressure in the pleural space, during spontaneous breathing and especially during mechanical ventilation increases. The consequences are concurrent disorders of breathing mechanics and hemodynamic disorders caused by problems in cardiac filling.

The diagnosis of the tension pneumothorax should be placed clinically, because the treatment should carried out immediately, before RTG checks.

Criteria (triad) for diagnosis are:

- breathing disorders,
- shock,
- absence of breathing sounds with hyper-resonoance percussive sound on one side of the chest

Immediately after the diagnosis it is necessary to puncture the chest with needle, and make open pneumothorax of the tension pneumothorax. It immediately eliminates the negative effects of the tension pneumothorax on hemodynamics. Classical it is punctured in the second intercostal space, in mamillary line or anywhere in the front wall of the chest, in addition to the projection of the heart. The use of iv. cannula 12 to 14 G is recommended.

Definitely care usually requires a chest drain by applying negative pressure (- 20 cm H2O).

Massive haematothorax is usually a result of bleeding from the central blood vessels of the chest, although the intercostal arteries can bleed to death.

The diagnosis should be suspected when:

- when the breathing is less audible by auscultation on one side of the chest , and
- when on the same side of the chest pecussion produces muffled sound

Treatment :

- A medium-sized haematothorax → thoracic drainage and monitoring of further bleeding
- The rapid loss of 1000-2000 mL of blood or bleeding greater than 200 mL per hour, which is not reduced in intensity → thoracotomy

21.4.3. Circulation (C)

Bleeding is the most common cause of shock and death of the injured. Consequently, hypotension should be considered primarily as the result of bleeding and hypovolemia, until proven otherwise! Clinical signs that may lead to the diagnosis of bleeding at the first contact with the injured are:

1) disturbance of consciousness, although aware injured (high GCS) may also have a significant blood loss,
2) pale skin color as a distinctive sign of hypovolemia,
3) rapid, rhythmic pulse.

It should be remembered that rapid, irregular pulse indicates the potential cardiac dysfunction (eg. in cardiac contusion)!

The occurrence and severity of certain symptoms will depend on the amount of blood lost, and provides an estimate on the amount of bleeding (Table 21-6).

Table 21-6. Assessment of blood loss based on clinical indicators

Clinical sign	Class1	Class 2	Class 3	Class 4
Blood loss %	<15%	15–30 %	30–40%	>40%
Heart rate	<100	>100	>120	>140
Blood pressure, mm Hg	Normal	Normal	Decreased	Decreased
Pulse pressure	Normal or increased	Decreased	Decreased	Decreased
Respiratory rate	14–20	20–30	30–40	>35
Mental status	Slightly anxious	Mildly anxious	Anxious, confused	Confused, letargic

Emergency procedure consists of:

1) Establishment of a wide venous acces by introducing two broad iv. cannula (12-14 gauge) in the peripheral vein. The alternative is canulation of femoral and / or subclavian vein
2) Compensation volume of circulating blood, usually with Ringer lactate. If shock persists after 2-3 L RL, start giving blood products. In emergency situations it O Rh (D) negative blood is suitable !
3) Stop the bleeding with digital compression and bandage for the duration of aggressive circulation recoupment. Bleeding in the pelvis may be reduced by using anti-shock trousers and bleeding in the fractured femur by immobilisation!

Monitoring condition of injured during the compensation of blood circulating volume, includes several options:

1) Non-invasive options:

- Continuous monitoring of ECG and SaO_2 during the stabilization period

- Evaluation of adequacy of compensation based on the general condition of the injured, blood pressure, pulse rate, skin color, body temperature, urine output,

2) Invasive options:
- The introduction of the arterial cannula for the continuous monitoring of blood pressure,
- Monitoring central vein pressure (CVP) to assess the adequacy of the compensation volume of circulation.

If there is no adequant response to the compensation of circulating blood volume, there are two options:
- Injured is still bleeding and his hypotension is result of development of hemorrhagic shock or
- Its hypotension may be due to the so-called non-hemorrhagic shock

Namely, if the injured remains hypotensive despite compensation volume of circulating blood and stopping bleeding is visible, it is possible that he has internal bleeding. The most common of occult bloodings are:

1) Chest: haematothorax → **drain and monitoring**!.

2) Abdomen: intraperitoneally (lavage or ultrasound examination) and / or retroperitoneal hemorrhage (CT abdomen) → **operate**

3) Pelvis: usually a venous bleeding → **consider artefitial embolisation of bleeding vessels and / or external fixation of pelvic bones**

The reasons for the existence of so-called. **"nonhemorrhagic shock"** may be the following:
1) Tension pneumothorax,
2) Pericardial tamponade,
3) A blunt injury (contusion) of the heart
4) Neurogenic shock

About tension pneumonthorax everything has been said.

Cardiac tamponade is more often a result of chest blunt trauma, than penetrating trauma of the heart (think of the mechanism of injury!). The accumulation of blood and an increase in pressure in the pericardial space stop further bleeding heart (usually from the atrium), but also interferes with the filling of the heart and performances obstructive shock.

The diagnosis of this condition should be set up clinically, on the spot, but the classic triad - jugular venous distension, hypotension and sound of the water wheel at auscultation of the heart, are seen in less than 1/3 of injuries (eg.it is hard that neck veins will be filled in persons who is bleeding). Nevertheless, the physician should be suspected pericardial tamponade in thoracic trauma with shock unresponsive to compensation volume of circulation, if the tension pneumothorax is off. In the treatment of pericardial tamponade surgical management is preferred (pericardial window), but sometimes that can not wait and it is necessary to do so. called needle pericardiocentesis, as a temporary measure.

Blunt trauma of the heart may manifest a range of clinical presentations, from asymptomatic cases to cardiogenic shock. Knowledge of the mechanism may help diagnosis (most often occurs after a direct blow to the chest or as a result of deceleration injury), while ECG (possible sinus tachycardia, atrial or ventricular tachycardia, RBBB, atrial fibrillation, VT, ..) and troponin levels in blood are not specific enough to help. The method can be an additional element of diagnosis is echocardiography, which shows hypocontractility of injured ventricle segment of the heart, but it is rarely available in the outpatient setting.

The procedure with the injured whom we suspect to have cardiac contusion is as follows:
1) Monitored injured at least 4 hours: if the injured is hemodinamicly stable after 4 hours of continuous monitoring, without the arrhythmias, does not need further treatment in this direction. If not, do ultrasound of the heart and consider introducing a pulmonary catheter that can provide important diagnostic and therapeutic information.
2) To all injured with suspect cardiac contusion make corrections of acidosis, hypoxemia and electrolytic disorders, carefully compensated fluids, pharmacological combat life-threatening arrhitmias. Give inotropes? – Maybe in some cases

Neurogenic shock resulting in injury of the cervical or thoracic spine. Elements of the diagnosis are mechanism of injury and the accompanying external injuries, and symptomatology – hypotension, which is often associated with bradycardia, flaccid paralysis, loss of reflexes and priapism.

In the treatment of hypertension in neurogenic shock volume replacement usually is not enough, but should be given vasopressor!

22. PAIN – TREATMENT OF ACUTE AND CHRONIC PAIN

Lenko Šarić**, Marko Jukić*

22.1. Pain

Pain is defined as unpleasant sensory and emotional experience associated with actual or potential tissue damage. It is always a subjective feeling.

Pain is universal human experience which is necessary for protection. Nevertheless, in cases of prolonged pain it affects everyday activity, lowers quality of life and can eventually become chronic pain.

There are different types of pain: acute pain, chronic non-malignant pain and cancer pain.

Most common causes of acute pain are injuries, surgical procedures, inflammations, malignant disease, hormonal disbalance etc. **Chronic pain** is defined as pain lasting for more than 3 months from expected healing of damaged tissue. Most common causes of chronic pain are degenerative and inflammatory diseases of musculoskeletal system, previous injuries and surgical procedures, malignant disease, neurologic conditions and many others. Europe has recognized the importance of chronic pain In 2001 *European Association for Study of Pain* issued *Declaration on pain* stating that "acute pain can be considered as a symptom of acute illness or injury while chronic pain is a specific health problem, an illness on its own" (Devor).

Chronic pain is a specific public health problem. It causes suffering that lowers quality of life and leads to depression and eventually results in large economic consequences. Also people are missing work. Their efficiency declines as they suffer from backache, arthritis and musculoskeletal pain. As time passes chronic pain leads to disability, temporary or permanent, that consequently leads to existential end economic issues.

As people are getting older, their physiologic reserves decline and comorbidities increase (Gibson and Helme, 2001). During aging, degenerative processes such as osteoarthritis, fibromyalgia, spinal canal stenosis, stroke, diabetes mellitus, peripheral neuropathies, post herpetic neuralgia and cancer advance are leading to development of pain.

Pain can be divided into nociceptive (somatic or visceral), neuropathic and psychogenic.

Somatic pain occurs when nociceptors located in skin and musculoskeletal system are stimulated.

Visceral pain on the other hand occurs when stimulus activates nociceptors located in internal organs and it is usually provoked by cutting, stretching, ischemia or inflammation.

Neuropathic pain is caused by damage or dysfunction of peripheral and/or central nervous system. It includes pain associated with diabetic neuropathy, polyneuropathies, postherpetic neuralgia, stroke etc. Neuropathic pain tends to be paroxysmal and sometimes lancinating with burning quality, and it is usually associated with hyperpathia. Pain can occur either spontaneously, without painful stimuli, or after stimuli that normally does not cause pain (allodynia). Peripheral neuropathic pain is caused by direct damage or disease of peripheral somatosensory system. Allodynia is type of pain that occurs after weak stimuli (gentle touch, e.g.) that normally does not cause pain. The term is used to define situation when stimulus which is usually not painful causes weaker or stronger sensation of pain. In cases where stimulus causes pain, and it is not entirely clear whether the stimulus itself is painful, we use term hyperalgesia. Hyperalgesia can therefore be defined as amplified response or increased sensitivity to painful stimulus. It includes states of lower pain threshold as well as those with stronger than normal response to painful stimuli.

Psychogenic pain is type of pain that is associated with psychiatric disorders.

Persistent chronic pain affects physical and psychosocial functions that significantly reduce quality of life. All that can lead to depression and even suicide, sleep deprivation, loss of appetite and loss of body weight as well as detoriation of cognitive functions.

Pain signal can be fast and slow. Fast pain is felt 0.1 second after noxious stimulus and it is usually sharp, stinging acute pain. Slow pain on the other hand starts a second or more after painful stimulus and it is felt as burning, dull, pulsating, persistent pain. These two types of pain are transmitted via different nerve types each with its own characteristics (see table 22-1.).

Fast pain (acute pain) is transmitted via A δ-fibers while slow pain (chronic) is transmitted via C-fibers. Pain receptors are actually free nerve endings located in the skin and in some internal organs (periostium, arterial wall, joints, falks cerebri and tentorium). These receptors are activated by three different

types of stimuli: mechanical, thermal and chemical. Regarding the transmission of pain, there are several phases: transduction, transmission, modulation and perception.

Table 22-1. Nerve transmission fibers and their characteristics

Type of fiber	Function	Diameter (*µm*)	Conduction velocity (m/s)
A-fibers			
α	**Motor**	**6-22**	**30-120**
β	touch, pressure	12-20	> 40-50
γ	muscle spindle	3-6	15-35
δ	pain, touch, temperature	1-4	10-40
B-fibers	Preganglionic, autonomic nervous system	< 3	3-15
C-fibers	Sensory Simpathic nervous system	Pain; 0.3 – 1.3 Postganglionic; 0.3 – 1.3	< 0.7-1.3 0.7-2.3

Nociceptors are free nerve endings sensitive to noxious stimuli or to a stimulus that can become harmful in case of prolonged effect. Nociceptors are able to encrypt and transmit noxious stimulus.

Nociception is a process of encrypting and processing of noxious stimulus in neuron. There is difference between pain and nociception. While nociception is physiological process, pain includes subjective feeling. Pain can exist without nociception as well as nociception can happen without pain. Nociception is central process in many painful conditions.

Central sensitization is an increased response of nociceptive neurons in nervous system to some normal or subnormal stimulus. It includes an increased response during endogenous pain control system dysfunction.

Sensitization means lowering of pain threshold or progressive amplification of a response to painful stimulus. It occurs when there is increased availability of neurons which are activated by normal stimulus or when there is increased response of neurons to a stimulus that is below the pain threshold. Also, it can occur because of spontaneous bursts and increased number of receptors. Sensitization is actually neurophysiological term which is used only when input and output of neural systems is known (laboratory studies, e.g.). Clinically, sensitization can be manifested only indirectly as hyperalgesia or allodynia.

Wind-up sensitization is a term that is defined as hypersensitivity of dorsal roots in spinal cord because of permanent stimulus of C-fibers. This process is dependent of NMDA receptor activation.

Chemical stimuli that cause pain are mediated by bradikinin, serotonin, potassium ions, acids, acetylcholine and different proteolitic enzymes. Prostaglandins and substance P increase sensitivity of nerve endings, but can not stimulate them on their own.

Impulses that occur after stimulation of nerve endings spread through afferent nerve fiber until they reach synapse in spinal cord. Acute pain is transferred via A δ-fibers, while chronic pain is transferred via C-fibers. Place where impulse spreads onto spinal neuron is located in superficial laminas of dorsal horn. Nerve fibers from spinal cord join to form tracts (spinothalamic, spinoreticular, spinomesencephalic). Via these tracts impulses are transferred to brainstem, mesencephalon and thalamus. From there on, the impulses are spread via synaptic neurons to cerebral cortex where impulses are analyzed.

In the dorsal horn of spinal cord the impulses are not simply transferred from primary neuron to spinal one. Rather there are many connections with interneurons and descending supraspinal systems. In pain modulation processes there are many different excitatory transmitters involved such as substance P, calcitonin gene related peptide (CGRP), cholecystokinin (CCK), glutamate and aspartate. Neurotransmitters act via receptor activation. The most important receptor in the spinal cord level of transmission and modulation of pain is N-metil d-aspartame (NMDA) receptor that is activated by glutamate. Besides these excitatory receptors, there are also descending inhibitory mechanisms which act through opioid, GABA-ergic, serotonin and adrenergic receptors.

There are many interconnections between reticular formation, hypothalamus and limbic system suggesting that spinothalamicoreticular system is responsible for emotional and autonomic reactions to pain.

Occurrence and transmission of pain described above describes mostly acute, biological and clinical pain. On the other hand, chronic pain is much more complex and there are many differences occurring in nociceptive system as well as in psychological and physiological functions compared to acute pain.

22.2. Treatment of Pain

It is physicians' duty to find the source of pain and to alleviate/remove pain. Even in cases when the cause of pain is not entirely clear, physician has to help patient and ease his pain. During the treatment, physician has to keep in mind all benefits as well as all potential harms for his patient since every treatment has its complications and side effects and can lead to undesirable outcome. Approach to treatment of chronic pain, and sometimes to treatment of acute pain as well, is multidisciplinary and involves both pharmacological and non-pharmacological methods (e.g. Physical therapy, TENS, ultrasound, laser, exercise, use of heat and cold...). Also, in some cases it is necessary to use complementary methods (e.g., acupuncture, chiropractic) and psychological therapy (e.g., relaxation techniques, cognitive-behavioral therapy). Patients should be protected against using non beneficial procedures, procedures that have no medical evidence of being efficient and from expensive procedures that have no results. The physician has to be competent and ethical and must not allow the patient being exploited.

While undergoing surgical procedures, some diagnostic procedures and some physiologic procedures (painful delivery) patients can experience pain that can be alleviated by anesthesiologists. The basic human right that we all have to respect is *life with no pain*.

Chronic pain is multidimensional problem and its treatment is rather complex so the approach to treatment of chronic pain is often multidisciplinary and multimodal.

Efficient treatment of chronic pain in elderly patients requires special education and skill. Physicians as well as others involved in treatment should be aware of possible harmful procedures, drug interactions and possible side effects regarding patient's comorbidities. Elderly people have many medical and nutritional difficulties so treatment with analgesics is more demanding considering possible drug interactions (Pickering et al, 2004). Furthermore, treatment can lead to undesirable outcomes, drug dependence and tolerance.

Drug tolerance occurs when body is repeatedly given same doses of same drug and it leads to weakening of drug effect (e.g., opioids) so it becomes necessary to increase the dosage in order to reach the same effect.

Drug dependence, which is also known as physical dependence, occurs after sudden cessation of drug (opioids, local anesthetics, and clonidine).

Abstinence syndrome occurs after sudden cessation of agents that have created physical and psychical dependence (alcohol, drugs, medications). It is manifested as sweating, vomiting, diarrhea, cardiovascular disturbances, tremor, epileptic seizures, tension, hallucinations, impaired consciousness (delirium, psychosis).

Because of subjective component of pain it is not always easy to assess quality and intensity of pain. Pain intensity is usually assessed using pain scales, e.g. *visual/verbal analog scale (VAS)*. Estimation is more difficult in elderly patients because of their impaired cognitive abilities, impaired sight and hearing. When dealing with those patients physician has to use nonverbal signs when assessing pain (facial expressions, movements…). In addition, when dealing with newborns, infants and small children assessment of pain can also be challenging and requires additional education and experience of both physician and other nursing staff, especially physiotherapists.

Treatment of chronic pain should be based on mechanisms that caused the pain. Therefore, one should differentiate between nociceptive and neuropathic pain. Chronic nociceptive pain is managed with specific treatment of cause that led to pain (e.g. NSAID for arthritis), and for alleviating pain we use usual analgesics (paracetamol, metamizol), NSAID, opioid analgesics as well as the rescue drugs. Choice of analgesic depends upon pain intensity and pathophysiologic processes.

Neuropathic pain, on the other hand, is usually treated by removing the cause (e.g., nerve decompression, decompression of nerve roots). However, mechanism of development of neuropathic pain is rather complex, with clear diagnostic criteria missing, making treatment of this kind of pain very difficult. When there is no clear cause of neuropathic pain, the treatment is usually focused on managing the symptoms and giving support for the patient. Drugs that are used are those that act transmission of painful stimulus and those that act on ion channels located in dorsal horn of spinal cord. Those drugs include antiepileptics, tricyclic antidepressants, sodium channel blocators, NMDA-receptor antagonists, opioids and nonspecific analgesics. Furthermore, non-pharmacological methods are also used (e.g., physical therapy, electrical nerve stimulation) and psychological therapy (relaxation techniques, biofeedback).

22.3. Pharmacological treatment of acute pain

For treatment of acute pain different drugs are used. These include nonspecific analgesics (paracetamol, acetylsalicylic acid), nonsteroid anti-inflammatory drugs (NSAIDs), opioids, local anesthetics and

other drugs (anticonvulsants, antidepressants). In addition to pharmacological treatment, physical therapy is also used. Pain is usually caused by injury, inflammation, surgical procedures and function disorders (e.g., spasm, kidney or gall bladder stones, intestinal volvulus). In any case, the procedure includes identifying the cause of pain and its elimination if possible and administration of analgesics.

