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INTENSIVE THERAPY IN TOXICOLOGY

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МИНИСТЕРСТВО ЗДРАВООХРАНЕНИЯ РЕСПУБЛИКИ БЕЛАРУСЬ
БЕЛОРУССКИЙ ГОСУДАРСТВЕННЫЙ МЕДИЦИНСКИЙ УНИВЕРСИТЕТ
КАФЕДРА АНЕСТЕЗИОЛОГИИ И РЕАНИМАТОЛОГИИ

Р. Е. Ржеутская

ИНТЕНСИВНАЯ ТЕРАПИЯ В ТОКСИКОЛОГИИ

INTENSIVE THERAPY IN TOXICOLOGY

Рекомендовано Учебно-методическим объединением по высшему медицинскому, фармацевтическому образованию в качестве учебно-методического пособия для студентов учреждений высшего образования, обучающихся по специальностям 1-79 01 01 «Лечебное дело»,1-79 01 02 «Педиатрия»

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Освещены основные вопросы интенсивной терапии различных видов острых отравлений

Предназначено для студентов 4-го курса, может быть полезным для студентов 6-го курса медицинского факультета иностранных учащихся, обучающихся на английском языке по специальности «Лечебное дело» и «Педиатрия».

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INTRODUCTION

Drug overdose and poisoning is a global public health problem. In the UK it accounts for 120 000 hospital admissions each year (around 1 % of the total number) and is a significant proportion of the Emergency Department workload.

In 2004 the World Health Organization estimated that 346,000 people died worldwide from unintentional poisoning, whilst 1 million people died as a result of deliberate self harm, and poisoning accounted for a significant number of these deaths.

Drug overdose is the most frequent presentation of deliberate self-harm often complicating medical management. However, most patients are young, otherwise medically well and, managed appropriately, the vast majority usually fully recover.

Toxicology is the study of the effects of poisons.

Poisonous substances are produced by plants, animals, or bacteria.

Toxicity — the adverse effects that a chemical may produce.

Dose — the amount of a chemical that gains access to the body.

Exposure — contact providing opportunity of obtaining a poisonous dose.

Hazard — the likelihood that the toxicity will be expressed. 92 % of all poisonings happen at home.

The **household products** implicated in most poisonings are:

- cleaning solutions,
- fuels, medicines,
- and other materials such as glue and cosmetics.

Certain **animals secrete** a xenobiotic poison called venom, usually injected with a bite or a sting; other animals harbor infectious bacteria.

Some household plants are poisonous to humans and animals.

Exogenic intoxication is a pathological condition that develops as a result of interaction between human body and substances of different origin, which entered the body from the environment.

Routes of Environmental Exposure:

- Ingestion (water and food);
- Absorption (through skin);
- Injection (bite, puncture, or cut);
- Inhalation (air).

The most common classification of intoxications is:

I. Accidental intoxication:

- occupational.
- domestic:
  a) as a result of self-treatment;
  b) alcohol or drug intoxication;
  c) medication overdose
- medical mistakes.

II. Deliberate intoxication:

− criminal:

a) homicide;

b) a way of bringing in a helpless state.

− suicide attempts

Classification according to the toxicity of substances:

1. *Extremely toxic* (chemical weapons, senile acid compounds);
2. *Highly toxic* (methanol, dichloretan);
3. *Moderately toxic* (benzol, phenol, herbicides);
4. *Low toxic* (some herbicides and insecticides).

Classification according to the system-organ tropism and clinical manifestations:

1. ***Heart poisons*** (arrhythmias, myocarditis): glycosides, tricyclic antidepressants, barium and potassium compounds;

2. ***Neural toxins*** (psychoses, seizures, comas): drugs, hypnotics, CO, alcohol and its substitutes);

3. ***Liver toxins*** (hepatopathy): toxic fungi, phenols, aldehydes;

4. ***Blood toxins*** (hemolysis, methemoglobinemia): anilines, nitrites;

5. ***Lung toxins*** (edema, fibrosis): NO-substances, phosgene;

6. ***Renal toxins*** (nephropathy, ARF): ethylenglycole, heavy metal compounds;

7. ***Gastrointestinal intoxication*** (gastroenteritis): acid and alkaline substances, heavy metals.

The total effect of endotoxin is a consequence of its specific characteristics and compensatory protective non-specific reactions of the body.

In the development of acute intoxication the following clinical stages are distinguished:

1. toxicogenic stage;
2. somatogenic stage.

Toxicogenic stage is defined as a period of time, when the toxin is in the organism in an amount that can cause a specific effect (exotoxic shock, coma). This stage includes the resorbtion period (maximal concentration in the blood) and the elimination period (complete withdrawal of toxins).

Somatogenic stage is defined as a period of time after the elimination or degradation of toxins with consequences of toxic injury of the organs and systems (acute renal and hepatic failure, pneumonia, sepsis).

The clinical picture of intoxication includes three phases:

1. *Latent phase* is a period of time from the incoming of the toxin to the body to the first clinical manifestations of intoxication.

2. *Phase of acute clinical manifestations* is a period of time from the first clinical manifestations of intoxication to the full-blown intoxication.

3. *Resolving phase* is a period of time from the full-blown intoxication to disappearance of intoxication symptoms.

After the intake of the toxic substance, its distribution in the human's bloodstream and other sectors occurs. The distribution of a toxin in the body is determined by three factors: the routs of intake and distribution of a toxin, time and concentration.

GENERAL PRINCIPLES OF INTENSIVE THERAPY IN TOXICOLOGY

Many drugs in overdose (e. g. opiates, tricyclics, benzodiazepines) can cause significant depression of the cerebral and cardiorespiratory function. Emergency management should always start with a rapid **initial assessment** and **resuscitation** of the airway, breathing and circulation (**ABC)**.

Careful history and examination will in most cases give an indication as to the possible severity of the overdose and guide subsequent management.

Treatment principles include the following strategies:

- reduce absorption,
- increase elimination,
- provide general supportive measures,
- use of specific antidotes.

History. A detailed and reliable account of taken drugs should be sought; this should include:

- the drug name;
- the drug amount;
- preparation type;
- time of ingestion;
- co-ingestion of other substances such as alcohol or recreational drugs, which might influence the patient's clinical state or drug clearance.

Presence of tablets in vomiting soon after overdose should be noted but it does not preclude significant toxicity.

The medical, social, psychiatric and therapeutic drug history will help identify high risk patients and also guide subsequent management.

The patient may be uncooperative or unable to give these details and so a collateral and confirmatory history should be acquired from available sources such as drug packets, the ambulance crew, witnesses, a suicide note and the patient's case notes.

Examination. The airway, breathing and circulation should be reassessed and treated accordingly as a priority. Basic airway maneuvers, simple adjuncts, supported ventilation and/or cuffed endotracheal intubation may be required if the airway and/or breathing is compromised.

The patient's level of consciousness may give an indication of the overdose toxicity, risk to the airway and guides the level of supportive care needed. It can be expressed on the «AVPU» scale or as a formal GCS (although not de-

signed for this purpose, it does give a reproducible score which is sensitive to subsequent changes).

A GCS equal or less than 8 (or responding to pain only) increases the risk of airway compromise and endotracheal intubation is indicated unless rapid recovery is anticipated.

Careful attention should be paid to the respiratory function, particularly with sedative drug toxicity. This should include respiratory rate and tidal volume and checking of oxygen saturations using pulse oximetry.

A low respiratory rate with decreased oxygen saturations may indicate hypoventilation, but note that a normal saturation does not exclude hypercarbia or hypoxia in carbon monoxide poisoning. In case of any doubts, arterial blood gases should be measured.

Tachypnoea can be seen with metabolic acidosis (e. g. tricyclics, methanol), anxiety, a stimulant drug overdose and as an early feature of salicylate poisoning (respiratory alkalosis). Supplementary oxygen via a facemask should be given to all patients initially, taking in the account pulse oximetry data (noting the limitations described above).

Many drugs exhibit cardiovascular toxicity in overdose (e. g. tricyclics, b-blockers, digoxin, lithium). This may be manifested as hypotension and or cardiac arrhythmias. Pulse, blood pressure and ECG data should be recorded, intravenous access established and initial fluid resuscitation given as appropriate.

General examination may give evidence of significant ingestions or clues in unknown overdoses. Many drugs (e. g. SSRIs, tricyclics, phenothiazines) have serotonergic or anticholinergic effects with pupil dilatation, and extrapyramidal movements, whilst opioid type drugs will cause sedation and pin point pupils.

Temperature, blood glucose (low in b-blocker, ethanol poisoning) and weight should also be recorded. Weight is important in calculating whether the patient is likely to have received a toxic dose and may guide treatment, for example in paracetamol overdose.

Examination should reveal any associated injury (accidental or deliberate self harm) which may require treatment, or the presence of other substances such as alcohol. If the clinical condition allows, an assessment of the patient's mental state should be made.

Additional investigations. Samples should be sent for laboratory investigation — urea, electrolytes and blood glucose as a minimum. Blood gases are helpful in providing a rapid assessment of acid-base disturbance as well as assessing adequacy of ventilation in patients with reduced conscious level.

Creatininekinase (CK) should be measured if there is a possibility of rhabdomyolysis or serotonin syndrome is suspected.

Appropriately timed drug levels (e. g. paracetamol, salicylate, lithium) should be taken when indicated. Paracetamol levels should be checked if there is any suspicion of paracetamol poisoning — this includes all unconscious patients.

Many Emergency Departments measure paracetamol levels in all patients in case s when poisoning is suspected, as paracetamol poisoning is associated with a lack of early clinical signs. There is no need to routinely measure salicylate concentrations in conscious overdose patients who deny taking salicylate-containing preparations and without features suggesting salicylate toxicity. Salicylate levels should be measured in all unconscious patients or when poisoning is suspected.

Treatment. Supportive treatment of the cardiorespiratory and neurological systems should be given by standard intensive care methods.

Induced emesis is no longer recommended and contraindicated in case of taking volatile or corrosive substances. Drug absorption can be reduced by the use of activated charcoal, given either orally or nasogastrically.

A single dose (50 g in adults, 1 g/kg in children) should be given up to one hour after the ingestion of a substantial amount of toxin (i. e. a dose expected to cause moderate to severe toxicity). After this time adsorption is reduced.

Multiple doses of activated charcoal should be considered for the adsorption and enhanced elimination of certain toxins.

Some other substances (including alcohol, ferrous salts and lithium) however, are not readily adsorbed by charcoal and this treatment is not indicated in case of poisoning with such substances. An unprotected airway is an absolute contraindication to charcoal administration, as aspiration pneumonitis is a risk.

Toxins, for which multiple doses of activated charcoal are indicated, are:

- Carbamazepine;
- Dapsone;
- Digoxin;
- Paraquat;
- Phenobarbitone;
- Quinine;
- Slow release preparations such as theophylline;
- Amanita phalloides fungus;
- Multiple doses may also be considered in life threatening overdose of other drugs (e. g. tricyclic antidepressants).

There is little evidence to support the use of gastric lavage and current literature suggests that this should only be considered in patients presented within 1 hour, who have ingested a substantial amount of a toxin with high lethality. It is contraindicated if the airway cannot be protected and in case of hydrocarbons (risk of aspiration and chemical pneumonitis) and corrosives ingestion.

If metabolic acidosis caused by poisoning persists, despite the correction of hypoxia and adequate fluid resuscitation, then correction with intravenous sodium bicarbonate should be considered.

Rapid correction is particularly important if there is prolongation of the QRS or QT intervals on the ECG. In adults the initial dose of 50 mmol of sodium bicarbonate may be given and repeated if necessary (as guided by arterial blood gas monitoring).

In cases of severe poisoning, hemodialysis should be considered as a means of extracorporeal toxin removal as well as for management of acute kidney injury.

Seizures should be controlled initially with intravenous diazepam (10–20 mg in adults; 0.25 mg/kg body weight in children) or lorazepam (4 mg in adults; 0.1 mg/kg body weight in children).

SPECIFIC FEATURES OF VARIOUS ACUTE POISONING TREATMENT

ALCOHOL

Ethanol is quickly absorbed in the intestines and in 1.5 h its blood maximum concentration is reached. Blood ethanol concentrations may be used to demonstrate exposure, but the levels are not reliable due to individual tolerance and do not exclude co-ingestions or head injury as a cause for symptoms or signs. They should therefore be interpreted with caution. 90 % is hepatically metabolized via alcohol dehydrogenase → to acetaldehyde → to acetic acid → then to CO_2 and H_2O. About 10 % is excreted through the lungs and kidneys unchanged.

Clinical features. With the increase of blood concentrations, features are progressing from ataxia, dysarthria, and nystagmus, to hypothermia, hypotension, stupor and coma. In severe cases, especially in children, convulsions, respiratory depression, cardiac arrhythmias and acidosis may appear.

Specific hazards. These include aspiration of vomit, hypoglycemia (especially in children), and rhabdomyolysis (especially following a period of unconsciousness).

Treatment. Alcohol is rapidly absorbed from the gut, and therefore gut decontamination is unlikely to be of benefit. Intravenous thiamine (e. g. Pabrinex®) should be given to chronic alcohol abusers to protect against the onset of Wernicke's encephalopathy. This should be achieved before administration of glucose to treat hypoglycemia. Hypoglycemia should be treated as quickly as possible with oral glucose if the patient is awake, or otherwise with intravenous 5 or 10 % glucose.

If facilities allow, hemodialysis should be considered in case the blood concentration is greater than 5 g/L, if arterial pH is < 7.0, or if the patient's condition deteriorates in spite of maximal supportive measures.