22.3.1. Treatment of postoperative pain

Acute postoperative pain occurs after surgical intervention. Its cause is tissue damage. This kind of pain is nociceptive (somatic and visceral) and neuropathic (nerve damage). It can be combined, pain before the surgical procedure and the pain after the procedure. Pain can also be caused by catheters, probes and drainage. Successful treatment of acute postoperative pain is of big importance because, if not treated properly, chronic pain can occur. Postoperative pain reduces mobility of the patient and it disrupts patients' sleep. It can also lead to development of pulmonary (hypoxemia, atelectasis, pneumonia) as well as thromboembolic complications. Furthermore, acute postoperative pain can lead to cardiovascular disturbances (tachycardia, hypertension, arrhythmias, increased oxygen consumption) and gastrointestinal complications (heartburn, obstipation). By treating postoperative pain properly we improve physical, psychical and social components of patients' life, we reduce his hospital stay and reduce possibility of complications and development of chronic pain.

However, pain treatment has its complications. It can be accompanied by nausea, vomiting, constipation, respiratory depression, neurological damage, cardiovascular depression, itching, allergic reactions etc.

In order to reduce possibility of chronic pain development, medications can be given before surgical procedure. This is called *preemptive analgesia* and it is efficient way for managing acute pain. Preemptive analgesia is, therefore, administration of analgesics before operation (premedication) and immediately before beginning of surgical procedure.

Approach to pain treatment is individualized and different factors have to be kept in mind (e.g., previous experience, comorbidities, patients' habits, his overall medical status etc.).

Pain intensity is assessed using VAS-scale. Values of VAS-score are noted in medical documentation and patients' status is checked frequently.

Pharmacologic treatment

There are four groups of drugs used for treatment of postoperative pain: non-steroid anti-inflammatory drugs (NSAIDs) and antireumatics, weak opioids, strong opioids, specific agents (see table 22-2.).

Table 22-2. Pharmacologic treatment of pain

Group	Analgesics	Side effects
Non-steroidal anti-inflammatory drugs	Paracetamol, NSAIDs, COX-2 inhibitors	Gastrointestinal, Renal
Weak opioids	Codeine, Tramadol, aracetamol/Codeine, Paracetamol/tramadol	Nausea, Vomiting, Respiratory depression, Obstipation, Tolerance, addiction
Strong opioids	Morphine, Diamorphine (heroin), Petidine, Piritramide, Oxycodone, Fentanyl	Nausea, Vomiting, Respiratory depression, Obstipation, Tolerance, addiction
Adjuvant analgesics	Gabapentin, pregabalin, Ketamine, Clonidine, TCA	Sleepiness, Loss of concentration, Confusion

Use of two or more analgesics with different mechanisms of action is called balanced or multimodal analgesia. This kind of treatment enables stronger analgesic effect without increasing the frequency of side effects that would develop if the dosage of single analgesic was increased (e.g., paracetamol + tramadol or NSAID + opioid or NSAID + special agent).

Table 22-3 shows non-opioid analgesic, and table 22-5 shows opioid analgesics used in postoperative pain treatment. Dosages and ways of administration listed in tables are general. Treatment is always individualized for each patient.

Table 22-3. Non-opioid analgesics

Drug	Usual dosage per os or rectal	IV dosage	Interval (hrs)
Metamizole	0.5 – 1 gr	1 gr max 5 gr/24 hr	4–6
Paracetamol	0.5 – 1 gr	1 gr	4–6
Diclofenac	25 – 50 mg	75 mg	8
Ibuprofen	0.2 – 0.4 gr		4–6

Table 22-5. Opioid analgesics

Drug	Administration	Dosage
Morphine	IV IM (not recommended because of frequent pain during administration)	Single dose: 1-4 mg Interval: 4 hrs or less, depends on patients' state 5-10 mg every 3-4 hrs
Codeine	PO	3 mg/kg, in combination with paracetamol; for adults: min 30 mg
Meperidine	IV, IM, PO	0.5-1.5 mg/kg; Interval 4-6 hrs
Tramadol	IV (slow injection; nausea +, vomiting) IM (avoid if possible) PO (as soon as possible)	50-100 mg; infusion:400 mg/24hr 50-100 mg every 6-8 hrs 50-100 mg every 6 hrs

Metamizole (dipyrone) is analgesic used for treatment of acute and chronic pain. It is sold as over-the-counter drug. In most of European countries it is not recommended for postoperative pain treatment. In USA this drug is not used in hospital settings due to "insufficient evidence regarding the safety of its administration" as well as increased incidence of agranulocytosis and aplastic anaemia. However, incidence of these side effects is small. Its advantages over salicylates and NSAIDs are less GI side effects, less impact on acid base status and availability of water soluble solutions enabling parenteral administration.

Regional anesthesia

Regional anesthesia techniques are methods of choice for postoperative treatment in abdominal aorta surgery, thoracic surgery and orthopedic surgery of lower extremities. Continuous epidural analgesia is the most commonly used technique. Analgesia is accomplished by administering solutions of long acting local anesthetics and opioids.

Also, these drugs can be applied intermittently. In patient controlled epidural analgesia (PCEA) patient can administer intermittent boluses of local anesthetic and/or opioids by himself. In order to make epidural anesthesia successful, it is important to place catheter properly. For major abdominal surgery the tip of catheter should be placed in level Th6-Th10 of spinal column, and for orthopedic procedures on lower extremities catheter tip should be place on L2-L4 level. For continuous and intermittent epidural analgesia special pump has to be available. 0.2% ropivacaine or 0.1-0.2% bupivacaine or levobupivacaine are most commonly used local anesthetics for epidural analgesia.

Postoperative analgesia can be treated with continuous peripheral nerve blocks (interscalene, infraclavicular, axillar, femoral block). By using this type of regional analgesia we avoid side effects of neuraxial blocks (hypotension, marked motor blockade, epidural hematoma or abscess).

Infiltration analgesia

Pain can be reduced by infiltrating the wound with local anesthetic. Success and duration of analgesia depends on the wound size and type as well as on amount of local anesthetic being used. Wound can be infiltrated with 0.25-0.5% ropivacaine, bupivacaine or levobupivacaine.

Non-pharmacological methods

There is variety of non-pharmacological methods that can be used in addition to pharmacological treatment of postoperative pain. Some of those are administration of ice, acupuncture, relaxation techniques and hypnosis.

22.3.2. Treatment of pain in outpatient surgery

Nowadays, there is increasing number of surgical procedures being done in daily surgery. In these procedures minimally invasive surgery is often used and choice of anesthesia is very important. Regional anesthesia techniques are used whenever possible, and long acting opioids are best avoided.

Guidelines for postoperative analgesia should define:

- Which drugs can patients take on their own (no prescription: paracetamol, NSAIDs, combination of oral analgesics);
- Which drugs must be prescribed by physician (prescription drugs: weak opioids, such as codeine and tramadol, and strong oral opioids like morphine and oxycodone).

Regional analgesia in outpatient surgery

Single shot techniques are often used for intraoperative analgesia but they can also be done after the surgery while patient is still anesthetized in order to provide postoperative analgesia. Long acting local anesthetic is used in this setting. Single shot blockade of brachial plexus or other major nerve blocks can

enable adequate analgesia in duration of 12-24 hours. In order to avoid sudden onset of pain when local anesthetic loses its action, it is important to start with proper analgesia before the pain occurs and continue it regularly.

Advantages of regional anesthesia are:
- Predictable duration of analgesia, ranging from 2-3 hours to 20-24 hours using single shot techniques, and up to 72 hours and more when using catheters;
- Adjustable intensity of block as intensive analgesia from start changes to less intensive depending on type, concentration and volume of local anesthetic;
- Reduced opioid consumption.

Systemic analgesia

Systemic analgesics should be given in some order, from weaker to stronger ones:
1) Paracetamol + NSAIDs administered properly in order to have maximal postoperative effect, or metamizole 2.5 gr 1-2 times a day (for adults; max 5 gr/day);
2) Weak opioids (tramadol) if necessary;
3) Strong opioids should be administered in small IV doses as a rescue drugs, e.g. 1 mg of morphine per minute, up to 5 mg max.

If very intensive pain occurs postoperatively, strong opioids should be administered immediately.

Special requirements in treatment of acute pain

Some factors like sex, depression, anxiety, existing pain syndromes and preoperative use of opioids can lead to increased analgesics requirements in postoperative period.

When dealing with patients who are unable to communicate adequately, special consideration should be given to hemodynamic monitoring as well as changes of consciousness and changes from their usual daily activities.

In patients taking opioids in preoperative settings, tolerance and pseudo addiction can occur. If opioids are suddenly stopped in those patients, withdrawal symptoms can develop. Furthermore, these patients should not be given partial opioid antagonists and agonists/antagonists like pentazocine or buprenorphine because they can cause withdrawal symptoms.

Assessment, documenting and treating pain after discharge (outpatient surgery)

Every patient in daily surgery should be assessed for pain intensity before being discharged, and that should be noted in his medical documentation. Patients should be given appropriate analgesics to use at home. They should also be given written instructions on how to take analgesics and other medications properly. As pain intensity reduces, so should dosage of analgesics. In cases when patient is unable to actively participate in decision making, proper instructions should be given to caregivers or members of patients' family, and for underage patients, those instructions are given to their parents or custodians. Every patient should also be given a phone number on which he can get all necessary information and consultation after discharge.

Patients are given a package of analgesics to use at home. Those packages can contain various analgesics, like paracetamol, codeine, diclofenac, NSAIDs or tramadol.

In outpatient surgery, every patient should be given written information on what to expect in couple of days after surgical procedure. They should also be given information on possible surgical and anesthesia complications and information on what to do in such cases in order to avoid unnecessary tension. Patients should have a phone number which they can refer to in cases when they need additional information.

22.4. Pharmacological treatment of chronic pain

Variety of drugs are used in treatment of chronic pain: non-specific analgesics (paracetamol, acetylsalicylic acid), NSAIDs, opioids, tricyclic antidepressants, antiepileptics, local anesthetics, corticosteroids, sympathomimetics.

Choice of drug and its dosage is determined individually, depending on patients' general condition (kidney and liver disease), possible side effects, patients' habits, drug availability etc.

Goal of chronic pain treatment is to facilitate inhibitory mechanisms in dorsal horn of spinal cord and therefore stop signals from being transferred to brain. Antinociceptive effect is mediated by serotoninergic, adrenergic, GABAergic and opioid receptor mechanisms.

When deciding on choice of treatment, WHO recommendations should be followed and pain assessment scales should be used.

Non-specific analgesics include paracetamol, acetylsalicylic acid and metamizole. These drugs are used for treatment of minor to moderate pain. Their mechanism of action involves arachidonic acid metabolism and inhibition of prostaglandin synthesis. They are also used for treatment of acute pain and in chronic pain treatment they are often prescribed for shorter period of time.

NSAIDs are used for treatment of minor to moderate pain. They can also be used in addition to opioids for treatment of severe pain. They have analgesic, antipyretic and anti-inflammatory effect. This is accomplished by inhibiting cyclooxygenase enzyme and therefore inhibiting prostaglandin, prostacyclin and thromboxane synthesis. Most common side effects are gastrointestinal mucosa damage and gastrointestinal bleeding. They can also impair renal function, especially in patients who already have renal disease. These drugs have effect on coagulation leading to increased time of bleeding. This group of drugs includes indomethacin, diclofenac, piroxicam, tenoxicam, ibuprofen, ketoprofen and coxibs.

Opioid analgesics act by binding to opioid receptors. By their activation they inhibit transmission of pain impulses. There are two groups of opioids: weak (tramadol, pentazocine, codeine) and strong ones (morphine, hydromorphone, oxycodone, fentanyl). Opioids are used for treatment of both acute and chronic pain, especially pain cause by malignant disease. Some of them are used for treatment of non-malignant chronic pain. However, opinions on use of opioids for that indication are not unanimous. Great care must be given to tolerance and addiction development. Therefore, when using opioids for non-malignant pain treatment strict protocols must be followed. Those protocols define which patients can be given opioid analgesics, the choice of opioid, its dosage and how the side effects and treatment effect should be followed. Continuous follow-up of these patients is mandatory. Opioids are given gradually, starting from lowest dose, and they are also withdrawn gradually in order to avoid withdrawal symptoms.

Withdrawal syndrome develops after sudden discontinuation of substances that cause physical and psychical dependence (alcohol, drugs and medications). Symptoms can vary from nausea and vomiting, diarrhea, cardiac and circulatory disturbances, tremor, epileptic seizures, tension, euphoria, consciousness disturbances (delirium, psychosis) and hallucinations. If withdrawal syndrome develops, opioid should be given again and then discontinued gradually.

Drug dependence is also known as physical dependence. It occurs after sudden discontinuation of drug (opioid, local anesthetic, clonidine).

Drug tolerance occurs when patient is repeatedly given same doses of drug and it leads to lesser effect (e.g., opioids).

Serotonin syndrome can occur in case of concomitant use of tramadol and other serotoninergic drugs (selective serotonin re-uptake inhibitors, MAO inhibitors). It manifests as confusion, agitation, increased body temperature, sweating, ataxia, hyperreflexia, myoclonus and diarrhea.

Tricyclic antidepressants inhibit re-uptake of serotonin and norepinephrine. They also block sodium channels and NMDA receptors and therefore inhibit transmission of pain stimuli. Side effects of these drugs are mouth dryness, constipation, urinary dysfunction, blurred sight. Cognitive changes can also occur, as well as orthostatic hypotension and sexual dysfunction.

Anticonvulsants and local anesthetics act as membrane stabilizers by blocking sodium channels. They also inhibit release of excitatory aminoacids in central neurons and/or increase GABAergic activity and therefore increase inhibitory mechanisms of signal transmission control. Carbamazepine blocks sodium channels in same way as lidocaine does and also facilitates inhibitory effect of GABAergic neurons. This drug is hepatotoxic so levels of liver enzymes should be checked before starting the treatment as well as during the treatment. Gabapentin acts through calcium channels and by increasing GABA levels in neurons. Lidocaine and other local anesthetics, mexiletine, phenytoin and amantadine act through sodium channels.

NMDA-receptor antagonists, such as ketamine, dextromethorphan and magnesium, have limited use in chronic pain treatment.

Surface analgesics include capsaicin products, local anesthetics, NSAIDs and opioids (TTS). Capsaicin acts by reducing substance-P and other peptides (CGRP, VIP, and somatostatin) concentrations in non-myelinized primary afferent neuron. NSAID act by inhibiting arachidonic acid metabolism and lidocaine by inhibiting sodium channels. Opioid patches (fentanyl TTS, buprenorphine TTS) are primarily used for chronic cancer pain. They can also be used for treatment of non-malignant pain in case of strong indication (severe pain that cannot be treated with other analgesics, patients in which opioids are not contraindicated).

22.4.1. Regional anesthesia and neurolytic techniques

In treatment of chronic pain blocks of sympathetic nervous system are often used. Those include ganglion stellatum block, plexus coeliacus, lumbar plexus, nerve block in cephalic area and interscalene block. Rationale use of these blocks is in stopping the transmission of peripheral stimuli which support central pain mechanisms and also in modulation of pain by using segmental blockades.

Ganglion stellatum block

Cervical sympathetic nervous system includes three ganglia: superior, middle and inferior one. Ganglion stellatum is located between transverse process of seventh cervical vertebrae and first rib. It is formed by inferior cervical and first thoracic ganglia. Thoracic ganglion is located behind and cervical one is located in front of vertebral artery. Sympathetic nerve fibers from this ganglion innervate neck and arm. Its blockade causes Horner's syndrome, which occurs during first ten minutes after blockade. It is manifested as ptosis, miosis, anhidrosis, nasal mucosa congestion, vasodilation and increased skin temperature. If catheter is placed, local anesthetic can be repeatedly administered in order to decrease pain. **Indications** for ganglion stellatum block are Raynaud disease, neurogenic painful syndromes (causalgia, herpes zoster, phantom pain), reflex sympathetic dystrophy, hyperhidrosis, arterial vasoconstriction on upper extremity (frostbites, intra-arterial application of barbiturates), Meniere disease, cervical syndrome. **Complications** include intravascular injection (possible toxic reaction), pneumothorax, subarachnoid anesthesia, phrenic nerve blockade, cardio-accelerator fibers blockade and neck hematoma.

Plexus coeliacus block

Plexus coeliacus is the largest sympathetic plexus that innervates abdominal organs (pancreas, liver, stomach, kidneys, and suprarenal glands). It consists of sympathetic and parasympathetic nerve fibers. It is located in retroperitoneum, in level of Th12-L1 vertebrae. **Indications** for this block include pancreatic cancer, malignant tumors of upper abdomen, acute and chronic pancreatitis. Coeliac plexus blockade can also be performed in order to differentiate visceral pain from pain originating from anterior abdominal wall. **Complications** of performing this block are intravascular injection, subarachnoid or epidural anesthesia, perforation of abdominal organs, retroperitoneal hematoma and hypotension (as a result of reflex spread from sympathetic blockade).

Lumbar plexus block

Lumbar sympathetic nervous system consists of five sympathetic ganglia that innervate pelvic organs and lower extremities. It is located on both sides of spine between transversal processes of lumbar vertebrae and medial side of psoas muscle. On the left side it is located behind abdominal aorta, and on the right side it lies behind inferior vena cava. **Indications** for lumbar plexus blockade are pelvic pain syndromes, vasospastic disorders of lower extremities and pain syndromes of lower extremities. **Complications** are: intravascular, intraperitoneal, subarachnoid, epidural or psoas muscle injection.

Every patient that is subjected to either of these blocks must be under supervision of anesthesia staff during the block performance as well as for at least two hours after the block.

22.5. Recommendations for acute pain treatment and treatment of chronic pain syndromes

Treatment of acute and postoperative pain

For treatment of acute postoperative pain analgesic best suited to patients' medical condition and type of surgical procedure should be used. If pain can be treated with weak analgesic (NSAID, paracetamol) then that drug should be given in appropriate doses. In cases where stronger analgesia is necessary (e.g. morphine), it is not reasonable to use weak opioid first. Analgesics can be administered orally, rectally, intramuscularly, intravenously, subcutaneous, transmucosaly, locally, epidural, spinal or patient controlled (PCA). It is important to determine which analgesic is most appropriate and in what doses should be administered. We can choose one of the following analgesics:

1) NSAID, paracetamol
2) Codeine, dyhidrocodein, tramadol, metamizol
3) Morphine (IV, SC), fentanyl (transmucosaly)

Treatment of acute musculoskeletal pain:

1) NSAID (orally, local), paracetamol (combination is not always better solution);
2) Coxibs;

3) Steroids (e.g. sub acromial), ultrasound;
4) Opioids (codeine, dyhidrocodein, tramadol, oxycodone, morphine, buprenorphine TTS, fentanyl TTS);
5) As adjuvants, anticonvulsants, antidepressants and muscle relaxants can be prescribed.

In acute phase: analgesics, resting (4-10 days), physical therapy.