ETHYLENE GLYCOL (ANTIFREEZE, COOLANT, BRAKE FLUID)

Ethylene glycol is clear, viscous fluid with sweetish taste. It is rapidly absorbed from the gut and peak plasma concentrations occur 1 to 4 hours after ingestion. The fatal dose is 100 g for a 70 kg adult. Inhalation and skin absorption are not serious hazards to health. Toxicity is caused by glycolic, glyoxylic and

oxalic acids which are products of ethylene glycol metabolism. Glycolic acid is largely responsible for the metabolic acidosis seen in severe cases. Early administration of the antidote prevents the production of toxic metabolites and minimizes the development of complications.

Clinical features. Onset of symptoms is rapid. In the first 12 h post-ingestion the patient appears inebriated but the smell of alcohol is not felt. Nausea and vomiting, ataxia and dysarthria occur followed by convulsions, coma and severe metabolic acidosis.

Between 12 and 24 h after ingestion, cardiac failure, hypertension, respiratory distress and oliguric renal failure may occur. If untreated death from multiorgan failure occurs in the period between 24 and 36 h after ingestion.

Specific hazards. Calcium oxalate monohydrate crystals precipitate resulting in cerebral oedema and renal failure (calcium oxalate monohydrate crystalluria is diagnostic of ethylene glycol poisoning). Hypocalcaemia occurs as calcium is consumed in the circulation.

As glycol is absorbed over the first few hours, patients develop a high osmolal gap. After this, as glycol is metabolized to acids the osmolal gap falls whilst the anion gap increases and acidosis worsens. A severely poisoned patient presenting shortly after ingestion may have a normal anion gap and normal pH, however their osmolal gap will be high.

METHANOL

Methanol is colorless, volatile, sweet tasting low toxic substance, but its degradation products (formaldehyde and formic acid) are highly toxic. Methanol is found in antifreeze, windshield washer, carburetor, duplicator and hobby engine fuels and gasohol. Methanol is rapidly absorbed from the GI tract; 90 % is hepatically metabolized via alcohol dehydrogenase → to formaldehyde — via aldehyde dehydrogenase → to formic acid.

Clinical Features:

- Depressed mental status, confusion, ataxia;
- Weakness, dizziness, anorexia, headache, nausea;
- Coma, seizures;
- Vomiting, abdominal pain;
- Cloudy, blurred vision, dense central scotoma «like stepping into a snowstorm»;
- Optic disk hyperemia;
- Pallor and cupping (indicating optic atrophy, poor prognosis);
- Sluggish or fixed pupil (poor prognosis).

Diagnosis. Severe anion gap metabolic acidosis is the hallmark of methanol ingestion. It occurs due to presence of formic acid. May be delayed from 12 to 24 h.

Methanol & Ethylene Glycol: Treatment guidelines. Consider gastric lavage if the patient presents within 1 h of ingestion. Charcoal is not indicated as it does not adsorb significant quantities of ethylene glycol. Ethylene glycol concentration levels can be measured but this assay is often not available locally and thus is not often determined early enough to be useful in emergency treatment. However, these should be taken and sent (at least 2 h post ingestion) as they will guide later treatment. Treatment should be commenced in case of clinical suspicion and presence of high osmolar gap or high anion gap metabolic acidosis.

Treatment with an antidote should be commenced if:

− There is suspicion that any amount of ethylene glycol has been ingested and objective evidence of toxic alcohol exposure (e. g. high anion gap metabolic acidosis, osmolal gap > 10 mosmol/kg, without another likely cause).

− There is strong suspicion that >10 g (in adults) or 0.1 g/kg (in a child) of ethylene glycol has been ingested within the last 12 hours whilst awaiting ethylene glycol levels.

Once initiated an antidote treatment should be continued until the plasma ethylene glycol concentration is less than 50 mg/L. Both antidotes — ethanol and fomepizole — work by competing with ethylene glycol for alcohol dehydrogenase, which is responsible for the conversion of the ethylene glycol to its toxic metabolites (see table 1 for examples of dosing regimes). Both are also antidotes to methanol poisoning. Fomepizole does not cause any alteration in the patient's mental state, hypoglycaemia, or respiratory depression, and may be preferable to the use of ethanol in pregnant patients or hepatic disease. The main drawback is cost.

Ethanol is cheaper and often more readily available, can be given orally or IV. However, adverse effects include hypoglycaemia (particularly in children and malnourished patients), respiratory and CNS depression, and clinical features of alcohol intoxication, potentially making the patient difficult to manage.

Correct metabolic acidosis with IV sodium bicarbonate. Hypocalcaemia should be corrected with 10–20 ml (0.2–0.3 ml/kg) IV 10 % calcium gluconate only if there is evidence of prolonged QTc on ECG or persistent seizures. Routine correction of hypocalcaemia may increase the formation of calcium oxalate crystals. In severe poisoning with evidence of cardiac or renal failure, hemodialysis is the treatment of choice.

CARBON MONOXIDE (CO)

Toxicity primarily occurs due to to impairment of oxygen delivery and subsequent cellular hypoxia. Carbon monoxide is combined with hemoglobin to produce carboxyhemoglobin, reducing the oxygen carrying capacity of the blood and shifting the oxyhemoglobin dissociation curve to the left. The half-life of carboxyhemoglobin is 320 minutes when breathing in the air. This is reduced to 80 minutes when breathing 100 % oxygen.

Clinical features. These are related mainly to tissue hypoxia as a result of impaired oxygen carrying capacity of hemoglobin. Therefore, headache, nausea, irritability, agitation and tachypnea, progress to impaired consciousness and respiratory failure. A metabolic acidosis and cerebral edema may develop in severe cases, and progression to multi-organ failure may occur.

Chronic carbon monoxide poisoning is less easy to diagnose, and usually occurs in more than one member of a household, associated with the use of gas heaters in underventilated areas. The main symptoms are headache and flu-like symptoms.

Specific hazards. Late complications, occurring weeks later in survivors of the acute exposure, may include psychiatric and Parkinson-like movement disorders.

Treatment guidelines:

− Remove from exposure.

− Give oxygen in as high concentration as possible to reduce the half-life of caboxyhemoglobin and hence improve oxygen delivery to the tissues. Pulse oximetry is unreliable in carbon monoxide poisoning, as it overestimates oxygen saturation.

− Metabolic acidosis generally improves with oxygen therapy. However, if acidosis persists or has a severe form it can be corrected with sodium bicarbonate.

− If a patient has been exposed to carbon monoxide due to a house fire consider the possibility of concurrent cyanide poisoning and treat accordingly.

− Treat raised intracranial pressure conventionally.

− Use of hyperbaric oxygen should be discussed with the national/ regional poisons unit.

ORGANOPHOSPHATES

Organophosphate compounds are a diverse group of chemicals used in a variety of settings including insecticides, nerve gases, and antihelminitcs. Organophosphate poisoning remains a significant issue in developing countries – globally there are estimated 300 000 fatalities each year.