Pain treatment in chronic pain syndromes

Chronic backache, pharmacologic treatment:
1) NSAIDs, paracetamol, tramadol, benzodiazepines;
2) Opioids (fentanyl TTS, buprenorphine TTS);
3) Adjuvant analgesics (antidepressants, anticonvulsants, α2-agonists, muscle relaxants);
4) Invasive procedures (epidural steroid and local anesthetic injection, stimulation of spinal cord, spinal administration of drugs).

Approach in treatment of chronic pain syndromes is multimodal. It includes pharmacologic therapy as well as physical therapy.

Fibromyalgia treatment:
• Tricyclic antidepressants (TCA; amitriptyline, cyclobenzaprine);
• Antidepressants, selective serotonin re-uptake inhibitors (venlafaxine, duloxetine, milnacipran, mirtazapine, olanzapine, tropisetron;
• NMDA-receptor antagonists (ketamine, dextromethorphan);
• Opioids (tramadol, tramadol + paracetamol);
• Anticonvulsants (carbamazepine, phenytoin, gabapentin, pregabalin);
• NSAID (as adjuvant treatment);
• Buprenorphine TTS (limited effect);
• Acupuncture, TENS, laser therapy (limited effect);
• Trigger points (injection of corticosteroids; limited effect).

Osteoarthritis chronic pain treatment:
1) First step: paracetamol + topical NSAID-,
2) Second step:
    a) codeine (PO) +/- NSAID, coxibs;
    b) dyhidrocodein;
    c) tramadol;
    d) buprenorphine TTS (small doses).
3) Third step:
    a) Oxycodone or tramadol (PO);
    b) Buprenorphine TTS or fentanyl TTS.

Intraarticular corticosteroid injection can also be used.

Pain treatment in herpes zoster and post herpetic neuralgia:

Acute phase:
1) Antiviral drugs in the first 72 hrs;
2) Amitriptyline (small doses) or desipramine;
3) Sympathetic block (if necessary).

Chronic phase:
• Gabapentin or pregabalin

Other treatment options include local injection of anesthetic and corticosteroids and lidocaine patch or TENS. NSAIDs are not given as adjuvant drugs, but amitriptyline, doxepin, trazodone, fluoxetine can be prescribed.

Pain treatment in acute coronary syndrome:

Morphine is used for treatment of strong pain. Additional cardiologic therapy is also used (oxygen, β-blockers, nitroglycerine).

Pain treatment in malignant disease:

Acute pain treatment in malignant disease:
1) NSAIDs, paracetamol, tramadol or

2) Opioids: morphine (PO, SC,IV), fentanyl (transmucosaly);

3) Combination of opioids and NSAIDs, oncologic therapy and surgical treatment.

Chronic pain treatment in malignant disease:

1) Specific oncologic therapy;

2) Pharmacologic therapy;

3) Non-pharmacologic treatment (physical therapy and other methods of treatment);

4) Invasive techniques (nerve blocks).

Pharmacologic therapy in malignant disease:

1) VAS 1-3: for treatment of weak pain or as adjuvants to stronger analgesics non-opioid analgesics are used. Those include paracetamol, NSAIDs (ibuprofen, diclofenak) and coxibs (celecoxib);

2) VAS 4-6: moderate pain is treated with weak opioids and adjuvant analgesics. Usually, codeine (PO), oxycodone (in combination with NSAID), propoxyphene, hydrocodone, dihydrocodeine and tramadol are used for this indication.

3) VAS 7-10: severe pain is treated with strong analgesics (opioids) with addition of NSAIDs, anti-depressants, anticonvulsants and other drugs. Severe pain can be treated with morphine, hydro-morphone, oxycodone, levorphanol, methadone, fentanyl, buprenorphine and diamorphine. During first 24 hours dosage of morphine should be titrated carefully and drug is given in regular intervals. After that, equianalgesic dosage of new opioid is calculated. When pain is well contro-lled dosage should be reduced by 25-50% when introducing new drug into the treatment. Dosage should again be titrated during first 24 hours and increased if necessary.

Long-acting opioids:

- Oxycodone: initial dose is 10 mg (5-10 mg every 3-4 hours), followed by determining daily dosage;
- Morphine-sulphate: initial dose is 15 mg (10-30 mg every 3-4 hours), followed by incremental dosa-ge adjustments;
- Hydromorphone: 1-3 mg every 4 hours;
- Methadone: initial dose is 2.5-5 mg po every 8-12 hours;
- Fentanyl: transdermal (TTS), initial dose is 25 μg/h, replace after 72 hours;
- Buprenorphine: transdermal (TTS), initial dose is 17.5 μg/h, replace after 96 hours.

Treatment should always be started by using lower doses and daily titration of dose. In addition to opioids, adjuvant drugs can also be prescribed (antidepressant, anticonvulsant).

Principles of opioid treatment:

- In patients with constant level of pain in case when breakthrough pain occurs, short-acting opioid should be administered (morphine or transmucosal fentanyl);
- When treatment is stabilized, short-acting opioids (morphine) should be replaced with long-acting opioids (oxycodone, hydromorphone, fentanyl TTS, buprenorphine TTS);
- Drug should be taken in regular intervals;
- In case of tolerance development alternative opioid should be given;
- Most common side-effects (nausea, obstipation, vomiting, respiratory depression) should be trea-ted preventively.

Adjuvants to opioids in treatment of pain include tricyclic antidepressants, selective serotonin re-up-take inhibitors, anticonvulsants and topical drugs.

For treatment of nausea during opioid therapy, following drugs can be used: metoclopramide, ondan-setron, thiethylperazine and dimenhydrinate.

For treatment of obstipation during opioid therapy following drugs can be used: lactulose, glycerol, bisacodyl, magnesium-hydroxide or sorbitol.

Pruritus can be treated with diphenhydramine or promethazine.

Delirium is treated with haloperidol.

Respiratory depression: in cases when respiratory depression is caused by long acting opioids (met-hadone), naloxone infusion should be given. In other cases, naloxone (0.4 mg/mL) is diluted with 9 mL of 0.9% NaCl. 1-2 mL of that solution should be given every 30-60 seconds until the respiratory depression is resolved. However, since the half-life of naloxone is shorter than that of opioids, it is necessary to repe-at the dose of naloxone. If total of 1 mg of naloxone is given and after 10 minutes there is still no impro-vement of respiratory depression, then other causes should be considered.

Pain treatment in hematologic disease (sickle cell disease, hemophilia)

- Opioids, morphine IV; Meperidine should be avoided;
- Hydroxyurea;
- Blood transfusion;
- Ketorolac iv or methyl prednisone;
- Oxygen.

Pain treatment in HIV infection (AIDS):

- Opioids;
- Lamotrigine for HIV neuropathy.

Pain treatment in non-surgical abdominal disease:

- Dysmenorrhea, renal and biliary colic, irritable colon syndrome;
- NSAIDs for renal colic; Meperidine or morphine can also be used;
- Spasmolytics for irritable bowel syndrome;
- NSAIDs + vitamin B1 for primary dysmenorrhea;
- Ketorolac or meperidine for biliary colic.

2. Treatment of chronic neuropathic pain:

Treatment of chronic neuropathic pain starts with pharmacologic therapy.

- Tricyclic antidepressants: amitriptyline, desipramine, nortriptyline; treatment starts with smaller doses which are increased every 3-5 days if necessary and if patient can handle it;
- Serotonin and norepinephrine re-uptake inhibitors (SNRI): venlafaxine, duloxetine;
- Anticonvulsants: gabapentin, pregabalin, carbamazepine, sodium valproate; treatment starts with lower doses which are increased every 3-5 days if necessary;
- Opioids: oxycodone, tramadol;
- Local anesthetics: lidocaine (iv, neural block), topical therapy (capsaicin, NSAID, lidocaine patch)
- NMDA receptor agonists: ketamine, antiarrhythmics, mexiletine, tocainide;
- In some cases invasive procedures are performed:
    - Nerve stimulator implantation;
    - Implantation of intrathecal infusion pump;
    - Surgical nerve decompression.

Pharmacologic agents most often used:

- Carbamazepine – central pain syndrome, trigeminal neuralgia;
- Pregabalin – diabetic neuropathy, post herpetic neuropathy;
- Topiramate – diabetic neuropathy;
- Lamotrigine – peripheral neuropathy (diabetic or HIV neuropathy);
- Dextromethorphan – postherpetic neuralgia;
- Amitriptyline – HIV neuropathy;
- Sodium valproate - spinal cord injuries;
- Cannabinoids – multiple sclerosis.

Complex regional pain syndromes (CRPS):

Pharmacologic therapy:

1) Antidepressants, anticonvulsants, opioids, capsaicin, lidocaine;
2) Corticosteroids, calcium modulators, free radical scavengers;
3) Phenoxybenzamine, prazosine, guanethidine, reserpine, clonidine.

Headaches

There are various types of headaches and different drugs are used in treatment of each one. Mostly used analgesics are:

- Triptans – severe migraine;
- Aspirin, metoclopramide – migraine with moderate symptoms;
- Caffeine, aspirin, acetaminophen – acute phase of tension headache;
- Ibuprofen, acetaminophen – migraine with moderate symptoms;
- Sumatriptan – cluster type headache;
- Opioids are not recommended for headache treatment; Meperidine especially should be avoided.

Migraine:

In cases of mild and moderate symptoms, migraine should be treated with following analgesics:

- Acetaminophen, acetylsalicylic acid;
- NSAID, ibuprofen, naproxen, ketoprofen.

In cases of severe migraine treatment includes:

- Metoclopramide + dihydroergotamine (DHE);
- Ergotamine: contraindications are coronary artery disease, angina pectoris, peripheral vascular disease, Raynaud syndrome, uncontrolled arterial hypertension, significantly impaired liver and kidney function;
- Sumatriptan (*Imitrex*) and triptans which selectively bind to $5\text{-HT}_{1B/D/F}$ receptors; these drugs have direct vasoconstrictive and anti-inflammatory effect on dural blood vessels. Furthermore, sumatriptan reduces nausea, vomiting, photophobia and fonophobia. It is efficient even when administered 4 hours after migraine attack.
- Butalbital: this drug is combination of barbiturates and caffeine, acetylsalicylic acid or acetaminophen in combination with other drugs;
- Ketorolac (IV, IM);
- Other $5\text{-HT}_{1B/D/F}$ receptor agonists: naratriptan, zolmitriptan, almatriptan, frovatriptan, eletriptan.

Side effects of these drugs include headache, sleepiness, dizziness, fatigue, and tingling sensations. Chest pain, nausea and vomiting can sometimes also occur.

Contraindications for DHE administration include Prinzmetal angina, pregnancy, coronary artery disease, uncontrolled arterial hypertension, peripheral vascular disease, significantly impaired renal and kidney function.

Some drugs have been used for migraine treatment but there is no evidence of their effectiveness. These drugs include carbamazepine, clomipramine, clonazepam, lamotrigine, indomethacin, nifedipine.

Tension headache:

Acute headaches are usually treated with NSAIDs.

For prophylaxis, tricyclic antidepressants or NSAIDs can be used.

Cluster headache:

This type of headache is characterized by periodic headaches which occur usually during the day. Pain is unilateral and pulsating with lacrimation and eye redness.

Acute treatment includes oxygen inhalation (10 L/min) with ergotamine or sumatriptan.

Prophylactic treatment includes one of the following: verapamil, ergotamine tartrate, lithium carbonate, steroids, occipital nerve blockade.

Indomethacin can be used for prophylaxis in cases of:

- Chronic and acute hemicranias;
- Cough-induced headache;
- Coital migraine;
- Idiopathic stabbing headache.

It is important to keep in mind possible side effects: gastrointestinal (stomach ulcers or bleeding), nausea, purpura, dizziness.

Pain associated with temporomandibular joint:

Pharmacologic therapy includes:

- NSAIDs, tramadol;
- Selective tricyclic antidepressants, selective anticonvulsants and other analgesics, muscle relaxants and anxiolytics; opioids are rarely indicated;
- Buspiron – for long term treatment.

23. INJURIES CAUSED BY ENVIRONMENTAL FACTORS

Nenad Karanović*, Mila Kavelj**

23.1. Drowning

23.1.1. Intoduction

Drowning is a severe public health problem because of its prevalence, morbidity and mortality. The classic image of a victim helplessly pounding on the water trying to stay afloat and desperately trying to breathe is rarely seen. More often the victim is seen floating or quietly sinking below the surface. The victim of drowning usually cannot shout or call for help because of laryngospasm, or lack of air required for phonation. At the same time, the typical position of the victim in the water is upright, along with out-stretched hands pounding and spraying with occasional submersion and emergence of the head or upper body, so that to a casual observer it might seem like a game. Victim may submerge and reappear on the surface several times. Children can be seen on the surface for only 10 to 20 seconds before permanent submersion. Unlike them, adults can resist submersion gasping for life on the surface for up to 60 seconds.

Annually, worldwide death rate caused by drowning is high. According to the World Health Organization, during the year 2000, around 449 000 people had drowned, while another 1,3 million died from the consequences of drowning. However, the exact number of victims is probably higher, but it is difficult to determine it because many deaths caused by drowning are not reported regularly. Such a large number of deaths puts drowning as the second cause of accidental deaths, especially in children, immediately after traffic accidents. Data for Croatia report on average a hundred deaths caused by drowning per year, while data on morbidity due to drowning are not known.

It is estimated that 40-45% of drowning cases occur during swimming. Drowning is the cause of 60% of deaths in diving accidents, while in nautical sports it causes 90% of death cases.

23.1.2. The definition of drowning

The new definition classifies drowning as the process leading to the damage of respiratory function due to submersion or immersion in a liquid medium.

23.1.3. Risk factors

Drowning occurs most often in different activities related to water (swimming, diving, etc.), but it can be caused by trauma, as well. Furthermore, men are more likely to drown than females. Children up to 5 years of age have the highest rate of drowning, as well as younger people between 15 and 29 years of age. Alcohol consumption is a significant risk factor in both adolescents and adults. Various chronic diseases or acute events like myocardial infarction, hypertensive crisis, diabetes mellitus (especially hypoglycemia), severe depressive or anxiety disorders, epilepsy, and certain congenital syndromes and genetic factors (eg, type 1 *"long-QT syndrome"*) can contribute to a higher incidence of drowning.

23.1.4. Pathophysiology

Pathophysiology in the case of drowning is complex. Primarily the duration of hypoxia (lack of oxygen) is responsible for mortality and morbidity later. Besides it, the consequences of drowning can be affected by body's response to stress, injury to the lungs due to aspiration (inhaling liquid or vomited mass), environmental factors such as hypothermia and individual ability to adapt.

More recent findings have shown that the differences in drowning, depending on the tonicity of water, are only theoretical and achievable in laboratory conditions, while not clinically relevant. So ultimately, there is no difference between immersion in fresh or salt water.

The consequences of drowning are manifested primarily by the impact on cardiovascular, respiratory and central nervous system. Primarily CNS injury is the most important factor related to the outcome and future quality of life of the surviving victims.

23.1.5. Treatment

Treatment success and later consequences largely depend on the speed of providing the necessary care and treatment. The basis of treatment is to establish adequate oxygenation (oxygen saturation) and perfusion (blood flow) of the tissues. Treatment is approached in two stages. The first stage is at the scene and during the transport to the hospital, while the second phase of the treatment takes place in a hospital.

23.1.5.1. Outpatient treatment of drowning

Immediately at the scene: Adequate resuscitation at the scene of the accident is of utmost importance for the survival and future quality of life.

The primary objectives are arranged in order of priority:
- The fast cessation of hypoxia - has the greatest impact on subsequent outcome
- Establishment of cardiovascular stability
- Prevention of further hypothermia
- Rapid and appropriate transport to a hospital

In the water or the sea: Be careful regarding the safety of rescuers, who should not be exposed to unnecessary risk. During the rescue of victims who are conscious, it is safe to use auxiliary floating objects that can be thrown to the victim to hold and to keep such an object between the victim and saviour. It's very dangerous to try to directly approach the victim, because of the danger of drowning the saviour, despite extraordinary swimming and training skills.

- Start rescue breathing "mouth to mouth" in apneic victims in the water. Do not attempt to drain the water from the respiratory tract. Use floating objects or resources to facilitate implementation of the aforementioned modes of breathing. The implementation of measures of rescue breathing in the water is extremely difficult and requires a well trained and physically fit rescuer.
- External cardiac massage cannot be performed in water. Therefore, it is necessary to pull the victim out on a stable surface, shore or boat deck and after that immediately begin cardiac compressions if indicated.
- The victim must be kept in a supine position, if possible, especially when being pulled out of the water. For pulling the victim into the boat at least two people should be present.
- If necessary, remove the vomited mass from the mouth and pharynx, if possible even in the water. Heimlich maneuver is not recommended. Instead of Heimlich maneuver, apply thoracic compressions. Do not use this maneuver for expelling water from the respiratory tract.
- During the resuscitation think of possible injury to the cervical spine especially in divers, "surfers" and yachtsmen.

After pulling the victim ashore/on land or to the vessel: Perform complete resuscitation measures.
- Do not attempt to expel the water from the victim's lungs. It is uncertain to check the heart rate by palpation of the carotid or femoral artery, so it is advisable to use a monitor or defibrillator, if at hand. When thoracic compressions are performed occurrences of vomiting and aspiration are possible, because the victim can swallow large amounts of water. They occur in 25% to 60% of cases. So endotracheal intubation is mandatory, if a trained team is present. Cricoid pressure (**Sellic's maneuver**) to some extent may help in preventing aspiration of vomit.
- The victim needs to be set parallel to the coast, not vertically with the head downwards, as was previously advised.
- If ventricular tachycardia without pulse or ventricle fibrillation is present the victim should be defibrillated. Before that the victim must be dried and moved to a dry surface. In hypothermic victims with cold myocardium there is a high possibility of defibrillation failure. Do not forget that there is a certain degree of danger (moist environment) for the rescuers when using defibrillators (electric shock).
- In order to prevent further loss of heat wet clothes must be removed and victim wrapped in suitable blankets. Hot drinks are not useful and should be avoided. Trembling is a good sign.
- Do not interrupt the resuscitation measures till reaching the hospital, no matter how hopeless the situation seems. In case the victim is unconscious and breathing spontaneously, but not intubated, they should be transported in a lateral position with head down. However, even in this position, the risk of regurgitation and potential aspiration is not completely avoided, so the escort should be careful. If the victim is hypothermic they need to be heated, with simultaneous implementation of resuscitation measures. During transport to the hospital the victim should be given a high flow of oxygen in the highest possible concentration, through a mask, nasal catheter or tracheal tube.
- Provide venous or intraosseous route.
- Condition of the victim that seems satisfactory may worsen, either in transport or later, and the escort must be prepared constantly for the possibility of the need for respiratory and cardio circulatory support.

Monitoring during transportation to the hospital: It is advised to use pulse and ECG monitoring, pulse oximetry, noninvasive blood pressure and deep body temperature measurement, if it is possible.

23.1.5.2. Hospital treatment of drowning victims

It is based on respiratory – ventilatory and cardiocircular support. The treatment depends on the individual condition of the victim and it is executed simultaneously in several directions. If necessary, resuscitation is continued together with treatment of individual organ failures as well as treatment of possible causes that led to the drowning, along with attempts to decrease further damage to the CNS. It is advised to adjust the treatment according to the continuous assessment of the victim.