Clinical features. Organophosphates can be absorbed throughthe skin, inhaled via the lungs or ingested. Poisoning causes:

− nicotinic effects (muscle weakness, fasciculations, and respiratory muscle weakness);

− muscarinic effects (hypersecretion, bronchospasm, vomiting and diarrhea, urinary incontinence);

− central nervous system effects (irritability, seizures, coma).

Treatment guidelines:

− Avoid self contamination – wear protective clothing.

− Prevent further absorption by removing source, including soiled clothing.

− Wash patients with soap and water.

− Consider gastric lavage if ingestion occured within 1 hour.

− If intubation is required avoid suxamethonium because of prolonged effects.

− Give atropine (2 mg for adults, 0.02 mg/kg for children) IV every 10–30 minutes until adequate atropinisation is achieved. Continuous atropine infusions can be used in doses of 0.02–0.8 mg/kg/h, titrated to effect.

− The maximum dose of atropine is required on day 1 and decreases over the next few days. When the patient improves the dose should be slowly reduced over the next 24 h. Rebound toxicity may occur due to organophosphates being lipid soluble.

− Oximes (pralidoxime, obidoxime) reactivate phosphorylated acetylcholinesterase before deactivation occurs, and are clinically used to reverse neuromuscular blockade (atropine has no useful effect on the neuromuscular junction). The World Health Organization recommended the following dosing regime: 30 mg/kg pralidoxime chloride bolus followed by 8 mg/kg/h infusion. Although the evidence base for this is limited, oxime application is still recommended for patients with moderate to severe organophosphorus poisoning.

− Benzodiazepines should be given to reduce agitation and control convulsions.

MANAGEMENT OF SNAKE ENVENOMATION

Out of more than 3000 species of snake identifiable worldwide, only one tenth of them are dangerous to human beings.

There are **three major families of venomous snakes**.

Elapidae (Land snakes like cobra, krait and coral snakes). Snakes of this family have short fixed fangs, containing venom channels. Their tricolor bands (black, red and yellow/white) encircle the body and they lack laurel shields (the shield on the lateral aspect of head separating the shields bordering the eyes from those bordering the nostril).

Viperidae (Russell's viper, bamboo snakes). These are further classified into pit vipers (crotalinae) and viperine vipers (viperinae). Their fangs are long and movable. Their pupils are vertically elliptical. The ventral plates, caudal to anus, are in a single row. These snakes have a heat sensing pit as a small depression on the side of head for location of prey.

Hydrophiladae (Sea snakes). These snakes have a flattened tail.

Epidemiology. Although a major public health problem in many countries the epidemiology of snakebite is still fragmentary, mainly due to lack of statistical data. This is due to the fact that the majority of victims come from rural areas, out of reach of available medical facilities. It is estimated that snakebites may exceed 5 million per year, out of whom approximately 100 000 develop severe sequelae. The incidence also shows a distinct seasonal pattern, with a higher frequency in summer and during rains when the reptiles come out of their shelters.

Epidemics of snake bite following floods, as human and snake populations are concentrated together, have been noted in Pakistan, India and Bangla-

desh. Snakebite is observed in all age groups, the majority (90 %) affecting 11 to 50-year-olds with males affected twice as often as females. Most bites occur between midnight and early morning and a large number of bites occur in fields, as most individuals are unable to spot the snake due to tall grass and crops.

Fortunately, every bite does not result in complete envenomation and more than half of victims escape without serious poisoning. However, if sufficient venom is injected during the bite to cause serious poisoning, the mortality can be high.

Table 1

Medically important snakes

Region	Types
North America	Eastern Diamond Rattlesnake (Crotalus adamanteus), Western diamond rattlesnake (C. atrox, C. viridis), Bothrops atrox (fer-de-lance)
Central and South America	Bothrops jararaca & tropical rattlesnake (C. durissus, C. terrificus)
Britain	European adder (Vipera berus)
Europe	Long nosed viper (V. ammodytes)
Africa	Night adder (Causus species), Puff adder (Bitis arientan), Mambas (four species of Dendroaspis)
Africa and Asia	Cobra (Naja species), Saw-scaled viper (Echis carinatus)
Part of Asia	Russell's viper (V. russelli) Malayan Pit viper (Agkistrodon rhodstoma) Sharp-nosed pit viper (A. acutus) Mamushi Pit viper (A. halys) Haliu viper (Trimeresurus flavoviridis) Kraits (Bungarus coeruleus, B. multicinctus)
Pacific-Australian area	Tiger snake (Notechis scutatus) Death adder (Acanthophis antarcticus) Taipan (Oxyuranus scutellatus) Papuan black snake (Pseudechis Papuanus) King brown (Pseudechis australis)

Pathophysiology. Snake venom is a very complex chemical poison, containing multiple proteins and peptides, in addition to carbohydrates and metals, which exert toxic and lethal effects on the skin and the hematological, nervous, respiratory and cardiovascular systems (tabl. 2).

Table 2

Snake venom components and their effects

Component	Pitviper	Coral snake	Effect
Enzymes			
Proteinases	Heavy	Minimal	Tissue destruction, coagulation, anticoagulation
Hyaluronidase	Moderate	Moderate	Hydrolysis of connective tissue stroma
Cholinestrase	Minimal	Heavy	Catalyzes hydrolysis of acetylcholine
Phospholipase A	Heavy		Haemolysis may potentiate neurotoxins
Phosphomesterase	Minimal	Heavy	Unknown
Phosphodisterase	Moderate	Moderate	Hypotension
Non-enzymes			
Neurotoxins	Minimal	Heavy	Flaccid paralysis

Different species have differing proportions of these agents. The picture may be further complicated by the release of endogenous mediators such as histamine, bradykinin and adenosine. Therefore, snake venoms cannot be classified purely as «neurotoxic» or «cardiotoxic», although they may have a predominantly specific action. The effects may be conveniently, though arbitrarily, classified into vasculotoxic for vipers, neurotoxic for elapids and myotoxic for sea snakes.

Viper venom. This is primarily vasculotoxic. It causes rapidly developing swelling of the bitten part. Local necrosis is mainly ischemic, as thrombosis blocks the local blood vessels and causes dry gangrene.

Systemic absorption is via the lymphatics. Some vipers such as Vipera berus (European Viper) cause vomiting, abdominal pain, explosive diarrhea and shock within a few minutes of the bite, which resolves spontaneously within half an hour. Persistence of shock may however be fatal.

Several viper venoms result in intracranial hemorrhage due to direct endothelial damage by «haemorrhagin» (a venom component), which interestingly does not affect coagulation. In contrast other viper venoms (Crotalus, Bothrops) do affect coagulation and a very small amount of venom can cause complete fibrinogen consumption. This feature can also differentiate various species of vipers, which can help in instituting appropriate antivenom therapy.