The diagnosis is most frequently established by clinical examination, anamnesis and heteroanamnesis.

- Recommended laboratory tests are acid – base status,
- Full blood count (FBC),
- Electrolytes (K, Na, Cl, P, Mg, Ca),
- Blood glucose,
- Urea, creatinine, lactate, urinalysis,
- Coagulation and microbiology tests are made if necessary, as well as toxicological analysis (in blood or in urine: alcohol, tricyclic antidepressants, benzodiazepines, narcotics).
- Depending on etiology, specific test are indicated, for example CK, CK-MB and troponin.
- ECG is required.
- Radiology tests: standard antero – posterior chest X – ray is required, while the images of spine, head CT scan and X – ray images of other parts of the body may be required if there is indication.
- In later stages of the treatment magnetic resonance, magnetic spectroscopy, EEG and evoked potentials are used.

Respiratory insufficiency: is treated with oxygen insufflation using mask with reservoir bag or endotracheal tube. Nasal catheter use is not advised. If needed, mechanical ventilation is started or continued using different modes. The most effective measure in treating hypoxemia, regardless of cause, is ventilation with continuous positive airway pressure wich should be started with approximately +10 cm H_2O. The decision about spontaneous or controlled breathing is up to clinician and his assesement of victim's ability to achieve work needed for breathing, efficient carbon dioxide excertion and maintaing ventilatory – perfusion ratio. It is advised to maintain peripheral saturation ≥95% (difference from transport) with CPAP or PEEP titration, while using the lowest FiO_2 possible (oxygen percentage). The PaO_2/FiO_2 ratio should be maintained above 300, while using FiO_2 ≤0,5 (50%).

Positive airway pressure should be reduced gradually, as lungs are being stabilized and ventilatory – perfusion ratio is being normalized.

Permissive hipercapnia is inappropriate and contraindicated in these situations. There is no evidence that mild or moderate hyperventilation improves neurogical outcome with these hypoxic – ischemic brain injuries. Mehanical ventilation strategy should be focused on the prevention of ventilator associated lung injuries.

Heart dysfunction: When admitted to hospital victims of drowning usually suffer from varying degrees of transitory heart dysfuntion.

The treatment of cardiac arrest and dysfunction is carried out as in other cases. The foundation is to establish satisfactory perfusion and oxygenation of heart muscle. However, if the victim is hypothermic, the resuscitation should be continued until the adequate level of rewarming. Core body temperature should be at least 34°C. If ventricular fibrillation in hypothermic patient is persistent after several defibrillation attempts, it is advisable to include antiarrhythmics. However, there is a great possibility that this measurre will also be ineffective. Therefore, with these attempts, the core body temperature should be increased above 28°C. Sporadic literature data indicate succsessful resuscitation with prolonged chest compressions of up to 3,5 hours. However, if a heart function is not achieved at body temperature of 35°C or higher, the resuscitation attempts are usually terminated.

During the treatment of cardiovascular issues it is required to achieve euvolemia. Hypotension and heart failure is treated with pharmacology resources, primarily to reestablish the adequate tissue oxygen supply and prevent secondary organ damage.

In case of cardiovascular instability and heart failure invasive hemodynamic monitoring may be used. Also, although rarely, pulmonary arthery catheter or alternative system for heart assessement, for example PiCCO, LiDCO, or similar can be used. Echocardiography is a standard method for assessement and state control in further treatment.

Acidosis: Drowning victims are almost always in significant acidosis, which contributes to depressed cardiac function. This needs to be adressed by establishing appropriate tissue perfusion, volume com-

pensation, and oxygenation. Only if these measures are not effective, pharmacological correction may be considered, particularly with pronounced metabolic component at pH < 7, 20.However, common stance regarding pharmacological resources usage in this situation does not exist.

Treatment of conditions that induced drowning: Immediately upon hospital arrival, and preferably at the scene of accident, the pathological conditions which led to the incident should be treated.

Rewarming: If the victim is hypothermic, rewarming is needed to prevent or treat primarily arrhythmias and cardiovascular instability. There are different possibilities: body insulation with warm blankets, inhalation of warm mixture of air and oxygen or pure oxygen using respirator, injection of isotonic intravenous fluids heated at 37°C, gastric and bladder lavage warmed with warmed isotonic fluids (37°C). If necessary, abdominal lavage with warm isotonic fluids takes into account. The temperature must be measured rectally (imprecisely), transurethrally, transesophageal and superficial.

Rewarming rate in cardiovasculary stable victims is 1°C/h. With core body temperature less then 28°C, possibility of ventricular arrhythmias exists, and rewarming must be faster. In cardiovasculary unstable victims in a severe hypothermia, depending on opportunities and necessities, thoracotomy with internal cardiac massage and warm mediastinal lavage, cardiopulmonary bypass or extracorporeal membrane oxygenation (ECMO) may be used for rewarming. These measures are used in intensive care units, although reports on the use of portable ECMO devices in these situations are becoming more frequent.

Infections: Prophylactic antibiotic use has no effect on outcome and is not recommended. Therefore, antibiotics should be used when necessary. However, lung infections are relatively frequent, particularly after drowning in unclean water, such as in pools, reservoirs and similar. Embolizations with infected lung material which led to brain abscess or death caused with systemic aspergillosis are also described. Sampling of blood and bronchial aspirate for mycrobiological analysis, monitoring of relevant laboratory results and radiological control of lung parenchyma is recommended for all victims who aspirated. If there are signs of infection or it is strongly suspected, broad spectrum antibiotics should be included in treatment, and later on the treatment should be adjusted according to mycrobiological results.

Corticosteroids have generally shown to be ineffective in treatment of lung lesions and they can even aggravate the condition by interfering with normal healing process.

Other: It is necessaryto find out from eyewitnesses or companions which activity led to the drowing, possible duration of submersion, approximate temperature of the water, basic resuscitation measures efficacy, and victim's chronic or other diseases. This information must be noted, as well as other information which may influence patient's treatment and outcome.

Minimizing neurogical injury: Unfortunately, thereis no evidence thatsome treatment measures or techniques, such as barbiturate coma, use of corticosteroids and osmotic diuretics, calcium channel blockers, prostaglandin inhibitors, inhibition of oxygen free radicals and monitoring of intracranial pressure may lead to minimizing CNS injury with significant outcome improvement. Although some authors suggest monitoring of intracranial pressure, common stance does not exist. Appearance of increased intracranial pressure is a bad prognostic sign, since that pressure usually increases in later stages of the treatment in victims with irreversible brain damage. Therefore, it is advised to set intracranial pressure (ICP) monitor in intensive care units. Layon and Modell advise monitoring ICP in comatose victims in which hyperventilation is taken into consideration.

Hyperventilation: According to Layon and Modell it makes sense to establish ICP monitoring in victims in which hyperventilation is taken into consideration in order to decrease increased intracranial pressure. If ICP is increased, ≥20 mmHg hyperventilation can be tested with target $PaCO_2$ 25-30 mmHg along with simultaneous maintenance of cerebral perfusion pressure from 60-70 mmHg. However, it should be pointed out that hyperventilation *per se* has not been proven effective in decreasing ICP in comatose victims of drowning.

Mannitol bolus at a dose of 0,25 mg/kg body weight can be used as an attempt to reduce elevated ICP. Unfortunately, increased ICP is probably only a sign of an already incurred brain injury.

Mild to moderate hypothermia (32-34°C) has shown better neurological outcome after cardiac arrest caused by ventricular fibrillaton, according to recent data from literature. Assuming that pathophysiological mechanism of an anoxic CNS injury after drowning is identical, one might assume that cooling comatose victims of drowning at 32-34°C during 12-24 h after event, or at least not to perform active rewarming, makes sense. However, currently there are no appropriate, strong enough and controlled studies for confirmation. Some authors advise maintaining of mild hypothermia of 32-34°C through 12-24h after drowning, and after that progressive rewarming. Hyperthermia must be avoided.

Glycemic control: In order to preventbrain damage, glycemic control is of great importance, since hyperglycemia can have a negative impact on ischemic CNS injury. Therefore, it is avised to maintain blood glucose levels normal or mildly increased, up to 8 mmol/L. Hypoglycemia mustd be avoided.

Control of epileptic seizures is carryied out with barbiturate and benzodiazepines.

Renal failure

Renal replacement therapy: Dialysis is carried out if necessary, and in ICU continuous venovenous (hemodia)filtration is more often used.

For now there is no indication that any hospital intervention or treatment changes the outcome. Additional measures of treatment are indicated for acute lung injury and other organic dysfunctions.

Prediction of treatment outcomes: There have been numerous attempts to define the clinical, epidemiological or laboratory-diagnostic values and signs for predicting the outcome of treatment and recovery either at the scene or in a hospital. Unfortunately, to this day there is no clear option for such estimation, therefore, on the site of the accident resuscitation of victims is recommended despite the initial state, without trying to predict possible future outcomes, except in the case of injuries incompatible with life. Identical attitude is adopted at hospital admission.

Complications: Post-drowning complications are frequent and serious. The most common are: neurological damage, serious lung damage and lung failure, even in 50% of cases of drowning. Further complications are multiple organ failure, the subsequent infection of the lungs and kidney failure. Very rarely blood clotting disorders appear, as well as destruction of muscle mass (rhabdomyolisis). It should be pointed out that, apparently satisfactory condition of the victim, in a short period of time can become serious and end up fatal.

Prevention is of great significance in these accidents. Swimming and diving in secluded areas should be avoided . This is especially important for people with health problems. Never overestimate your abilities despite good swimming skills. Avoid alcohol and various drugs or substances before swimming or other water related activities. Never swim in rough seas, especially near rocks or cliffs. Avoid swimming where the water or sea currents are strong or in river rapids. Carefully handle a drowning person, because the rescuer can be drowned too. Never leave children without appropriate supervision and always be at hand for possible assistance, whether they swam in the sea, a lake or in the bathtub. Use the fence around the pool. Never leave toys that can attract the attention of young children in the pool. Teach children to swim as soon as possible. Learn the basics of life support.

Conclusion: Despite the development of technology and modern methods of treatment, mortality and morbidity in drowning victims depends almost exclusively on avoiding longterm brain hypoxia.

Aggressive resuscitation measures already at the scene are the key to a successful outcome and return to normal life. The main therapeutic challenge is to fight for the reduction of damage to the central nervous system in survivors. For now there are no appropriate protocols or resources to adequately achieve this goal. Therefore, prevention is of utmost importance.

23.2. Injuries caused by heat

Damage/injuries to the organism caused by heat are generated by the influence of a high-temperature environment, often accompanied by physical exertion and disorders of thermoregulation.

23.2.1. Hyperthermia

Elevated (core) body temperature, usually measured rectally. Often it is the continuation of a primary disease related to the inability of the organism to properly respond to a high temperature.

Hypothalamus (located in the brain) regulates the body temperature, and basically it is the body's thermostat. After processing the data received from temperature sensors, it generates measures for temperature regulation. The importance of the function of the "thermostat" is evident in the prevention of occurrence of high temperature which can denature body proteins, destabilize phospholipids and lipoproteins, leading to disorders at cellular and subcellular levels, which in further course can cause disruption of various organ systems and ultimately lead to their failure and death. Temperatures ≥ 41.1 ° C are detrimental to the organism and require urgent and aggressive treatment. However, survivals with body temperature of 46 ° C were recorded, and so were fatalities at significantly lower body temperatures.

Heat regulation: Organism absorbs heat in the same way it emits: by conduction, convection, radiation and evaporation. For the function of thermal emission, undisturbed integrity of the skin, function of the sweat glands and autonomic nervous system are essential.

Factors affecting the development of heat disorders: High temperature and humidity of the environment, disturbed evaporation, increased physical activity, age, body weight (obesity), chronic alcoholism and a variety of acute and chronic diseases, medications and drugs.

The most serious disorder associated with inadequate thermal regulation is the heat stroke. Heat stroke, heat cramps, and heat exhaustion are the three main heat disorders of the human organism.

23.2.2. Heat stroke

Life-threatening condition. Mortality is about 10%. It is defined as a body temperature ≥ 41.1 ° C, accompanied by neurological symptomatology.

Pathophysiological mechanism: Inappropriate or prevented emission of heat results in hyperpyrexia. It can be dependent or independent of physical exertion. The first type occurs in young people, while the other one is not related to physical effort and is common in the elderly, chronically ill and young children.

Etiology: Elevated temperature and humidity of the environment, increased body heat production (increased metabolism - sepsis, thyrotoxic crisis, increased muscular activity - exercise, convulsions, tetanus), reduced ability of physical cooling, various drugs and poisonings (cocaine, amphetamines).

Clinical signs:
- Sudden onset, sometimes preceded by headache, dizziness and fatigue
- Increased heart rate 160-180/min
- Blood pressure is often lowered
- Circulatory collapse, congestive heart failure
- Rapid breathing
- Disorientation precedes unconsciousness and convulsions
- Delirium, confusion, tremors, disturbed speech
- The feeling of burning
- Red, dry, hot skin
- Rapid increase of temperature to 40 - 41°C

Consequences:
- Heart failure, pulmonary edema
- Permanent brain damage due to hyperpirexia
- Renal damage (25-30%)
- Damage to the liver, usually transient
- Damage to the lungs
- Destruction of muscle mass (rhabdomyolysis)
- Lethal outcome

Prehospital Treatment:
- The removal of victims from the overheated environment
- Ceasing all medical interventions that can lead to temperature increase
- Wrap the victim in wet blankets and allow air circulation (fan)
- Immersion in water (not ice)
- Ice cooling the areas around main arteries (femoral, subclavian, carotid artery)
- In the case of loss of consciousness ensure airways - endotracheal tube, laryngeal mask, airway, etc.
- Oxygen
- Intravenous access and administration of crystalloid solutions
- Antipyretics do not necessarily have an effect
- If the victim starts to tremble stop with cooling (shivering increases heat generation)
- Cease cooling measures at victim's body T of 38°C
- Urgent transport to hospital
- Hospitalization is mandatory

Hospital treatment:

Support measures, further hypothermia and prevention of further damage to the body.

After the heat stroke organism's abilty to adapt on external temperature remains weaker at least temporarily.

Heat exhaustion

It occurs due to excessive loss of fluids and electrolytes, resulting in hypovolemia and electrolyte disbalance. It occurs very often due to excessive sweating without water and salt compensation.

Clinical presentation:
- Low blood pressure
- Faintly palpable pulse
- The gradual development of malaise and weakness
- Nausea
- Excessive sweating
- Pale, clammy skin
- Fainting

Treatment: Compensation of fluids and salts by the oral route. Intravenous administration of electrolyte and water solution is rarely necessary.

This disorder has a good prognosis if circulatory instability is not prolonged.

Heat cramps

Heat cramps occur during physical exertion due to excessive intake of water without enough replacement of salt (so-called water intoxication) or because of loss of salt due to strong sweating during physical stress at high temperature (usually above 38 ° C).

Clinical presentation:
- Sudden onset
- Severe muscle aches and muscle cramps
- If only abdominal muscles are affected it can mimic acute abdomen
- Blood pressure and pulse are normal
- Body temperature may be elevated
- Skin is dry and hot or sticky and cold, depending on the humidity of the environment

Prevention and treatment:
- Awareness of the potential disorder is sufficient for prevention
- Liquids with kitchen salt (NaCl)
- If the victim cannot drink, normal saline infusions (0.9% NaCl) are given intravenously

Prevention of heat disorders

Be aware of the possibility for development of these disorders ("common sense"). Avoid heavy physical exertion in hot weather or in a hot environment. Take care of small children, the elderly and those with chronic or acute health disorders. Compensate liquid and salts. Be aware that the lack of a sense of thirst may not be an indicator of good hydration (especially in the elderly). Enable evaporation, using appropriate devices. If these disorders are already present, it is necessary to act promptly to avoid further deterioration.

23.3. Burns

23.3.1. Basic characteristics of burn disease

A person injured by a burn is a unique and extremely demanding patient. Burn disease is related to the anatomical and physiological changes, including endocrine and immune system and a very significant catabolism. The main feature of the burn disease is hypermetabolic state associated with massive loss of protein and significant weight loss. Furthermore, the stress response of the body further initiates a cascade of negative developments. Hyperglycemia can be difficult to control. A patient with burns is unique in its needs for fluid replacements, suffers from severe metabolic stress, has a high possibility of complications and an uncertain outcome.

Unfortunately, many problems remain difficult to resolve, especially the control and the treatment of the hypermetabolic status, characterized by massive protein and lipid catabolism, peripheral insulin resistance, high energy needs, etc.

Severe burns are a great challenge and require a multidisciplinary approach.

23.3.2. Epidemiology

Globally, burn injuries represent a serious problem. According to the World Health Organization, the estimates are of approximately 322,000 deaths per year from the conflagration and fire while the data for

electrical burns and burns caused by hot liquids are unavailable due to high frequency. The mortality rate per 100,000 population is about 5.2%. Burns belong to the top 15 causes of death in children and young people from 5-29 years of age.

Some diseases, like epilepsy and alcoholism markedly increase the possibility of burns or death. Deaths from burns usually involve two extreme populations; the youngest and the oldest because of reduced mobility and relative immunological immaturity or weakness and of course comorbidity.

US data claim an annual rate of burns of over half a million cases. It is estimated that around 3500 of these were with a fatal ending and the rest were burns with non-fatal consequences. Between 1971. and 1991. the number of fatal burns in the United States decreased by about 40% with a further reduction in deadly consequences of inhalation injuries by about 12%. Since then the trend of mortality decreases further, so that a reduction by further 25% is estimated. These data result from improved measures of prevention, but at the same they stem from the development of technology and a more successful medical treatment measures, which include the development of resuscitation protocols, improved respiratory support, support in hypermetabolism, infection control, early surgical management and early enteral nutrition.

Future improvements, along with a further reduction of mortality and morbidity, are expected in the fields of prevention, rapid improvement of burned body part functions and equally important aesthetic and cosmetic effects.

23.3.3. Prehospital procedure

The primary objective is to prevent further injuries and to limit the damage to the body as soon as possible. If the victim is conscious and capable of drinking, a sufficient amount of fluids should be given, especially water. If that is not enough, administer intravenous fluids - crystalloids. Analgesics should be given mandatorily. Morphine or morphine preparations are advised together with an urgent transport to hospital. If necessary intubate the injured patient with an endotracheal tube, even the conscious victim, especially if airway burns are suspected.

It is necessary to immobilize the victim before transportation in order to prevent further injuries and reduce pain.

Intravenous solutions are administered by special protocols.

23.3.4. Hospital treatment

Required is the continuation of resuscitation measures initiated prior to the hospital treatment. Apply special protocols for fluid administration and treatment. Treatment and care of burned victims is very demanding and multidisciplinary in character, therefore it consists of continuous monitoring of laboratory results. More to follow, in the paragraphs below.