Elapid venom. Local necrosis causes a picture like «wet gangrene» with a characteristic putrid smell due to direct cytolytic effect of the venom. Systemic absorption occurs through venous channels. These result in primarily neurotoxic features, causing selective neuromuscular blockade of the eye muscles, tongue, throat and chest leading to respiratory failure in severe poisoning.

Sea snake venom. The effects are both myotoxic and neurotoxic, resulting in clinical and pathological changes typical of segmental myopathic lesions in skeletal muscles. Muscle pain may last for several months unless treated.

Clinical features of snakebite. The clinical presentation of a snakebite victim varies with the size and species of snake, the number and location of bites, and the quantity of venom injected. About 30 % of Pit viper bites, and 50 % of elapid bites result in no envenomation, sometimes referred to as «dry bites».

The venom channel is recessed above the tip of the fang and the venom injected may be reduced by poor penetration or glancing blows, causing venom to be lost over the skin and clothing. The volume of the venom available to a particular snake may also be reduced by previous bites.

The age and health of the victim are also important determinants in the clinical presentation. However, whether the snake is poisonous or non-poisonous and regardless of the venom injected, the commonest symptom following snakebite is fright, which may lead to a vasovagal episode (faint). Usually the minority of victims who receive a venom dose large enough to cause systemic poisoning will already have signs of this by the time they seek medical help. Differentiation of viperine from elapid systemic poisoning is usually obvi-

ous from simple clinical evaluation. Persistent bloody ooze from the fang marks may suggest the presence of snake venom anticoagulant.

In difficult cases the presence of pain out of the proportion to the size of the wound suggests snake envenomation whereas mild pain is more normally caused by non-venomous snakes, anthropod bites (centipedes, spiders), bacterial fascilitis or myonecrosis.

Local manifestations. After envenomation, local swelling starts within few minutes. Fang marks may be difficult to see. Local pain with radiation and tenderness and a small reddish wheal are first to develop, followed by oedema, swelling and the appearance of bullae, all of which can progress quite rapidly and extensively. In most viper bites paresthesia commences around the wound, and tingling and numbness over the tongue, mouth and scalp may follow. The local bite may become necrosed and gangrenous.

Russell's viper has been reported to cause the Raynaud's phenomenon and gangrene in a limb other than the one bitten. Secondary infection including tetanus and gas gangrene can alsooccur.

Since the venoms are largely absorbed by the lymphatics, lymphangitis may appear early. Petechiae or purpura may also be present due to the anticoagulant effect of some venoms. These characteristic changes are useful clinically - for example, if after a known Crotalid bite the victim demonstrates no local changes over several hours of observation, he can be released from the hospital as significant envenomation is unlikely. In contrast Elapid snakebites are associated with minimal local changes. Systemic manifestations of Cobra and vipers bites produce symptoms within a few minutes to several hours after the bite.

Sea snake bites almost always produce myotoxic features within 2 h, so that the bite can be reliably excluded if no symptoms are evident within this period. Although snakes are classified into predominantly neurotoxic, hemorrahagic and myotoxic types on the basis of their venoms, each species can result in any kind of manifestations.

Viper bites. 75 % cause envenomation, 35 % mild, 15 % severe. Pit viper venom can involve virtually every organ system. Nausea and vomiting are common and, if present early, suggest severe envenomation. Weakness, sweating, fever, chills, dizziness and syncope may occur.

Some patients complain of a minty, rubbery or metallic taste in their mouths with increased salivation. Tingling or numbness in the tongue, scalp, face and digits are indications of moderate to severe envenomation, as are fasciculations of the face, neck, back or the bitten extremity.

Systemic anticoagulation can lead to gingival bleeding, epistaxis, hemoptysis, hematuria, hematemesis and rectal bleeding or melena. Intra-abdominal or intracranial hemorrhages may occur.

Visual disturbances may result from retinal hemorrhages. There may be tachycardia or bradycardia, often accompanied by hypotension. Delayed shock may occur due to excessive blood loss and hemolysis.

Severe envenomation can result in pulmonary oedema due to destruction of the intimal lining of the pulmonary blood vessels and pooling of the pulmonary blood. The venom itself and associated hypotension along with hemoglobin, myoglobin and fibrin deposition in renal tubules, can contribute to nephrotoxicity.

Elapid bites. The venom of elapid bites is primarily neurotoxic. Neurotoxic features are a result of selective d-tubocurarine like neuromuscular blockade, which results in flaccid paralysis of muscles.

Ptosis is the earliest manifestation of cranial nerve dysfunction followed closely by double vision. Then paralysis usually progresses involving the swallowing muscles, but not strictly in that order. Generally, muscles innervated by cranial nerves are involved earlier. However, the pupils are reactive to light until the terminal stages. The muscles of the chest are involved relatively late, with the diaphragm being most resistant. Respiratory paralysis is therefore often a terminal event. Even prior to respiratory failure, airway obstruction due to vomit or secretions can result in sudden death.

Reflex activity is generally not affected and deep tendon jerks are preserved until late. Symptoms that suggest severe envenomation include repeated vomiting, blurred vision, paresthesia around the mouth and hyperacusis (increased sensitivity to sound), headache, dizziness, vertigo and signs of autonomic hyperactivity.

Tachycardia, hypotension and ECG changes may occur. Tetanic contraction of heart following a large dose of cobra venom has also been documented.

Sea snakes. Muscle pain is the most common presentation. Muscle necrosis may result in myoglobinuria and severe sea snake poisoning causes myoglobinuria and respiratory failure within a few hours.

Coagulopathy is not a feature of coral snake bites. In severe systemic poisoning following either elapid or viper bites, the electrocardiogram may show T-wave inversion and ST segment deviation.

In sea snake bites, an ECG is especially valuable in detecting hyperkalemia, which can result from damage to muscles. Tall, peaked T-waves in the chest leads may appear within a few hours of bite and give early warning of impending death or acute kidney injury.

Unusual presentations of snake envenomation:

− Naja nigricollis (spitting cobra) can eject venom from a distance of 6–12 feet. The venom is aimed at victim's eyes resulting in conjunctivitis and corneal ulceration. It may also cause anterior uveitis and hypopyon. A dull headache may persist beyond 72 hours.

− Occasionally a recently killed snake or snakes with severed heads can eject venom into those handling them.

− Rarely recurrence of snake envenomation manifestations may occur hours or even days after an initial good response to the antivenom. This may be due to ongoing absorption of the venom.

Management of snake bite. The management of snake envenomation is controversial. It can be divided into first aid and prehospital care, specific antivenom therapy and supportive therapy.

First aid and prehospital care. Reassurance and immobilization of the affected limb, with prompt transfer to a hospital are of prime importance. The application of a «constriction band» to delay absorption and venom spread has been advocated during transit to hospital for bites to a limb.

A firm, but not tight, ligature may be applied just above the bite. The tension is correct if one finger can pass between the limb and the bandage. This will impede lymphatic drainage, but not arterial or deep venous flow. It should preferably not be released until the administration of antisnake venom. If the limb becomes oedematous the band should be advanced proximally. However, the band should not be left in place for too long, due to the risk of venous thromboembolism and distal ischemia. An increase in local envenomation has also been reported subsequent to release of the band.

Venous or arterial tourniquets are contraindicated. The site of the bite should be cleaned and covered with a handkerchief or dressing. Incision and mechanical suction of the bite (intended to open the puncture wound so that suction can be more effective) may be beneficial when performed by a health care worker within a few minutes of the bite, in a victim who is more than 30 to 60 minutes from hospital.

The incision should be parallel to the axis of the extremity and should be only approximately 6 mm long and 3mm deep. Cross cuts or multiple cuts should be avoided.

Mechanical suction (e. g. the «extractor» device found in a Sawyer first aid kit) is preferable to mouth suction, in order to avoid wound contamination with oral flora and to prevent possible envenomation of the rescuer through breaks in their oral mucosa. Suction should be maintained for about 30–60 minutes for maximal benefit, but due care should be taken as laceration of nerves, tendons and vessels has been reported following suction by untrained rescuers.

Application of cooling measures such as ice packs or cryotherapy, at the site of bite, were initially advocated, but have not been proven to be effective and this practice is not now recommended.

Antitetanus toxoid should always be given following snakebite. There is controversy about the use of drugs as a part of first aid care. It has been suggested that NSAIDS may be beneficial to relieve local pain but may precipitate bleeding, especially if the venom is vasculotoxic.

Paracetamol and/or codeine may be useful, however, there are no clear-cut recommendations for the application sedatives.

If the snake has been killed, it should be taken to hospital, or it should be left alone, since attempts to find or kill it may result in further bites. The snake,

even if judged to be dead, should be handled very carefully, since decapitated heads can bite for up to one hour!

Patient assessment. Evaluation should begin with the assessment of the airway, breathing and circulatory status. Oxygen should be administered to every envenomed patient and a large bore intravenous line with normal saline or Ringer's lactate established in the unbitten limb.

Cardiac monitoring and pulse oximetry, if available, is indicated. Attempts should be made to determine whether a venomous snake has actually bitten the patient, and the severity of envenomation should be assessed (tabl. 3).

During the initial evaluation, several locations on the bitten extremity (at the bite site and at least two sites more proximal) should be marked and the circumferences should be measured every 15 min until swelling is no longer progressing and every 1–4 hours thereafter. The extremity should be placed in a well-padded splint for at least 24 hours.

Table 3

Assessment of envenomation severity

No envenomation	Absence of local or systemic reactions. Fang marks +/–
Mild envenomation	Fang marks. Moderate pain, minimal local oedema (0–15 cm), erythema +, ecchymosis +/–, no systemic reactions
Moderate envenomation	Fang marks +, severe pain, moderate local oedema (15–30 cm), erythema and ecchymosis +, systemic weakness, sweating, syncope, nausea, vomiting, anaemia or thrombocytopenia
Severe envenomation	Fang marks +, severe pain, severe local oedema (> 30 cm), erythema and ecchymosis+,hypotension, parasthesia, coma, pulmonary oedema, respiratory failure

Laboratory investigations. Although laboratory tests are of little value in the diagnosis of snake envenomation, nevertheless they are useful for monitoring the patient's state and deciding about specific interventions and prognosis. They should include a full blood count, electrolytes, glucose, creatinine, serum amylase, creatinine phosphokinase (CPK), prothrombin time (PT), partial thromboplastin time (PTT), fibrinogen and fibrin degradation products (FDPs).

Commonly hyperkalemia and hypoxemia with respiratory acidosis may be noted, particularly with neuroparalysis. Urine examination may reveal hematuria, proteinuria, hemoglobinuria or myoglobinuria. Arterial blood gases and urine examination should be repeated at frequent intervals during the acute phase to assess progressive systemic toxicity.

Blood changes include anemia, leukocytosis (raised white cell count) and thrombocytopenia (low platelet count). The peripheral blood film may show evidence of hemolysis, especially in viperine bites. Clotting time and prothrombin time may be prolonged and a low fibrinogen may be present. Blood should be typed and cross matched on the first blood drawn from the patient, as both direct

venom and antivenom effects can interfere with later cross matching. Some specialized centers can identify the species of snake involved.

Non specific ECG changes such as bradycardia and atrioventricular block with ST and T segment changes may be seen. Recently electroencephalogram (EEG) changes have also been reported in many patients of snake envenomation. They may manifest within hours of bite without any clinical features suggestive of encephalopathy.

Antivenom therapy. Antisnake venoms (ASV) are prepared by immunizing horses with venom from poisonous snakes, extracting serum and purifying it. The WHO has designated the Liverpool School of Tropical Medicine as the international collaborating center for antivenom production and testing. Antivenoms may be species specific (monovalent) or effective against several species (polyvalent) (tabl. 4).

Table 4

Types of antivenom

Name of Antivenom	Species
Polyvalent Wyeth Labs [Antivenin (cortalidae) polyvenom] United States	All North American pit vipers
King cobra antivenom	King cobra (Ophiophagus hannah)
Polyvalent Naja naja serum (common cobra) antisnake venom CRI, Kausali, India	Vipra russelli (Russell's viper) Bunqarus ceruleus (common krait) Echis carinatus (saw scaled viper) Indian species
Mono specific Echis carinatus antivenom, India	Sea snakebite & Afro-Asian elapids
Tiger snake antivenom, Australia	Trimeresurus albolabris, Trimeresurus monticola
Green pit viper antivenom Bothrops antivenoms, Brazil	
Monospecific antivenom from South African Institute for Medical Areas (SAIMR), Northern Nigeria	Echis pyramidum leakeyi
Poly specific German & French antivenoms	

Storage of ASV: Liquid +20–+80 °C, Lyophilized — cool & dry place. The correct use of antivenom is the most important component of hospital care and not every bite, even with a poisonous snake, merits its use. Administration of antivenom should be selective and based on the severity of clinical symptoms. The main concern about the empirical use of antivenom is the risk of allergic reactions, its relative scarcity in some centers and the cost. Moreover, in a study of Elapid envenomation, all victims with neuromuscular paralysis survived without receiving any antivenom.

Shemesh *et al* did a preliminary evaluation of the possibility to reduce the dose of anti-venom or totally avoid it in some viper species. They concluded that about half of bitten patients in their study did not show systemic symptoms and therefore did not require antivenom treatment. They further observed that antivenom treatment based on systemic symptoms was effective and the dose re-

quired was also less than the fixed amount advocated for each patient, thereby reducing the incidence of serum sickness.

Administration of antivenom

Antivenom should be given within 4–6 h of the bite and the dosage required varies with the degree of envenomation. Serum sensitivity should be tested by injecting 0.2 ml of antivenom subcutaneously. **If a severe reaction occurs within 15 minutes, antivenom is contraindicated**.