Burn disease complications

Complications arising from the burn disease can be of diverse origin, whether linked to the burn disease itself or a condition caused by the state or comorbidity of the injured patients or even factors of treatment. A number of complications that can occur is large, from relatively banal, to severe and often even fatal. Burn shock always occurs in burns with a higher percentage of burned area. Infections which can always occur, and are often difficult to treat must be specified among other complications. Sepsis and septic shock occur very frequently. Abdominal compartment syndrome and intestinal ischemia are also, potentially, a deadly complication. It often occurs with inhalation injury pneumonia, lung function disorders (ARDS - Acute respiratory distress syndrome) and multiorgan failure, accompanied by a very high mortality.

Burn shock: Although burn shock is a regular occurrence in severe burns and can not be classified as complication, it will be briefly described due to its importance and impact on morbidity and mortality. Burn shock is a unique combination of distribution and hypovolemic shock. This manifests in the reduction of intravascular volume, low pulmonary wedge pressure, increasing vascular resistance and reduced cardiac output. Decreased heart MV is the result of increased afterload, reduced cardiac contractility and reduced circulating volume. Several studies suggest that impaired contractility of the heart is the result of different mediators that are released due to tissue damage, however, at the cellular level, Ca + 2 is also included. The exact mechanism of changed cardiac function is unclear and probably complex. Severity of the cardiac stress response is important in the acute post-injury phase and its severity determins the outcome. Cardiac stress is increased ten to twenty times due to the release of catecholamines, mediators in the post-burn hyper-metabolic response. All mechanisms involved in the control of fluid and proteins in the vascular space are changed upon burn injury. The consequences are a loss of circula-

ting volume, haemoconcentration, massive tissue edema, decreased urine output and worsening cardio-vascular function.

Treatment of burn shock

A proper treatment of burn shock is the most important measure in preventing fatality. Due to lack of evidence-based research, treatment of burn shock is based primarily on the local customs and habits. However, the only measure that is universal and not disputable is rehydration. All the formulas regarding the treatment should be used merely as a recommendation, not as a strict recipe because the treatment depends on the patient and its particular needs, which in turn depend on the patient's age, burn depth, the existence of inhalation injury, pre-existing diseases and joint injuries. None of the aforementioned formulas is to be considered optimal. Colloids and hyertonic saline seem to be of significant interest.

There are various protocols for the treatment, such as computer algorithms, for example.

Crystalloid fluids: TheParkland formula, also called the Consensus formula, is the most commonly used and recommended. Administration of Ringer's solution in a quantity of 4 mL x kg bw x percentage of total body surface area is recommended. Half of the calculated amount is recommended to give in the first eight and the rest in the next 16 hours. However, lack of experience can lead to errors in the calculation, resulting in too little or too much of administered fluid. Unfortunately, even with the most experienced staff, there is a significant possibility of inadequate calculating of required amount of fluid during resuscitation. The second formula is a modified Brooke formula, developed in the burn center of the US military and it repesents a model that provides giving 2 mL / kg body weight x% burned area / 24 h as a starting point.

Colloids: There is a notable controversy regarding their role and their type during resuscitation in burn shock. In more recent times their use is suggested, even in the first 24 hours, but there has been no registered clinical progress, thus far. An older meta-analysis comparing albumin with crystalloid showed 2.4 times higher risk of death when using albumin. Several studies indicate that colloids give small clinical effect in burned patients, especially if given within the first 12 hours after the occurrence of burns. Colloids can increase the content of water in the lungs after resuscitation phase. So far there is no consensus on the use of albumin in the treatment of the acute phase. But the attitude is gradually changing.

Some clinicians have accepted the so-called "middle-of-the-road" approach and give colloids in the second half of the first 24 hours. This compromise is perhaps the most popular method of administration of colloids in burn centers in the US. The Parkland formula is applied in most centers, 78%, while the largest number of clinicians use colloids in the 24 hours following the injury.

Fresh frozen plasma should not be used as a plasma expander. American Association for burn injuries recommends it only in cases of active bleeding and clotting disorders.

Hypertonic solutions have no place in the routine management of burns. They should be reserved primarily for experienced clinicians with close monitoring of sodium concentration in plasma. However, when hyertonic infusions are administered, the reduction of risk of abdominal compartment syndrome occurs.

Monitoring: Reliance on the hour diuresis as the primary index of optimal resuscitation is in contrast with the sophisticated and available devices. Intensivists have at their disposal a variety of possibilities to assess the physiological state of the patient. The value of the lactates and the bases in the arterial blood is correlated with the size of the injury. Their inadequate control affects mortality. Unfortunately, there are no prospective studies that support the use of these parameters in guiding the resuscitation with fluids. However, invasive monitoring withcentral venous catheter or pulmonary artery catheter can still be used occasionally in special circumstances and for specific patients such as older people with severe comorbidity or those that "do not respond" to treatment. A catheter for measuring blood pressure is much more reliable than a standard non-invasive measurement of arterialpressure. The use of a pulmonary catheter has to be considered because it has shown significant benefits. PICCO system showed a good correlation with the values obtained by the pulmonary artery catheter in burned patients. Traditionally,urine is used as the primary indicator of tissue perfusion but despite its widespreaduse urine is not generally accepted as a perfect measure of the overall tissue perfusion.

Setting of nasogastric tube is advisable in patients with> 20% of burned body surface area. Traditionally, diuresis of 0.5 mL / h / kg body weight is considered to be sufficient for the resuscitation of adult patients and heart rhythmof <110 / min represents a satisfactory condition while the pulse> 120 / min indicates hypovolemia.

Treatment should not be based on any single laboratory or other values.

Intraabdominal complications - abdominal compartment syndrome (ACS) and intestinal ischemia

Intraabdominal complications in burn-injured patients without direct abdomen or abdominal organs injury are dramatic and often associated with poor outcome. Markell et al. indicate the incidence of 1 case per 20 burn injured patients. There is a broad spectrum of abdominal complications and their mean mortality rate is around 45%. The most dramatic abdominal complications are abdominal compartment syndrome and intestinal ischemia.

These authors reported about the incidence of 2.8% in burn-injured patients with a mortality rate of 78%, in contrast with burn-injured patients without abdominal complications where the mortality was 20%. These complications rised linearly in accordance to burned body surface area. The onset of abdominal problems usually takes place within 3 days following the injury and it was not only related to resuscitation phase. In some cases it occurred much later.

Abdominal compartment syndrome in severely burned patients is often unrecognized, undertreated and it evolves rapidly to fatal outcome. Although it has already been observed 100 years ago, it was just recently considered as a significant problem in burned paatients without abdominal trauma. The occurrence of this syndrome is further complicated by the fact that urine output becomes unreliable as an indicator of good resuscitation and can very often lead to wrong treatment (e.g. further adding volume which ultimately leads to a vicious circle of worsening and further deterioration in the general condition).

Unfortunately, this condition often ends fatally. It is defined as intraabdominal pressure ≥20 mm Hg with at least one new organ dysfunction.

Clinical picture: abdominal distension with intraabdominal hypertension. Decreased cardiac output is dominant in cardiovascular symptomatology while respiratory problems are characterized by elevated peak airway pressures associated with hypoxia and hypercarbia. There is disturbed renal function with a significant reduction in diuresis. In burn-injured patients we should constantly expect the possible development of mentioned syndrome. The use of vasopressors was an additional risk factor for the occurrence of abdominal compartment syndrome and intestinal ischemia. It is advised for all burned ≥30% of body surface area to check intraabdominal pressure.

Treatment: Must be aggressive and multimodal including appropriate fluid resuscitation and body position, pain management, sedation, nasogastric decompression if indicated, neuromuscular relaxants and chest escharotomy. Percutaneous abdominal decompression is a minimally invasive procedure that is used before laparotomy. In patients who require decompression laparotomy mortality rate is between 88-100%.

It is therefore suggested that the amount of fluid calculated according to the formula has to be carefully titrated and based on urine-output and that the formula is only a landmark for resuscitation and fluid infusion.

Unfortunately, diuresis and arterial blood pressure are not as adequate indicators of the efficiency of resuscitation as tissue and gastric pCO_2 are. In the first hours of resuscitation diuresis may not be a good indicator of the appropriateness of treatment.

Also, it is commonly considered that the inhalation burns need much more fluid which can lead to the development of ACS and intestinal ischemia. Studies have shown that the quantity of fluid required for burn-injured patients with associated inhalation burns, based on urine output, is not significantly different than those without inhalation injury, which is contrary to the common attitude. Unfortunately, that problem still remains open for consideration, at least until consensus is reached.

The simplest guidelines for fluid administration and prevention of any unintended consequences are haemodynamic monitoring and maintaining adequate urine output.

It is advised to avoid excessive fluid infusion regardless of the formula and protocol. All protocols should be only used as guidelines for appropriate treatment. Also, a careful and strictly indicated use of vasopressors and nutritional strategy with careful monitoring of intraabdominal pressure in burned over 20% -30% of body surface area can reduce the occurrence of these serious complications.

Sepsis and infection in burn victims

Infection, sepsis and systemic inflammatory response (SIRS) are more specific in burn victims than in any other group of patients, either surgical or non-surgical. We should not forget that the body temperature of patients with extensive burns continuously increases to approximately 38.5 ° C and tachycardia and tachypnea can persist for months, while continuous release of mediators of inflammation results with permanent leukocytosis.

SIRS: The SIRS concept is scarcely applicable to burn victims. Although the concept has merit when dealing with other groups of patients, it has been deemed as wildly insufficient in cases with burn

patients. Therefore, it should not be used for burn patients because they are exhibiting symptoms of SIRS for the entire duration of their treatment, chronic SIRS. Biochemical markers were also evaluated, but for now they are hardly applicable to the specific pathophysiology of burn patients. It is similar with the onset of sepsis, which was redefined for burn victims. The definition of sepsis is shown in Table 23-1.

Table 23-1. Definition of sepsis in burn patients by Greenhalgh and colleagues

- Temperature > 39 ° C or <36.5 ° C
- Progressive tachycardia: adults > 110 / min
- Progressive tachypnea: adults > 25 / min or > 12 L / min on a ventilator
- Thrombocytopenia (3 days after initial resuscitation), adults <100.000
- Hyperglycemia in the absence of diabetes mellitus > 11 mmol/L
- Insulin resistance 25%> increased need for insulin within 24 hours
- Inability to continue enteral feeding 24 h>, abdominal distension
- In addition, it must be confirmed with positive microbiological culture and isolation of microorganisms and with a positive response to the applied antibiotics

If the clinical picture shows that there is a need for increased liquid resuscitation in a patient with an altered mental and respiratory status, as well as an impaired renal function, who exhibits the above signs and symptoms (Table 23-1.), we should suspect of sepsis.

Treatment is, of course, the same as when dealing with non-burn patients, but there are some specifics. It should be noted that due to the specifics of burn injuries, sepsis can occur several times during treatment.

Inhalation injuries: it is important for the diagnosis to show the anatomical changes in the tracheobronchial tree. The gold standard for diagnosis is bronchoscopy, however, the problem is that this method can not exactly predict the severity of the inhalation injury within the first 24 hours. There is no ideal respiratory strategy for patients with inhalation injuries. All algorithms and recommendations are only general guidelines.

It is obligatory to take care of the patient to lower the risk of pneumonia. According to the literature 70% patients with inhalation injuries develop pneumonia associated with ventilator use (VAP). For patients who do not show improvement with standard measures of ventilation, it is necessary to consider extracorporeal membrane oxygenation (ECMO), if available.

Pneumonia: a common complication of inhalation injury.

Lung injury: respiratory insufficiency is accompanied with hypoxemia with the evolution of an acute pulmonary injury (ALI) and ARDS. Even in patients without inhalation injuries occurrence of ARDS is associated with a negative outcome. In patients with associated inhalation injuries and the development of ARDS mortality exceeds 50%.

In cases of pulmonary injuries an appropriate diet plays a very important role, especially the so-called anti-inflammatory pulmonary enteral nutrition. However, further evaluation of a special diet for burn patients is necessary, and special attention must be paid to its implementation.

Infections of burned areas: Almost always present.

Multiorgan failure is a bad predictor of survival.

Burned area has a significant impact on morbidity and mortality.

Other complications

- Hypothermia
- Pulmonary embolism
- Deep venous thrombosis (DVT), occurring in approximately 25% of the burn. Despite the high incidence, mortality from DVT is at approximately 0.14%.
- Metabolic imbalances, particularly electrolytic, are very common.
- Hyperglycemia is also almost always present due to insulin resistance
- Anemia is possible after major surgical reconstructions and it is often combined with a coagulation status disorder, which is affected by bleeding and hypothermia during and after surgery
- CO and cyanide poisoning are possible additional complications in the first hours after the occurrence of the burns. Cyanide compounds are created by burning plastic, wool and silk.
- With renal failure mortality is at around 44%. The encouraging fact is that those who survive also regain their renal functions, although the laboratory values do not have to be completely normal
- Rhabdomyolysis

23.4. Injuries caused by electricity

Injuries caused by an electrical current are relatively rare. Nevertheless, they are often dramatic and potentially lethal. A percentage of electric shock victims usually dies at the site of accident before it is even possible to provide help, while survivors often have severe injuries that demand quick and adequate treatment and their outcome is uncertain.

Data shows that in the USA an average of 1 electric shock per 200.000 citizens occurs over a 1 year period, out of which 1000 end lethally and 5000 demand urgent medical treatment. A large number of these accidents is related to work places. One third occurs in houses and apartments, with children being the most frequent victims. The frequency of lightning impact is low. It is estimated that a few hundred of these kind of injuries occur in the world every year, with 30% being lethal and 70% leaving severe morbidity in survivors.

Injuries caused by electricity are divided into injuries caused by lightning and low and high voltage electricity.

Most injuries occur with a low voltage electrical current (voltage <1000 V). These strikes carry a high risk of cardiac arrest. Injuries caused by high voltage electricity (> 1000 V) also bring about the occurence of cardiac arrest, as well as very severe damage and destruction of tissue.

23.4.1. Pathophysiology

Injuries caused by an electric current can range from transient discomfort to immediate cardiac arrest. A high voltage electrical current causes the most serious consequences, however, fatal accidents from low voltage current or so-called "home electricity" also often occur.

The factors that determine the nature, seriousness and consequences of electric shock depend on:

1) Voltage levels
2) Electric current strength
3) Tissue resistance to the passage of current
4) Current type - direct, alternating
5) The length of contact with electricity
6) The manner in which the current spreads

With current with a voltage of<1000 V, a direct mechanical contact is required for electric shock to occur. In contrast, with currents that are > 1000 V, the appearance of an electric arc usually causes the electrical impact.

The electrical current encounters greatest resistance in the skin and bones. Resistance of dry and well-keratinized, intact skin is around 20,000-30,000 Ω /cm^2, for skin on the palm even as high as 2.3 million Ω / cm^2. Resistance of moist, thin skin is about 500 Ω / cm^2. However, if the skin is damaged by abrasion, puncture or cut, resistance can be reduced to 200-300 Ω / cm^2. Unfortunately, in these situations an electrical shock which usually causes less injury can turn into a life-threatening shock. Muscles provide less resistance, while blood vessels and nerves provide the least.

The resistance of the skin can be reduced by prolonged exposure to the current flow, which occurs in an alternating current of 50 Hz / sec. This type of power can produce tetanic contractions of skeletal muscles and prevent the release of the source of electricity and thus lead to prolonged exposure. This phenomenon usually occurs with a >14-16 mA current and it can lead to dislocation of joints and fractures. With ≤15 mA alternating current it is often possible to break free of the electrical conductor. With direct flow current this value is ≤ 75 mA in individuals weighing at about 70 kg.

Due to its frequency, alternating current can very often pass through the heart during the vulnerable period of the cardiac cycle and trigger ventricular fibrillation (VF). The above-mentioned phenomena most often happens with alternating currents of > 50 mA, while with the direct current this phenomenon is possible at 300-500 mA.

Severe injuries and destruction of cell membranes of skeletal muscles and nerves occur with currents of > 0.5-1 A. The damage occurs within a few milliseconds. A few seconds of prolonged contact can lead to thermal injuries of subcutaneous and deeper tissues. All tissues, regardless of their type, are sensitive to temperature exposure, so thermal damage is inflictedto all of the tissue on the path of the electrical current.

The spread of electricity also has impact on the type of possible injury and its consequences. So transthoracic shock (hand-arm) has a higher probability of a lethal outcome than vertical (hand-foot) or wide apart (leg-foot). Vertical shock, however, often causes heart damage due to the direct effects of electricity and spasm of the coronary arteries.

It can be summarized that electric shock injuries are the result of two effects: the direct effect of the current on the cell membrane and the smooth muscles of the heart and blood vessels and the conversion of electrical energy into heat as it passes through different tissues. In the light of this, an injury can be direct (primary) - caused by the electricity or heat energy and delayed (secondary) - caused by vascular blockages.

23.4.2. Complications

Kidney failure. Fractures and other injuries of musculoskeletal system due to tetanic contractions or falls are frequent. A premature formation of cataract of the eye is possible and even amaurosis - blindness.

Heart symptomatology covers a wide spectrum. Different arrhythmias and asystole often appear. They can occur immediately or they can be deferred. However, it seems that if arrhythmias have not developed in the initial stages of injury, such events are rare later on. Furthermore, damage to the heart muscle and vascular systems can also occur.

Neurological effects appear in more than 25% of victims. The central and peripheral nervous system are affected. Electrical contact with the head most often causes short-term unconsciousness with the occurrence of transient convulsions similar to epileptic seizures. Common symptoms are confusion, deafness, amaurosis, headaches and retrograde amnesia. There is also a possibility of delayed consequences.

23.4.3. Lightning strike specificities

Injuries from lightning strikes are the result of impact caused by an electric arc, rather than by direct contact. An enormous amount of electricity generates a very strong magnetic field around itself, which can induce electrical currents in the nearby body. This current is strong enough to cause heart disturbances and central nervous system damage. The temperature of the electric arc reaches ≤30000 ° K, which induces thermoacustical shock waves, called thunder. Shock waves reach a pressure of 4-5 atmospheres near the arc, while this pressure is already much lower at a distance of 1 m and is at 1-2 atm. When lightning strikes the ground, electricity spreads radially in an area. This event can be very dangerous for people in the vicinity, as a voltage difference of about 1500-2000V between the feet of an individual can occur, with the emergence of a 2-3 A current that lasts for several μsek.

Victims of lightning strikes acquire multiple injuries. It seems that the strike stops all electrophysiological processes in the body. It is actually an immediate and massive direct current electric shock. The primary cause of death from a lightning strike is cardiac arrest due to ventricular fibrillation (VF) or asystole.

In many cases cardiac automaticity may spontaneously return, however the concomitant respiratory arrest due to spasm of the chest muscles and suppression of the respiratory center may remain. Therefore, it is often necessary in trauma patients just to provide respiratory assistance and support.

Lightning can also cause a release of adrenal hormones and subsequent disturbances.

A lightning strike may cause a wide range of neurological injuries, which can be primary, as a result of the direct effect on the brain, or secondary, as a result of cardiac arrest and hypoxia.

Victims who survive lightning strikes or successfully respond to resuscitation have a good prognosis, because subsequent cardiac arrest is not common. The delay in resuscitation is the most common cause of death. Unfortunately, bystanders are afraid to approach the victim until a couple of minutes pass, fearing that they too may suffer from the "residual current". However, unless the victim is not on an isolated platform, there is no residual electricity after a few milliseconds. Therefore, there should be no hesitation about initiating CPR.

23.4.4. Treatment

On the site of accident

Primarily stop the flow of electricity. For low voltage current (so-called home voltage - 220V) it is possible to achieve that by moving the victim away from the source of electricity with a dry cloth, a piece of wood or a rubber or leather belt. However, if the conductors are high voltage, one should not attempt to separate the victim until the power is turned off. Unfortunately, the problem is that the high and low voltage conductors are difficult to distinguish. After excluding the victim from the electrical circuit, measures are taken to resuscitate the victim if needed. It must be kept in mind that electrical injuries often lead to trauma of limbs, spine and the spinal cord. It is necessary to provide immobilization. If ventricular fibrillation is present, defibrillation must be performed. If possible, it is advisable to remove any burned clothes and shoes. Securing the airway in victims with facial burns can be difficult due to edema. Sometimes it is necessary to intubate a trachea of a conscious victim to prevent suffocation due to edema of the glottis mucosa. It is recommended to replace the volume as fast as possible, with crystalloid solutions

in the shocked victims or those with significant destruction of tissue. Emergency transport to a hospital facility is required.

Hospital treatment

Supportive measures, fight against shock and prevention of further damage to organs, primarily the prevention of damage to the CNS. Treatment of complications. Sometimes surgical procedures may be necessary because of severe destruction of tissue and the onset of compartment syndrome.

Prognosis

Prognosis for injured patients without burns is based on the function and condition of the central nervous system. However, this can be complicated. Victims who exhibited neurological deficits when admitted to the hospital often recover completely, while in those with a delayed appearance of neurological symptoms a permanent progression over the course of months and years may occur. However, it is possible to stop the progression in a particular stage.

In cases of burn victims, the prognosis can be changed by improving the condition of the burned area.

Conclusion

Electric current injuries can range from transient discomfort to immediate cardiac arrest. They are divided into immediate and deferred. All organ systems may be affected. The effects of electric shock depend on the voltage and current, the type of power, the length of contact, tissue resistance and expansion path.

Treatment includes basic measures of resuscitation at the scene and specialist treatment in hospitals.

23.5. Hypothermia

23.5.1. Introduction and definition

One of the most common causes of hypothermia is exposure to low temperatures. In urban areas, along with the cold, additional factors are the abuse of different drugs and alcohol.

The most acceptable definition of hypothermia says that it is decreased internal (core) body temperaturetoalevelwherenormalmuscularandcerebralfunctionsareimpaired.Accordingto the literature this is the temperature below 35 ° C.

Hypothermia can occur gradually, with continued exposure to low temperatures or sudden, when exposed to extremely low temperatures.

Itmaybeintentional-inmedicalproceduresorrandom-befalling.Itisalsodividedintoprimary and secondary. Accidental hypothermia arising from the influence of external factors are considered as primary, and at the same time the patients have no organ damage as the cause of the disorder of thermoregulation, which is the main characteristic of the secondary.

23.5.2. Classification

It is based on measured core body temperature (rectal, esophageal). It should be noted that this classification into three levels depending on the temperature is not absolute and varies from author to author.

Mild - 32- 35 C; Moderate - 29- 32 C; Grave - < 29 C.

23.5.3. Incidence, mortality and morbidity

Mild hypothermia is generally well tolerated and not associated with significant mortality or morbidity. On the other hand, multi-center studies have shown 21% mortality at a moderate to severe hypothermia (28 - 32 C). However, in previously healthy individuals, mortality was less than

5%, while in patients with already existing chronic disease mortality was significantly higher and reached a figure of more than 50%.

Children and the elderly are at an increased possibility of the occurrence of hypothermia.

23.5.4. Pathophysiology

Thermoregulatory center is located in the hypothalamus. It reacts to the temperature of the circulatingbloodwiththeintegrationof datafrom peripheralcutaneous sensors. Systems involved in the response to heat loss are somatic and autonomic nervous system, as well as endocrine system.

Heat can be lost by radiation (55% - 65%), conduction and convection (15%), while respiration and evaporation are responsible for the rest. However, changes in the environment can significantly changethemodalityofheatloss. Thebestexampleisimmersionincoldwater,whenthereisa considerable 25-fold increase of conductive heat loss.

Hypothermia affects all organ systems, but perhaps the most significant are the changes that occur in the cardiovascular and central nervous system.

Effect on cardiovascular system

Hypothermiaresultsinreduceddepolarizationoftheheartpacemaker,causingbradycardia.As this bradycardia is not caused by a vagal mechanism, it can be refractory to atropine. Mean arterial pressure and cardiac output are reduced, and , according to some authors, a typical Jor Osborne wave can develop in the ECG. However, this indicator is not specific only for hypothermia, because it can also occur, although rarely, in sepsis and myocardial ischemia, and can also be seen in healthy individuals.Atrial (already at 30 ° C), and ventricular arrhythmias with asystole and ventricularfibrillation,canoccurspontaneouslyatcorebodytemperatureof25°C.Thereisan increaseinbloodviscosity,andreducedtemperatureleadstoareductioninthereleaseofoxygen from hemoglobin, with subsequent tissue hypoxia.

Effects on the central nervous system

Hypothermia is responsible for a progressive depression of the CNS, with a linear reduction in metabolism,ascorebodytemperaturefalls.Loweringthecorebodytemperatureby1°Cresults indecreasedmetabolicactivityofthebrainby6%-7%.Asaresultsensorychangesoccur:apathy and euphoria, amnesia, aphasia and eventually coma. Cerebral activity is stopped at brain temperaturesbelowthe22°C. Accordingtosomeresearch,brainelectricalactivityisabnormal below33°C,andtheEEGmaybecomeidenticaltothatofcerebraldeathattemperatures between 19 ° C and 20 ° C.

Between 30 ° C and 29 ° C core body temperature, pupils can be significantly enlarged and with minimalreactionstolight.Below29°Cpupilsarenonreflexive,fixed,anddeeptendonreflexes are also absent.

Vasoconstrictionisperceivedasvolumeoverloadandthereisaninterruptioninsecretionof antidiuretic hormone - increased diuresis.

Effects on the gastrointestinal system: Slowing of intestinal (bowel) activity.

Effects on the renal system: increased excretion of urine. It can lead to blood electrolyte disbalances and some other changes.

*Effectsonlocomotorsystem:*Shiveringcauseslossofmovementcoordinationanddifficultyin performing fine actions. Loss of muscle strength and fatigue also occur.

*Skinreactions:*A rapidreleaseofhistamineispossibleinsusceptiblepersons,whichleadstothe so-called"coldurticaria".Occasionaldeathcasesareregistered.Theskinfreezesatatemperature of about - 0.5 °C.

Causes of hypothermia

Causes of hypothermia can be divided into several groups:

1) Reduced heat production:
   - Various diseases and disorders
   - Severe starvation
2) Increased heat loss:
   - Includes accidental hypothermia, frequently during immersion in cold water, but also non-immersion accidents
   - Due to vasodilation due to the effects of some medications, toxins, alcohol
   - Various diseases
3) Impaired thermoregulation - due to various causes, but most often due to disorders in hypothalamus, like: CNS trauma, CVI, tumors, etc.
4) various causes eg. : pancreatitis, uremia, polytrauma, burn injuries.

23.5.5. Prehospital care

It is crucial to avoid refractory ventricular fibrillation with non-indicated reanimation attempts, awkwardshiftsorcarearoundhypothermicpatients.Theliteraturedescribescasesofoccurrence of ventricular fibrillation (VF) in hypothermic but conscious patients, resulting from clumsy care. Occasional cases of occurrence of VF during intubation seem to be exaggerated, because such cases are with adequate preoxygenation, fortunately rare.

   - Warm up the patient immediately. If necessary, take off wet clothes.
   - Gently move the patient into the environment which does not allow the heat.
   - If necessary, apply measures of resuscitation.Take into account that the metabolism is decreased, so bradypnoea and bradycardia do not have to be life-threatening. Only if a rescuer is

certaininthediagnosisofclinicaldeath,itisallowedtobeginwithresuscitationmeasures. This requirement is difficult to ensure if there is no heart rate monitor at hand.

- Becarefulwithcatecholamines-especiallyadrenaline.UsethemifindicatedinCPR.Thereisa possibility of initiation of refractory VF.
- Anti-arrhythmic drugs are ineffective for hypothermia induced ventricular arrhythmias.
- Defibrillationisgenerallyineffective.ContinueCPRmeasures,withheating,untilsuccessful defibrillation is possible.
- Avoid tea, coffee and other diuretics, and alcoholic beverages in conscious patients.

23.5.6. Hospital care

Itisimportanttocontinuewithprehospitalcarewithwarmingupthepatient.Also,it'snecessaryto continue with supportive care and to treat properly complications.

- Continue with CPR, if it is necessary.
- Ventilatedwithheatedoxygen.Theconsumptionandneedforoxygengrowwhenthepatienthas been warmed up.
- GivetothepatienttheatedsolutionsofO,9%NaCl+5%glucose.AvoidRinger'ssolutionbecause of cold liver's inability to metabolite lactate.
- Be careful and try to avoid catecholamines for hypotension.
- Warm up the patient can be done:
  - slowly (0,3 - 1,2°C/hour – i.v. solutions heated to 45 °C, heated and humified oxygen through a oxygen mask or endotracheal tube, heated blancket).
  - mild (3°C/sat – heated gastric lavage, heated i.v. solutions, peritoneal lavage with solutions heated to 45°C 4 L/hour)
  - quickly (thoracic lavage 500 mL/min – 6,1°C/hour or thoracic lavage 2L/min - 19,7°C/hour; cardiopulmonary bypass, ECMO – 18°C/sat; immersion in heated water - similar like last two procedures)

23.5.7. Immersion in heated water is best noninvasive procedure.

If there is a ventricular fibrillation (VF), start with CPR - defibrillate with antiarrhythmics. Cardiopulmonary bypass or ECMO is indicated for V.F. situations or in severe forms of hypothermiawithdeteriorationorprolongedcardiopulmonaryarrest.Ithastobedonequickly.If you expect delay in those situations, in meantime it's recommended to place catheters in femoral vein and artery, and then start with bypass.

In the case there is no possibility of treating the patient with some of above interventions, it's justified to do emergency sternotomy and open heart massage while pouring warm 0,9% NaCl solution in the chest.

Diagnostic procedures

Laboratory tests

1) *Acid-base status*
   - Inhypothermicpatientstheresultsshowhighervaluesofoxygenandcarbondioxide,whilepHis lower.
2) *Blood tests*
   - Hematocrit-canbeveryhigh-foreverydegreeCelsiuslowerthannormal,valuesincreaseby 2%
   - Electrolytes - show wide fluctuations, however, the value of K more than 10 mmol/L means very poor outcome.
   - Chronic hypothermia occasionally can lead to hypokalemia
   - Hyperglycemia lead to acute hypothermia, in chronic and secondary hypothermia may be present hypoglycemia.
   - Coagulation mechanisms are damaged. It can be presented as a DIC. It seems that the cause of thisisfailureinthecoagulationcascadereactionsinenzymes,allbecauseofthelowerdeep body temperature.
   - It must be remembered that the laboratory tests carried out at 37 °C. Coagulation parameters can be *"false normal"*, while the clinical condition can be serious and coagulopathy can be presented.

3) ECG
- Osborn wave (J wave) can be presented
- Hyperkalemia is not always accompanied by changes in ECG

4) Diagnostic Radiology

Traumapatientsorthosewithalteredmentalstatusrequirecertainradiologicalexaminations, including CTdiagnostics.

23.5.8. Complications
- Cardiac arrhythmias
- Hypotension secondary to significant vasodilation while warming
- Pneumonia
- Pancreatitis
- Peritonitis
- Gastrointestinal bleeding
- Acute tubular necrosis
- Intravascular thrombosis and DIC
- Metabolic acidosis

23.5.9. Conclusion

There are major controversies about the start of resuscitation in hypothermic patients. It is reasonable to start resuscitation measures in all hypothermic patients, unless they have other obvious injuries that are incompatible with life or have a frozen chest.The patient must be aggressively warmed and reanimated until core body temperature (measured rectaly or esophagealy)isatleast32°C. Afterreachingthisparameter,iftherearenosignsoflifeorthe patientdoesnotrespondto ACLSmeasures,resuscitationcanbediscontinued. Adheretothe principle that "the patient is not dead until he is warmed up and dead." Individual assessment is of invaluable importance in such situations, and other factors, such as age and coexisting disease, must be taken into account.

Thelevelofpotassiuminthebloodcanbehelpfulindecidingwhentostopresuscitation.Patients with a level of 10 mmol/Lor more have a very poor prognosis.

On the other hand, patients can be successfully resuscitated after deep hypothermia without any neurological sequelae, however insistence on prolonged warming and return of normal temperature in a person who does not give signs of life is inappropriate.

	°C	Symptoms
Safe zone	37	
	36	Feelings of cold, confusion, mistake making, disorientation
	35	
	34	Very cold skin, coordination inabilities, dysarthria, aphasia, lethargy, passiveness
	33	Amnesia
	32	Cardiac arrhytmia (mostly atrial fibrillation), delirium, bradycardia
Danger zone	31	Cyanosis, respiratory alkalosis, delirium, shivering replaced by muscle rigidity, weakened
Half - consciousness	30	reflexes, difficult blood pressure measurement, dilated pupils
	29	Hypoventilation (3-4 breaths per min), lactate acidosis
	28	Decreased kidney blood flow, absence of the deep tendon reflexes
	27	Ventricular fibrillation if heart is stimulated
Unconsciuousness	26	Clinical appearance of death, decreased muscle rigidity, pupils fixed and dilated
	25	Hypotension
	24	Spontaneous ventricular fibrillation
	23	Apnea
Maximal risk of ventricular fibrillation	21	Heart stillness
	18	Lowest accidental hypotermia with reported survival
	17	Isoelectrical EEG
	9	Lowest artificialy induced hypothermia with complete recovery

23.6. Bites and stings of venomous animals

23.6.1. Snakebite

There are about 3,000 species of snakes world wide, of which 375 are considered poisonous. Snake venom poisoning is called ophidism (Greek ofis = snake). In tropical and subtropical regions itisasignificantpartofnationalpathology.AccordingtotheWorldHealthOrganization,everyyear about 80,000 people in the world die from snake bites. In Europe, this number is significantly lower, about 50 people per year. Mortality from the European adder is about 0.3-5%.The mortality rate for cobra bites is about 20%, while the for the black mamba bite even up to 100%. Snakes secrete poison that has haematotoxic and neurotoxic effects. Haematotoxic effects prevail in domestic Croatian snakes. Croatia is one of the areas on the European continent where poisonous snakes are most widespread.

Croatia is inhabited by 16 species, of which only three are poisonous, two semipoisonous and 11 non-toxic.

The poisonous are horned viper, common adder, and meadow viper.

Hornedviper(Viperaammodytes)isEurope'slargest(about1m)andthemostvenomoussnake. It lives in dry and rugged areas; in Croatia is it spread along the river Drava. It is also known as the nose-horned viper and sand viper. It differs from local-area snakes by the eponymous horn at the top of the triangular head. Body color varies, and along the back a dark brown or black stripe stretches in zigzag pattern. Bites are more common in the summer months.

TheMeadowViper(Viperaursinii)isthesmallest(50cm)Croatianpoisonoussnake.Itissaidto beasmallversionoftheCommon Adder.Itproducesasmallquantityofweakpoison,soitisnot as dangerous to humans as the horned viper and common adder. In Croatia it inhabits the Dinara mountain , but it is also present in areas along the Cetina river.

InCroatia,hornedviperbitesaremorefrequentthanthoseofthecommonadder,whilethoseof the meadow viper are almost negligible. It often occurs that the victim does not see a snake, just feels the sting.

Local signs and symptoms: Edema occurs locally shortly after the bite (dotted sores), accompanied withnumbnessandredness,andsubsequenthematoma(after20-30min). Theedemacanspread from a finger to the whole fist, and later to the hand and hinder the circulation. Sometimes it can extendtotheshoulderandtorso.Blistersfilledwithbloodycontentsmayoccuratthesiteofthe bite , along with vascular thrombosis and infection.

General symptoms and signs: headache, thirst, diarrhea, vomiting, general weakness and numbness. Bleeding from the gums, colon, stomach or urinary tract may follow. Shock can occur, ending with lethal outcome.

*First Aid:*Firstdetermineifindeedtherewasavenomousbite(dottedsoresandclinicalpicture). Calmthevictim.Cleanthebitewoundwithsomedisinfectant. Thevictimmustrest.Immobilizethe bittenlimbwithsplints,orsimilarmeans. Transportthevictimtothenearesthealthfacilityona stretcher, if possible. If the victim has to get by herself to the doctor, running is not recommended, but instead walking with breaks. Depending on the site of the bite it is recommended to put a tourniquet a few inches above the bitemark and squeeze in a manner that it would be hard to put fingerunderneaththetourniquet.Tourniquetshouldbewide,andnotbearopeorawire.Theaim is to prevent the flow of lymph, not the return of venous blood.

What not to do: Sucking the poison from the wound is not recommended, and neither is cutting the bite wound with a razor blade, knife or similar means, because there is a possibility of doing severe injuries to the victim.

*Treatment:*Serumantiviperinum. Administeronlyinhealthinstitutions,wheretherearemeansfor treating allergic and anaphylactic reactions.

Prevention: It is very significant. Wear suitable clothing and footwear in areas where 86

poisonous snakes live. Snakes usually bite when surprised, therefore, banging a stick on the rocks, breaking branches etc. announces the arrival, so that snakes can escape in time. In a sudden encounter with a viper keep presence of mind, do not run, because it will scare the snake and cause her attack.

23.6.2. The sting of the black widow spider

Spiders of the latrodectus type are spread throughout the world. Our Mediterranean black widow spider in habits the coastal area sofEurope and Africa, all the way to the south of the European part of the former USSR. The spider was named after the brigh tred spots, which are 13 in number (tredecim). However, the number of spots is variable, it can be up to 17, or a spider can appear evenwithoutspots.

Only female sare poisonous, and it is distinguished by a body length of about 1.5 cm.The male is smaller, the average body size about 5 mm.

The venom of the black widow is a neurotoxin, which strongly stimulates the release of neurotransmitters. Venom is reabsorbedfrom theplaceof thebiteandexpands at first by lymph ducts,andonly aftert hat by the circulatory system.Aconsiderableamountofpoisonremainsat the injection site. Thespiderwillstingin self-defense, if it is accidentally pressed or if it climb sup the sleeve, and is in a tight position between the body and clothing. It does not dwell in the cities. Bites occur most frequently in the summer, but can occur throughout the year. Latrodectus appears cyclically.

*Clinicalpresentation:*Thestingisverysuperficialandalmostpainless,sothat50%ofpeopledo not register or do not pay attention to it, thinking that there was a sting of a blade of grass or thorn. Peoplestabbedduringsleepwerenotawakenedbythesting.Timeintervalfromthebitetothefirst signs is variable (10-60 min).