Epinephrine should be readily available in a syringe for moderate reactions that may occur despite negative tests for sensitivity. The initial dose should depend upon an estimate of amount of envenomation (tabl. 5). However, no upper limit has been described and up to 45 vials have been successfully used in a patient. In children and small adults (body weight < 40 kg) up to 50 % higher dose of ASV should be administered, to neutralize the relatively high venom concentration.

Table 5

Antivenom Doses

Envenomation	**Dose**
Mild	5 vials (50 ml)
Moderate	5–10 vials (50–100ml)
Severe	10–20 vials (100–200 ml) or more

ASV is administered intravenously, either in an undiluted form at a rate of not more than 1ml per minute, or diluted in 500 ml of IV fluid and administered as rapidly as tolerated over 1–2 h. Additional infusions containing 5–10 vials (50–100 ml) should be repeated until progression of swelling in the bitten part ceases and systemic signs and symptoms disappear. However, it is not advisable to infiltrate ASV at the local site. Delayed reactions may occur following antivenom therapy and their frequency of occurrence is proportional to the amount of the administered antivenom. Therefore, all patients receiving ASV should be observed for several days.

The role of anticholinesterase agents. Since Elapidae snakes result in primarily neurotoxic features due to selective d-tubocurarine like blockade, the post-synaptic toxin of the venom leads to pathophysiological changes resembling those of myasthenia gravis.

This prompted use of anticholinesterase agents, such as neostigmine, in addition to a conventional antivenom therapeutic regimen with dramatic results. However the use of anticholinesterase drugs alone, without ASV, has also been recommended.

Neostigmine, 50–100 mcg/kg 4 hourly, or as a continuous infusion can be given. Edrophonium can also be used in the dose of 10mg in adults or 0.25 mg/kg in children within 2 min. If the response is positive, then one can switch over to long acting preparations like neostigmine. Glycopyrrolate 0.2 mg preceding neostigmine can be given, as, unlike atropine, it does not cross blood brain barrier.

Supportive therapy. The patient should be moved to an appropriate area of the hospital — ICU will be required for severe envenomation. Fasciotomy should be undertaken in patients with the compartment syndrome and debridement should be performed for necrotic tissue.

Coagulopathy should be corrected with fresh frozen plasma and platelets. Blood transfusion should be given to replace blood loss from hemolysis and bleeding.

Ventilatory support and hemodialysis may be necessary for pulmonary and renal complications, due to severe envenomation.

Corticosteroids are of no proven value and in fact may interfere with the effect of ASV. However, corticosteroids may be used for hypersensitivity reactions to ASV.

Prophylactic antibiotics are of no proven value. If infection occurs, broad spectrum antibiotics, such as ciprofloxacin and clindamycin, should be used.

Intravenous immunoglobin therapy has also been used for envenomation and it may improve coagulopathy, but has no effect on neurotoxicity. Certain reports on the evaluation of intravenous immunoglobin suggest that it may reduce the need for repeated antivenom therapy for envenomations associated with coagulopathy.

A compound (2-hydroxy 4-methoxy benzoic acid) isolated and purified from anatamul (Hemidesmus indicus), an Indian herb, has also been observed to have potent anti-inflammatory, antipyretic and antioxidant properties, especially against Russell's viper venom. Analgesia should be given — opioids may be required.

BENZODIAZEPINES

The group of benzodiazepines includes Elenium, Diazepam, Nitrazepam and others.

It's clinical features are as follows:

- Drowsiness;
- Slurred speech;
- Nystagmus;
- Hypotension (mild);
- Ataxia;
- Coma;
- Respiratory depression;
- Cardiorespiratory arrest (in case of iv administration).

If patients are hospitalized within 1 hour, it is required to empty the stomach by gastric lavage and give 50 g activated charcoal. Severe overdose may require use of the benzodiazepine antagonist, flumazenil, e. g. for comatose patients particularly when the diagnosis is uncertain and patients with significant cardiorespiratory depression.

Flumazenil is given as an iv bolus of 0.2 mg followed by a further bolus dose of 0.1mg every 2–3 min until the patient is arousable. Avoid giving excess flumazenil to completely reverse the effect of a benzodiazepine.

BARBITURATES

Depending on the terms of the substances half-life in the body, several types of barbiturates are distinguished: **ultra-short acting** (Brevital, Surital, Pentothal), s**hort- and Intermediate-acting (**Pentobarbital, Secobarbital, Amobarbital, Aprobarbital, Butabarbital, Fiorinal, Talbutal), l**ong-acting:** (in doses to achieve anticonvulsant effects without sedation) Phenobarbital, Mephobarbital.

In case of acute overdose barbiturates decrease transmission in autonomic ganglia, activity of myocardium, GI tract, excitation caused by acetylcholine. In case of toxic doses they cause hypotension, venous pooling, interfere with the body compensation mechanisms.

The effects of barbiturates range from mild sedation to coma. In case of mild toxicity they cause drowsiness, slurred speech, ataxia, unsteady gait, nystagmus, emotional lability, impaired cognition.

Signs of Severe Acute Intoxication include:

- CNS depression – stupor to deep coma & resp. arrest;
- Pupils small & reactive; In case of hypoxia pupils will be dilated & nonreactive;
- Corneal and gag reflexes diminished and absent;
- Muscle tone: flaccid, absent reflexes, + Babinski reflex;
- Decorticate and Decerebrate posturing not from structural damage;
- Hypotension;
- Normal or increased HR;
- Hypothermia.

Changes of consciousness and drug levels depend on GI motility and absorption fluctuations.

Treatment

Supportive treatment of the cardiorespiratory and neurological systems should be given by standard intensive care methods. A GCS equal or less than 8 increases the risk of airway compromise and endotracheal intubation with mechanical ventilation is indicated unless rapid recovery is anticipated. Intravenous access should be established and initial fluid resuscitation given as appropriate with vasopressors or cardiotonics (norepinephrine, dopamine, dobutamine) to maintain blood pressure.

After gastric lavage, in mildly severe cases, forced diuresis is performed followed by plasma alkalizing with $NaHCO_3$, which increases renal clearance of phenobarbital. In case of severe intoxication extra renal detoxication methods such as hemodialysis, peritoneal dialysis, hemosorption are indicated.

OPIOIDS

Opioid is a term applied to all natural, synthetic, and semi-synthetic agents with morphine-like actions. It is more inclusive than the term opiate, which refers only to natural agents. Both terms are derived from opium, the Greek word for juice in reference to poppy juice. The term narcotic refers to any agent that induces sleep.

The term endorphin applies to any of the peptides of the three endogenous opioid families: enkephalins, β-endorphins, and dynorphins. Pharmacologic actions of opioids involve the gastrointestinal, genitourinary, cardiovascular, pulmonary, and central nervous systems and lead to many clinical effects.

Sedation and analgesia are the most common therapeutic goals of opioid medications. Additional uses include antitussive and antidiarrheal effects.