Clinical presentation:

a) minor local symptoms (most commonly),
b) strong localised pain, which lasts several hours, but without general symptoms, c) general symptoms a few hours after the disappearance of local symptoms
c) general symptoms and generalised severe condition, the rarest.

Localfindings: First,thepainoccursinregionallymphnodesclosetotheedema.Onlythe puncture site is not changed in a significant matter. One or two dotted spots on the skin that are raisedasinurticariacanbeseen. Afterafewhours,abluish-purplering,thesizeofasmallcoin, appears around faded areas.

Generalsymptomatology: The general condition rapidly deteriorates. Severepainspreads from the regional nodes, accompanied by cramps with a feelings of tightness in the abdomen and chest. Musclespasms and shivering frequently appear. Theabdomenmaybetenseandfirmandmimic acuteabdomen. Theskinof the entire body may become sensitive totouch, andprofuses weating canoccur. The victim is of tenun able to walk, rest less and scared andmay have afever. Astateof shock can also appear. The facemaybe distorted due to spasmofmasseter. Tearingfromthe eyes occurs. Salivation is present, but the feeling of dry mouth is more common. Heart rate is initiallyrapid,withelevatedbloodpressure. Asthetoxinaffectstherespiratory system, small bronchi become narrow while mucus secretion is profuse. Convulsive contractions of the diaphragm and the muscles of the abdomen and chest may develop, making it difficult to breathe. Hoarseness and speaking difficulties also occur. Nausea and vomiting are the gastrointestinal symptoms. Urinating may be difficult due to spasm of the sphincter of the bladder.

The main symptom is severe pain that is often described as "tearing the body by pliers", "rolling on thorns" or "grinding bones".

The clinical presentation is more severe in children and the elderly. Paresthesia, insomnia, dizziness, joint pain, photophobia, psychological disorders (memory loss, confusion, hallucinations, delirium)alsooccur. After a few days, arashmay appear similar to that found inscarlet feveror measles. Untreated persons suffer for about a week. Death from a black widow bite is rare.

Firstaid: Incisionswithaknifeorsimilardevicesortoolsarenotrecommended,aswellas attempts at sucking out the venom. Ice cooling relieves pain at the beginning. Urgent transport to hospital is necessary.

Treatment: Serum. Provide in medical institutions only because of the risk of anaphylaxis.

*Prevention:*Avoid habitat of black widows. Wear appropriate clothing and shoes.

24. INTRAVENOUS INFUSIONS

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24.1. Introduction

Administration of intravenous infusion solutions is very common in clinical practice. To understand this issue, it is necessary to have knowledge about the distribution of the body water (Table 24-1.) and about the effect of favoring certain infusion solution (Table 24-2.)

Table 24-1. Distribution of the body water in 70-kg man

TBW (total body water)	60% of the body weight	42 lit
ICF (intracellular fluid)	66% TBW	28 lit
ECF (extracellular fluid)	34% TBW	14 lit
A) interstitial	75% ECF	10.5 lit
B) intravascular	25% ECF	3.5 lit

The proportion of fluid in the cells is almost double in relation to extracellular fluid. It is also important to note the ratio of interstitial versus intravascular fluid inside the extracellular fluid compartment (3: 1 ratio – i.e. 10.5 lit:3.5 lit).

Table 24-2. The effect of applying different infusions on the body water composition (70-kg man)

	TBW (lit)	Intracellular (lit)	Extracellular (lit)	
			Interstitial	Intravascular
1 lit. 5% glucose	43	28,8	10.6	3.6
1 lit. Ringer solution	43	28	11.2	3.8
100 mL 20% albumin	42.1	28	10.5 (initial) 10.05 (after inf.)	3.6 (initial) 4.05 (after inf.)

From Table 24.2. it is evident that the glucose solution is distributed mainly intracellularly (80%), and only 10% remains intravascular (therefore it is not used in resuscitation of hypovolemia). Ringer solution (crystalloid solution) is distributed exclusively in the extracellular fluid, however, only 30% remain within blood vessels ("escape in the interstitial space"). Albumin solutions (colloidal) are maintained solely intravascularly. Also, because of their colloid-osmotic pressure, they draw water from the interstitium and expand the intravascular space.

The most common classification of infusion solutions is on the crystalloid and on the colloid solutions.

24.2. Crystalloids

Crystalloids are aqueous solutions of low-molecular ions with or without glucose; they achieve rapid equilibrium within the intravascular compartment and diffuse in the entire extracellular space. Indications for their use are: the maintenance of electrolyte and water in the body, and expansion of the intravascular volume. In relation to plasma osmolality these solutions may be isotonic, hypertonic and hypotonic. Isotonic solutions are most commonly used.

Table 24-3. shows the composition of some crystalloid solutions. It is necessary to pay attention on the following facts: concentration of sodium and chloride in saline solution (0.9% NaCl) is greater than one found in plasma (normal values for Na 137-147 mmol/L, Cl 95-105 mmol/L), Ringer's lactate solution is the so-called buffered solution (about them in Table 24-4), slightly hypoosmolar, and, like Ringer's solution, contains potassium. A solution of 5% glucose is the most hypotonic solution; therefore it is used in the treatment of hypernatremia.

24.2.1. Normal saline, 0.9% NaCl

The saline (in Croatian often called physiological solution) has the higher osmolality than the plasma (due to the higher sodium concentration). It has a very high content of Cl⁻ ion, therefore the big question is whether this solution is physiological at all?! In addition, its pH is much lower, so it can cause hyperchloremic metabolic acidosis after excessive administration.

Table 24-3. The crystalloid solutions composition

	0.9% NaCl	Ringer lactate	Ringer	5% glucose	5% glucose in ½ saline (0.45%) solution	10% glucose
Na	**154**	**130**	147	**0**	77	0
K	0	**4**	**4**	0	0	0
Cl	**154**	109	**156**	0	0	0
Ca	0	3	2,3	0	0	0
Mg	0	0	0	0	0	0
lactate	0	28	0	0	0	0
pH	5,7	6,7	7,4	5,0	4,9	4,9
mOsm/L	308	**273**	307	**253**	407	**505**
glucose	0	0	0	50 g /L	50 g/L	100 g/L
calories/L		9	18	170	170	340

Its application is preferred in relation to the Ringer solution in these conditions (Ringer has a lower content of Na and some potassium):

- brain injury,
- kidney disease (no potassium)
- hypochloremic metabolic alkalosis
- hyponatremia
- for dilution of red cells concentrates.

24.2.2. Balanced (buffered) solution

These include lactated Ringer's solution, Ringer's acetate, Plasmalyte (Table 24-4), and the Hartmann's solution which is very similar to Ringer's lactate solution (Na 129, Cl 109, K 5, Ca 2, Lactate 29 mmol/L).

Ringer's lactate solution has been on the market for a long time. However, there is no sufficient evidence about its higher efficiency when compared to normal saline; also, there is no evidence of lactate buffering effect. Additionally, calcium within this infusion may bind to certain medications and reduce their bioavailability. Amounts of other electrolytes are insufficient for the daily maintenance. It is slightly hypotonic, and delivers approximately 100 mL of free water per liter.

Plasmalyte isa newer product, very similar to plasma with its composition and osmolality. Possible advantages are shown in Table 24-4.

Balanced solutions are increasingly recommended in the last decade. The reason for this trend is a lower level of chloride in the newer solutions, and the difference of strong ions (SID = strong ion difference) which is similar to plasma (in the normal saline SID equals 0, i.e., Na = 154, Cl 154 mmol/L). It seems that the main adverse factor for normal saline is precisely the high supranormal amount of chloride. It can cause hyperchloremic acidosis, and in some animal models higher circulating levels of proinflammatory cytokines in sepsis and renal vasoconstriction. In an experimental model and after giving the volunteers it can cause hemostasis disorder due to hemodilution. Increased levels of chloride and subsequent reduction of bicarbonate ions persist for more than 6 h after administration of these infusion solutions. These biochemical changes put the body under stress because of the need to eliminate such high load of electrolytes. In addition, it is believed that it can affect the function of organs and surgical outcome. Furthermore, some studies in surgical patients showed that a balanced crystalloid solution with greater SID (similar to plasma) and a lower share of Cl⁻ ions can reduce postoperative morbidity and costs.

Table 24-4. Crystalloids - buffered (balanced) solution

	Na^+	K^+	Ca^+	Mg^+	Cl^-	Acetate	Lactate	Gluconate	HPO_4^-	mOsmol/L
NaCl	154				154					308
Ringer lactate	131	5	4		111		29			278
Ringer acetate	130	4	4	2	110	30				277
Plasma-lyte	**140***	5	**0***	3	**98***	27		23		295*
Plasma	136-145	3,5-5	4,4-5,2	1,6-2,4	98-106	Bicarbonate	21-30		2	290-303

*Highlighted are the physiological concentrations of Na and Cl ions, the absence of calcium (compatible with blood transfusions), and physiological osmolality.

Some national associations (UK) in its guidelines for crystalloid supplementation in adult surgical patients have already made a recommendation that, whenever possible, 0.9% NaCl should be replaced with balanced solutions (high level of evidence 1b, exception: vomiting-associated hypochloremia).

Serious scientific analyses (Cochrane) conclude that buffered solution adminsitration during surgery is just as safe and effective as giving non-buffered (saline). However, buffered solutions lead to significantly lower rate of metabolic disorders (hiperchloremia, metabolic acidosis). The additional, larger studies are needed to assess other outcomes such as mortality.

24.2.3. Hypertonic and hypotonic NaCl solution

These solutions are rarely used. Hypertonic solutions attract water from the intracellular compartment into the extracellular and thereby lead to cell dehydration. Some time ago, hypertonic solutions combined with dextran were relatively popular in the resuscitation of hypovolemic shock. Hypertonic solutions include 3-10% NaCl (the most common is a molar solution of 5.84% NaCl). The hypotonic solution include 0.45% NaCl and, for example, *glucosalina III* (2.5% glucose + 0.45% NaCl). These solutions are rarely used, mostly in children and with complications of diabetes (ketoacidosis, hyperosmolar coma).

24.2.4. Glucose (dextrose) solutions

These solutions are used for:
- water supplemenation
- parenteral nutrition
- diabetic patients for prevention of hypoglycemia
- hypernatremia treatment

They include solutions of 5%, 10%, 25%, and 40% glucose. 5 and 10% solutions can be administered through the peripheral vein; however, 25% and 40% hyperosmolar solutions used in parenteral nutrition should be administered through the central vein. On the market there are also ampoules of 37, 40 and 50% glucose, commonly used in the treatment of hypoglycemia. For glucose infusions, the rule says they should not be given in resuscitation of traumatized persons, and certainly not in cranial trauma situation!! (see Table 24-2. - solutions diffuse into the cell – brain edema).

Crystalloids - summary:

Benefits:
1) they are not allergens, they are non-immunogenic
2) maintain low blood viscosity
3) smaller danger for overload as quickly secreted by urine

Shortcomings:
1) Do not carry oxygen
2) Quick redistribution through the interstitial space (within 1 hour)
   - Peripheral edema, lung edema
3) In large quantities possible dilution coagulopathy
4) Often need for large quantities

24.3. Colloids

Colloids are solutions containing larger molecules, which relatively slowly diffuse through the semi-permeable cell membranes. Therefore they are retained mainly intravascularly. Unlike crystalloids, whose plasma elimination half-time is short (20-30 minutes), most colloids have a half-time of at least 3-6 hours. They are significantly more expensive than crystalloids. There are several types of colloids (Table 24-5.). They are composed of either plasma proteins or glucose synthetic polymers, which are dissolved in saline solution. The most common classification:

a) Natural colloids derived from the blood:
   - all blood products
   - albumins
b) Synthetic colloids:
   - dextran
   - starch (hydroxyethylstarch = HAES)
   - gelatin (only in Europe)

Synthetic colloids are usually diluted with 0.9% NaCl, but there is also combination with other electrolyte solutions. Colloids cause less tissue edema compared to crystalloids and expand blood volume very efficiently. They can also reduce amount of hemoglobin (which is not always so bad), perform dilution of plasma proteins and coagulation factors. Colloids can be triggers for anaphylaxis.

The ideal colloid should not be accumulated in tissues and plasma, should not affect hemostasis or have any effects on the immune system. Furthermore, the colloid should not be an allergen and it should not affect the diagnostic tests. It should be compatible with other fluids and medications; also, it should be well tolerated and completely eliminated. In the following paragraph, it will become evident that such a colloid is still missing.

Table 24-5. The properties of some colloids

Colloid	COP (mmHg)	Plasma volume expansion	$T_{1/2}$
5% albumin	20	0.7-1.3	16 h
25% albumin	70	4-5	16 h
6% HAES	30	1-1.3	17 days
10% dextran 40	40	1-1.5	6 h
6% dextran 70	40	0.8	12 h

COP = colloid osmotic pressure

The main indications for colloids are fluid resuscitation in severe shock before the arrival of the blood, as well as severe hypoalbuminemia or conditions associated with hypoproteinemia (e.g. burns).

24.3.1. Albumin

Albumin is a natural protein with a large number of functions. It is the key protein to maintain the colloid osmotic pressure (COP). 1 gram of the albumin binds 18 mL of water. It is also an important transport protein (hormones, iron, bilirubin, drugs, ...), and it is also considered to be an antioxidant.

Albumin is given in situations when crystalloids are not able to maintain plasma volume more than a few minutes because of low cardiac output (such as when an abnormal loss of protein from the vascular space occur - peritonitis, burns, etc.). Sometimes it is applied in hypoproteinemia with edema, to accomplish the shift of fluid from interstitial to the vascular space (controversial indication?!). It is also used for plasmapheresis. It should not be used for resuscitation in hypovolemia.

Albumin can be administered in concentration from 3.5 to 25% (in Croatia we mostly use 5% and 20% of albumin). The benefits of albumin are:
- no risk for transmission of viral diseases
- no negative effect on kidney function
- rare allergies and coagulopathies
  - Anaphylactoid reaction 0.03%

The main disadvantage is a high price.

In clinical use of albumin preparations there are plenty of unresolved questions. Cochrane systematic review from 2011. point out:
1) In hypovolemic patients there is no evidence that albumin reduces mortality when compared with cheaper alternatives (saline).
2) There is no evidence that albumin reduces mortality in critically ill with burns and hypoalbuminemia.
3) There is a possibility that highly selected populations of critically ill patients could have benefit from giving albumin.

Furthermore, in the SAFE study (Saline vs Albumin Fluid Evaluation), in patients with traumatic brain injury, patients who received albumin had a worse outcome than those given saline.

24.3.2. Polygelines

These are degraded gelatin polypeptides (bulls bone), MW = 35.000, with isotonic electrolyte composition similar to plasma. They have the same pH as plasma; t1/2 is 8-10 h. The most common commercial preparation is Haemaccel. Lately, polygelines do not take up a significant share of the market.

Polygelines are not expensive. Furthermore, they not affect the coagulation, and also can be administered in a large volume without problems. Because of the relatively low molecular weight, renal elimination is rapid. They have a relatively short duration of volume effect (2-3 hours). The incidence of anaphylactic reactions is about 0.1%. According to some studies it seems they do have an effect on renal function.

24.3.3. Dextrans

Dextrans are synthetic colloids isolated from sugar beet contaminated by bacteria Leuconostoc mesenteroides. They include 6% solution with an average MW = 70,000 (Dextran 70) and a 10% solution with

an average MW = 40,000 (Dextran 40). Today dextrans represent less then 10% of colloids in the market. Production costs are relatively low. In a glass packaging can be stored up to 10 years.

Dextrans have two characteristics:

a) accomplish effective plasma expansion

b) have antithrombotic effect and hemodilutional one too (especially dextran 40)

The latter is considered to be very favorable for the microcirculation, therefore their use was common in the prophylaxis of postoperative thromboembolism, which was effective (though, lately less frequently administered, because of the availability of other drugs like low molecular weight heparin). So today, we do not recommend routine thromboprophylaxis with dextran, due to the unpredictable impact and the existence of safer alternatives.

However, dextrans have negative effect on platelet aggregation and perform dilution of coagulation factors. Patients receiving dextrans, therefore, have a tendency to bleed particularly if the dose exceeds 1.5 g/kg/day. Anaphylactic reactions have incidence 3-7:10.000. These reactions are often fatal (4:100.000), and occur usually after the first 100 mL. Among other shortcomings, possible disturbance of renal function can be expected, particularly in already existing renal disease; it is considered that molecules >50 kDalton disturb the flow in the renal tubules. Furthermore, some studies found difficulties in cross-matching of blood (dextran is coating the erythrocyte membrane), and immune function disorder.

Because of fear of turbulent anaphylactic reactions, dextran 1 solution appeared in the market. This solution acts as a monovalent hapten of the dextran, and binds any of circulating antibodies to dextran. By binding to the dextran-reactive IgG antibodies (DRA), it prevents the formation of immune complexes responsible for the anaphylactic reactions. It reduces incidence of anaphylactic reactions, but does not prevent mild allergic reactions to high molecular dextrans (skin changes, disturbances in the digestive and respiratory system) that are usually independent of the antibodies. Dextran 1 is packaged as 20 mL bottle, containing 15% solution of low molecular weight dextran MW = 1000. It is given slowly IV, in about 60 seconds. After its application dextran 40/70 has to be infused within less than 15 minutes. If there is a 48 hours gap from the last administration of dextran, dextran 1 should be administered repeatedly.

Conclusions - dextrans:

- dextran 70 – strong plasma-expander
- dextran 40 – additional effects on microcirculation, prevention of thromboembolism
- dextran 1 – hapten, coupled with immunoglobulins, but this complex does not lead to life-threatening reactions, on contrary, prevents them; should always be administered prior using dextrans 40 and 70

24.3.4. HAES

HAES or **H**ydroxy**AE**thyl-**S**tarch is lately the most widely used colloid in clinical practice, although his future is quite uncertain (see later in text).

The starch is the energy storage carbohydrate of plants (corn, potatoes) and is made up of two types of glucose polymers: amylose and amylopectin. HAES is manufactured from amylopectin, and a starch hydroxyaethylation makes the molecule more stable. Small molecules of HAES solution (MW<50.000) are easily secreted in the urine, while large diffuse slowly into the interstitial space where enzymatic degradation with the enzyme amylase occur. It is eliminated from the plasma in 2 days; however, it remains in the body for a very long time. For example, HAESmolecules can even diffuse into the reticuloendothelial system and in the perineural cells, the result can be itching (even one month after the administration).

There are four main determinants of the HAES solution:

1) Concentration – mostly 6% and 10%
2) Mean molecular weight (MMW) – these above 200 kD are considered to be higher molecular weight
3) Molar substitution (MS)
4) The hydroxylation pattern (C2/C6 ratio)

The higher the molar substitution and C2/C6 ratio, the slower is the degradation. On HAES backpacking there is always a concentration, mean molecular weight and molar substitution (i.e. which proportion of glucose units in starch molecules is modified by hydroxyethyl units). For example, the preparation named 6% Voluven 130/0.4 is frequently used nowadays; it is clear that concentration is 6%, the average molecular weight is 130 kDa and molar substitution is 0.4.

Several generations of HAES products are established. Older generations have a high average molecular weight and high molar substitution. The first generation include Hetastarch (HAES 400/0.7) and

Hexastarch (HAES 200/0.62), while the second generation includes Pentastarch (HAES 200/0.5). The maximum dose of these solutions is 1.5-2 g/kg/day.

Newer products (the third generation, Tetrastarch, i.e., the already mentioned Voluven) have favorable pharmacological characteristics: rapid onset, rapid renal clearance, no accumulation in plasma and tissues, and significantly less effect on coagulation. The maximum daily dose is increased to 50 mL/kg BW/24h h or approximately 4000 mL/day.

Indications for HAES use are:
- therapy and prophylaxis of hypovolemia and shock as a result of
  - surgery,
  - trauma,
  - infection,
  - burns,
- saving allogenic blood transfusion in surgery = acute normovolemic hemodilution.

Contraindications for HAES use are:
- serious bleeding disorders,
- congestive heart failure,
- kidney failure with oliguria or anuria,
- allergies to starch,
- hyperhidration.

Regarding the possible side effects, allergic reactions are very rare, because HAES solution does not have antigen properties as dextran (the incidence of these reactions is the lowest among all synthetic colloids = 0.019%). However, it can cause mild coagulation disorder (dose-dependent, at dosages > 20 mL/kg), and sometimes an increase in serum amylase. It does not interfere with the blood group determination or cross matching. Effects on renal function are possible. Two recent multicenter studies have shown significant deterioration in renal function in critically ill, however, the older preparations "hexastarch"and "pentastarch" were used.

In July 2013, a regulatory body of European Medicine Agency proposed the suspension of further marketing authorization for all HAES solutions in Europe, mostly because of higher incidence of renal failure in septic patients; it was based on the results of three large clinical studies. This was soon joined by the US FDA warning about the increased mortality and incidence of kidney failure (http://www.fda.gov/biologicsbloodvaccines/safetyavailability/ucm358271.htm). According to them HAES should not be used in critically ill patients, especially those with sepsis and pre-existing renal insufficiency. FDA pointed out that the effect of HAES on renal function is possible even 90 days after application. A further warning is for open-heart surgery, where greater amounts of HAES solution may be accompanied with coagulopathy.

In conclusion, HAES is still used in clinical practice, however, probably not so often as before. The following studies will surely provide more information about the issue.

24.4. Infusion therapy - newer concepts

Until recently, the main debate among clinicians was which of the intravenous infusion solutions should be used, particularly in resuscitation: crystalloids or colloids. These are the present facts:

1) There is no evidence that colloids resuscitation reduces mortality compared to crystalloids resuscitation. Furthermore, the use of HAES may increase mortality. Since colloids do not increase survival, and are significantly more expensive than crystalloids, it will be difficult to explain their continuing use in clinical practice.
2) Colloids still have their place in the fluids therapy (see later in text)
3) If using crystalloids, balanced crystalloid infusions are increasingly recommended as the first choice (SID >> 0); Many authors suggest avoiding routine use of 0.9% NaCl in resuscitation (SID = 0), and consider that it should only be given with the simultaneous administration of the blood products.

However, besides these facts, it is necessary to be informed with further changes in terms of infusion therapy. It is surely necessary to avoid hypovolemia (poor perfusion), but also hypervolemia. This fluid load is increasingly being recognized as a factor which contributes to morbidity and mortality.

There is no defined "universal strategy" for all situations, i.e. fluids administration can be liberal, restrictive and goal-directed. Liberal administration of fluids can be performed in low risk patients and out-

patient surgery. Restrictive administration is recommended in the elderly, and with major surgery. It would be best for the patient, if possible, to use a goal-directed fluid administration. This kind of fluid administration use hemodynamic variables in the resuscitation of patients, with defined aims to achieve. Fluids administration is done in order to optimize the specific hemodynamic parameters, to increase oxygen delivery, and to improve outcomes. According to this method we use a bolus of fluid, or the vasoactive drugs (vasoconstrictors, inotropes). Clearly, this method is not simple, and depending on the disease level involves various methods of invasive monitoring (starting from the invasive measurement of blood pressure, central venous and pulmonary artery pressure and the measurement of saturation of mixed venous blood). More specifically, this concept uses the index of continuous blood flow and/or tissue oxygenation in order to optimize the organ function - cardiac output, saturation of mixed venous blood, variations of stroke volume, etc.

Furthermore, the importance of the vascular endothelium integrity during the critical conditions is being highlighted increasingly. This vascular barrier is a fragile structure which comprises of plasma proteins, proteoglycans and glycosaminoglycans, also known as endothelial glycocalyx (EGL). In order for the barrier to be efficient, endothelial glycocalyx must be intact which is often not the case in the perioperative period. EGL is often compromised in trauma and sepsis. With the new concept of EGL, classic Starling law for fluid shifts loses its importance, because COP (colloid-osmotic pressure) from the layer below the EGL must be recognized. To simplify, crystalloids are indicated in sub-normal capillary pressure (hypovolemia). Colloids are indicated only in the case of the higher capillary pressure, e.g. increasing stroke volume in euvolemic patient, but never with a damaged EGL and hypovolemia.

Another paradigm: any loss of fluids perioperatively should be strictly compensated for. Exclusively measurable losses should be compensated. For example, any calculations in mL/hr due to losses in the injured tissue are being abandoned, i.e. the concept of a "third space" and "loss in the third space" is completely rejected. Preoperative dehydration is recognized as an important factor and should be minimized with reducing the fasting time and the use of oral fluids up to 2 hours before the procedure.

24.5. Conclusions

There is increasing evidence that treatment with intravenous fluids can improve the outcome. More knowledge on the kinetics of the fluids at the level of the endothelial glycocalyx is needed. We still have unresolved issues about the effects of surgery, anesthesia, and intensive care on this barrier. In critically ill patients fluids should enhance the perfusion of organs. Hypovolemia and hypervolaemia should be avoided. Individualized approach with right fluid in the right dosage at the right time is being highlighted. The goal-directed treatment with hemodynamic monitoring can improve the outcome.

25. INTENSIVE CARE UNITS

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25.1. Introduction

Progress of medicine is a result of scientific progress and medical technology development. The latter has enabled new methods of treatment, new approaches to treating chronic and acute illnesses, special procedures of resuscitation, maintenance of organs and life, transplantation of organs, implantation of prothesis and devices (electrostimulator), and enable elongation and quality of life. Today`s medicine is successful in treating acutely ill or injured patients, saving lives, decreasing disability and regaining working ability.

Severely ill patients are treated in intensive care units (ICU). These units provide the highest possible level of medical care. It is estimated that in highly developed countries ICUs comprise approximately 10% of acute care hospital beds (ICUs of 1st, 2nd and 3rd level). By providing adequate space, special equipement and specially educated staff, achieving desired goals is facilitated. Locating medical care for severely ill patients at a single facility has multiple advantages: special equipement is gathered in one place, highly educated personnel is present, novel strategies and protocols of treatment are created and applied, treatment efficiency is monitored, treatment expences are controlled, scientific trials are conducted etc.

Treating patients in ICUs is expensive, and using novel technologies makes it even more expensive. Those expenses contribute with 20 to 30% to total hospital costs, and in the USA the percentage is higher than 20%. In year 2002., costs of treatment in ICUs in UK were 1500 to 2000£ per day. The expenses can be fixed (hotel costs) and variable (diagnostic procedures costs, special treatments and drugs costs, surgical procedures costs, etc.) Those are the reasons why health care workers have to be rational when it comes to treating patients. Maintaining of body and life can not be primary objective. One has to keep in mind recovery of the patient and quality of his life after the treatment.

25.2. Intensive care units

Intensive treatment is multidisciplinary and multiprofessionaly and it represents the highest level of medical care. It is performed within special units, using special methods and procedures (performed by educated health care personnel), special equipement and drugs.

There are several types of intensive care units: anesthesiological (general and surgical), surgical (cardiosurgical, neurosurgical, traumatological and those specialized for burns), pediatric (pediatric, neonatological), internal medicine critical care (general, cardiological, pulmonary, gastroenterological), psychiatric, neurologic, infectious diseases critical care units, etc. According to the level of care, they are divided into three levels: the first, the second and the third level. First level units are those in smaller hospitals where patients with less severe illnesses are treated; their condition is monitored, and reanimation is performed. Severely ill patients in need of a higher level of care, or patients in need of post-resuscitation care are transmitted to units of the third level (units in regional, university or special hospitals). Those units provide the highest level of intensive care; hence, more health care providers (doctors, nurses and other personnel) are employed in those units.

Intensive care units

Intensive care units are units of intensive care and supervision of patients, which are observed due to possible critical condition, or have been transferred from ICU to the lower level units for observation and care, before being transferred to hospital ward or released from the hospital. In these units patients are cared for by their doctors (working in other units, wards) and the unit head takes care about organization and functioning of the unit.

Due to development of new technologies and advanced surgical procedures (liver, kidneys, heart and lungs, small intestines and pancreas transplantation), there is a need for novel and special units for intensive care. Bone marrow transplantation is an additional reason why those units have to exist.

Intensive treatment comprises: observation, care, treatment and maintainig of life of severely ill or injured patients. These patients are unstable and even small changes in functioning of their organs (heart, kidneys, liver, etc.) can be the reason for severe damage to entire organism with irreparable damages to organs that have lethal consequences.

Purpose and task of intensive treatment is to recognise threatened patients, to monitor them, to recognise signs of critical condition in a timely manner, and to quickly supress and treat disorders of organs and organism as a whole.

If critical condition arises, the task is to maintain life as long as there are chances that vital functions can be restored. Therefore, characteristics of intensive care are: maintaining of functioning of organ and of organism as a whole, and a quick and specific treatment when necessary.

Constant observation of patient`s vital signs and organ functioning enables noticing of even small changes and treatment as soon as these changes appear, in order to prevent permanent damage to organs that can have fatal outcome. It should be stressed out that intensive care is more than just monitoring patients and maintenance of their vital functions; intensive care involves multiple factors (legal acts, ethical norms, available economic possibilities etc.)

There are 6 main factors to consider when determining health care:

- A patient has to be in the center of attention,
- The care has to be provided in a timely manner,
- The care has to be safe,
- The care has to be effective,
- The personnel has to be educated for the work they perform,
- The care has to be fair.

Units are organized in city, regional, university, military and private hospitals, as well as in special reference hospital centers.

There are open and closed models of intensive care unit. In an open intensive care unit patients are under care of doctor who comes when needed or on his own schedule, but he does not work in the ICU. He comes to the ICU only when one of his patients is admitted to the ICU. This type of intensive care units is most common it the USA. Closed intensive care units have personnel that works in the unit permanently and they are responsible for everything that happens in the unit. Other doctors are consultants and they can recommend a way to treat the patient, but they can not prescribe therapy. The doctors working at the ICU decide whether to accept the colleague`s opinion (they are not obliged to), they are responsible for the patient`s condition and only they are entitled to give orders in ICU.

Every unit has its unit head, a specialist of intensive care, and a head nurse, specialized for working in intensive care unit. Depending on the unit type and the level of medical care, an intensivist is temporarily (as a consultant) or permanently available (on full-time basis) in the unit.

Multipurpose ICU has five characteristics:

- Unit head and head nurse are experts in the field of intensive treatment
- Educated nurses, respiratory therapists, physiotherapists, pharmacist or clinical pharmacologist, dietetian and spiritual advisor are team members
- Standard work methods, protocols and guidances are used
- Decision making and coordination when treating and comunication between team members and with other specialities
- Emphasized are practical licenses to work, explore, educate, promote ethical values and protect patients.

Above mentioned is important to ensure quality of treatment. Moreover, it enables the highest level of treatment. Multidisciplinary approach to patients` treatment improves the level of care, can improve efficiacy of the treatment itself, and, at the same time, decrease expenses. Adopted working protocols are used and after longer period of time in use, results are analized. In that way, new protocols or guidelines concrning ICU work are created. Following protocols and scoring patients using available scales enables work analysis, analysis of treatment costs, effectiveness assessment, assessment of incidence of nosocomial infections, assessment of complications and mortality and assessment of patient`s satisfaction with the treatment. Assessment of ICU`s effectivenessis is made by: analyzing morbidity and mortality in the unit, effectiveness of the treatments used, complications that have arisen during treatment, length of stay in the ICU and analyzing treatment costs.

Intensive care unit comprises: space, medical equipment, technological equipment, energy supplies and personnel according to adopted standards.

25.2.1. Indications for admission of patients into ICU

- Patients with life-threatning conditions, regardless of etiology,
- Patients in need of mechanical ventilation,
- Patients in shock,
- Acutely comatosed patients,

- Patients in need of post-resuscitation care,
- Patients in need of postoperative care, especially after major surgery, transplantation, etc.

25.2.2. ICU space requirements

Every state has it`s own space requirements. Units must not be neither too small, nor too large. It is recommended that the adult ICUs have 10 to 12 beds, and neonatalogical up to 20 beds. Regarding occupancy of ICU, it shouldn`t be more than 80%. It could be quite chaotic to work in large units (20 beds). On the other hand, small units (less then 4 beds), are not cost-effective and often interpersonal problems arise.

Intensive care unit must have a reception area (reception desk and administration office), visitors` room, room suitable for interviews and breaking bad news (crying room) where information on losing organs and lives are given and consent to organ transplantation is asked.

In ICU, patients are accommodated in rooms with more than one bed (patients` room with 4 to 12 beds) or in rooms with one bed (isolation). Required ratio of regular beds to isolation beds is 6:1. The more rooms there are, the more personnel is necessary for treating patients, for caring and observation of patients. Rooms can be of semicircular, circular or rectangular shape.

Rectangular room requires more space (43m^2 per hospital bed) than circular one (29,8m^2 per hospital bed). Above mentioned rooms consist of main area (hospital beds and working area) and additional area (drug storage, area for cleaning and preparation of appliances, sterilization area, equipment and bed linen storage, area for disposal of used medical and non-medical materials – it is stored separately).

The management station of a single or multi-bed room must be situated in such a way that it has a clear, unobstructed view of the whole area. This station serves as the central communications area where monitors are installed and all patients`data are gathered (ECG, RR, body temperature, SaO$_2$ etc.). The same monitors and video surveillance have to be installed in doctor`s room as well, so he could have timely insight into events in unit.

Intensive care unit has to have an operating room for minor surgical procedures (tracheotomy, chest drainage, drainage of abdomen, vein preparation, wound bandaging), bronchoscopy and other endoscopic procedures, hemodyalisis and laboratory.

It is recommended that ICU has a special room for patients` administration and cardiopulmonary reanimation. It should also have a seminar room, staff sitting room, lavatories, showers and cloakrooms, room for unit head and head nurse, doctor`s room, rooms for on-call personnel and a library.

Intensive care unit has to have good lighting. Moreover, it is essential that patient areas and staff rooms have large windows that permit natural daylight (stress, dezorientation of patients and personnel are decreased in daylight).

25.2.3. ICU equipment

Unit has to have: specially designed beds, mechanical ventilators, intubating, tracheotomy and bronchoscopy equipment, equipment for defibrillation and permanent monitoring of vital functions (cardiac, pulmonary and brain functions, as well as body temperature). Moreover, suction devices, chest drainage pumps, inhaling devices, a bronchoscope, an endoscope, oxygen connections (3 per hospital bed), connections for compressed air (2 per bed), connections for vacuum (3 per bed), enough electrical sockets (16 per bed), special sockets for X-ray machine, alarms for nurses, connections for audio and video surveillance, transport ventilator, transport monitor for cardiac function, body temperature and oxygen saturation, an X-ray apparatus, an unltrasound, transport hemodyalisis/hemofiltration device, perfusion pumps (at least 4 – 6 per bed) and other equipment for administering drugs, parenteral and enteral nutrition are needed.

Intensive care units must have drug storage with all drugs necessary for intensive treatment of patients.

25.2.4. Information technology support in ICU

The nineties of the 20th century are often associated with the begining of information society. Huge progress of information and comunication technology has happened in the field of mobile telephony, computer and multimedia technology, etc. Above mentioned development of technology has happened in medicine as well. Medical devices are, hence, more developed, sophisticated and offer wide range of possibilities intended to improve health care and satisfaction of patients, while being cost-effective.

Huge amounts of data are generated every day in health care facilities. Data are product of doctors` observations while examining patients and are recorded on devices while patients are being monitored. These data can be only one-time recorded (e.g. X-ray recordings) or can be continously recorded (data on different monitors that record patients` vital functions). When data are obtained, they need to be saved in

order to be compared with new ones. In that way a trend or changes in patients` condition can be monitored.

Some data are automatically written in memory of the devices used, while others need to be handwritten and recorded manualy. Based on saved data, different entities and treatment options can be analyzed in order to decide whether to continue the treatment or to change it or even start with something completely new. Access to the saved data and to archives they are kept in is possible only if well designed and composed information system is used.

Hospitals have several information subsystems which work within themselves, but they are also interconnected in order to exchange data among them.

Clinical information systems automatize process of gathering data from monitors, ventilators, perfuzors, hemodialysis devices and other electronical devices that are connected to patients. They provide automated collecting of accurate data in the form of tables, in real time. That, together with the other clinical documentation, creates comprehensive and readable source of information.

Above mentioned data are available from different locations, whether from other work stations within the same ICU, from the same hospital, or even from distant locations.

25.2.5. ICU staff

Working in an intensive care unit is a team work with members that know their own roles and responsibilities but also those of other team members. Members of a team working in ICU are: an intensivist (subspecialist anesthesiolog or internist, pediatrician, surgeon or some other specialist/ subspecialist), nurses with special eduaction in woking in ICU, clinical pharmacist or pharmacologist, respiratory therapists, physiotherapist and/or some other therapist, dietetitian, social worker, hospital`s chaplain and administrative worker. Moreover, every ICU needs consultants for monitoring nosocomial infections (microbiologist, infectious diseases` specialist, epidemiologist), monitoring quality of work and treatment costs.

Besides above mentioned employees, an intensive care unit needs to have professionals for technical, energetical and information technology support (energy and electronics experts, information technology specialists and statisticians). Every unit has to have a head unit and a head nurse who take care that everything within the unit is done according to the medical and legal regulations.

According to the norms, there should be one doctor per 2,5 beds per 24 hours and 2,5- 3,6 nurses per ICU bed per 24 hours. First level ICUs have less personnel because less complicated actions are performed there. On the contrary, third level ICUs have 1 doctor per 2,5 patients and 4 nurses per 1 patient (per 24 hours). When patients are mechanically ventilated, one nurse should care about one patient, and when patient are stable (breathe on their own) there should be one nurse per 2 to 3 patients.

Intensivists take care about every procedure that is performed during patients` treatment, they avoid unnecessary investigations and procedures, but also avoid ineffective treatment and maintaining of life at all costs. They should respect medical and legal regulations and maintain professional and ethical relationship to patients, personnel and patients` relatives.