Opioid toxicity occurs as an adverse effect of therapeutic use, intentional overdose, or intentional abuse. In general, opioids are well absorbed after GI (oral, rectal), parenteral, nasal, buccal, pulmonary, and transdermal administration. Opioid toxicity is less pronounced but more prolonged with oral ingestion than with parenteral administration.

Clinical features

Opioid toxicity is associated with the toxidrome of the CNS depression, respiratory depression, and miosis. Opioids decrease both respiratory rate and tidal volume in a dose-dependent manner. The hypoxic drive is overridden in severe poisoning.

Bronchospasm can be triggered by heroin use in asthmatic and nonasthmatic patients. Noncardiogenic pulmonary edema may occur with therapeutic opioid use but is much more common after overdose. Miosis is seen in more than 90 % of heroin overdoses. Opioids cause mild hypotension and relative bradycardia.

Nausea and vomiting are common side effects of therapeutic opioid use and also seen with overdose. Decreased GI motility is a common finding with therapeutic use and in severe cases may develop ileus. Pruritus, flushing, and urticaria are common. Hypoglycemia is common after opioid overdose, but the mechanism is unclear.

Opioid Withdrawal. Withdrawal is associated with the CNS excitation, tachypnea, and mydriasis. Pulse and blood pressure are also increased. Neurologic manifestations include restlessness, agitation, anxiety, and seizures. Cognition and mental status are unaffected. Dysphoria and drug craving may be severe and prolonged. Nausea, vomiting, diarrhea, and abdominal cramps are common and can lead to dehydration and electrolyte abnormalities.

Opioid Toxicity-Diagnosis

Opioid toxicity diagnosis is based on history and physical examination. Respiratory acidosis with hypoxemia on arterial blood gas measurement sup-

ports the diagnosis. A CXR should be obtained to evaluate noncardiogenic pulmonary edema, which can occur particularly after IV heroin use. An abdominal X-ray may identify packets of opioids or other illicit substances in a body packer or body stuffer.

Opioid Toxicity-Management

Airway and breathing; significant CNS and respiratory depression are the most common life-threatening developments. It is reversal with antidote therapy. Patients with noncardiogenic pulmonary edema may require oxygen and BiPAP, CPAP, or mechanical ventilation with PEEP.

GI decontamination may be considered after oral overdose. Syrup of ipecac is contraindicated. Gastric lavage is not routine. Naloxone, a pure opioid antagonist, is the antidote most frequently used to reverse opioid toxicity. Naloxone has a rapid onset of action. IV, SC, and IM routes can be used, as well as an ET tube. Naloxone is indicated for patients with opioid intoxication who have significant CNS or respiratory depression. The duration of naloxone effect is 1 to 2 h.

Naloxone administration can precipitate acute withdrawal in chronic opioid users. When naloxone is used in this population, the dose should be started very low and slowly titrated to clinical response without withdrawal. Clinical response to naloxone administration is not pathognomonic for opioid intoxication. Other intoxications may improve with naloxone therapy as well, including valproic acid, clonidine, tramadol, captopril, and ethanol.

CAUSTICS

The extent of the injury is dependent on several factors including the type of caustics, concentration, volume, viscosity, duration of contact, Ph, presence or absence of food in the stomach.

Contact of **acids** with epithelium creates a coagulum or eschar. It limits further spread of the acid. Contact of **alkaline** causes liquefaction necrosis, fat saponification and protein disruption. This allows further penetration into the tissue.

Damage occurs in four steps:

1. Necrosis. Occurs by invasion of bacteria and polymorphonuclear leukocytes.
2. Vascular thrombosis. Increases the damage.
3. Tissue sloughing. Occurs within 2–5 days.
4. Granulation. May lead to esophageal stricture.

Caustic injury is classified as 1st, 2nd or 3rd degree

1st degree. Edema and hyperemia

2nd degree. Superficial ulcers, whitish membranes, exudate, hemorrhage, and friability. 15–30 % chance of esophageal stricture development.

3rd degree. Full thickness burns. 90 % result in esophageal stricture.

Clinical Features

Airway edema and esophageal/gastric perforation are the most acute emergent issues to consider. Laryngeal edema occurs over minutes to hours requiring rapid intubation. Systemic toxicity is manifested by hemodynamic instability, fever, and acidosis. Acetic acid causes severe metabolic acidosis and hemolysis of erythrocytes.

Patients may be presented with severe oral pain (41 %), abdominal pain (34 %), vomiting (19 %); drooling (19 %). Other common presenting features include stridor, dysphonia, chest pain and visible burns. The pain and hypovolemia lead to the development of exotoxic shock. Exotoxic shock, hemocoagulation violations, presence of free hemoglobin results in the toxic nephropathy in 80–85 % of cases. Severe nephropathy is usually accompanied by hepatopathy.

Severe intoxication with acetic acid resembles burn disease, which consists of the following stages:

1. Exotoxic shock;
2. Toxemia;
3. Infectious complications;
4. Stenosis and burn asthenia;
5. Recovery.

Management

Analgetics and spasmolytics are recommended for treatment of pain, associated with burns.

Early intubation if airway compromise is suspected. Cricothyrotomy may be necessary if oral intubation fails. Blind nasotracheal intubation is contraindicated.

Normalization of hemodynamics, rheological properties of the blood, correction of acidosis and coagulopathy, withdrawal of free hemoglobin prevent ARF and AHF. IV access with vigorous fluid resuscitation is recommended in exotoxic shock treatment. At the same time 4 % sodium bicarbonate solution is administered. Forced diuresis provides withdrawal of free hemoglobin in case of stable hemodynamics and urine alkaline reaction. Rapid infusion of 10–20 % glucose solution with insulin is performed to stop hemolysis. In severe cases hemodialysis, plasmapheresis, ultrafiltration are performed.

Emesis induction and activated charcoal are not indicated. Gastric lavage is usually not recommended.

Corticosteroids may prevent stricture formation. Application of 2 mg/kg/day in children × 14–21 days 40 mg tid in adults × 14–21 days remain controversial. These should be followed by tapered dosing.

HYDROCARBONS

Hydrocarbons are a diverse group of organic compounds that contain hydrogen and carbons. Most are byproducts of crude oil, and are called Petroluem distillates. The majority of human exposures are confined to petroleum distillates.

Hydrocarbons poisonings are generally classified into four types:

1. Accidental ingestions
2. Intentional inhalation
3. Accidental inhalation or dermal exposure
4. Massive oral ingestion in a suicide attempt.

Pathophysiology

Acute HC toxicity usually affects three main organs: lungs, CNS, and heart. HC enters the body through the skin or GI tract with the most acute damage occurring in the lungs. Fatality usually occurs after ingestion and is accompanied with aspiration. A small amount of HC in the trachea can be devastating whereas a much larger amount of the same compound in the stomach can be benign.

Pulmonary disease is mediated through several mechanisms:

1. HCs are poorly water soluble allowing them to penetrate into the lower airway producing bronchospasm and inflammatory response

2. Volatilized HCs can displace oxygen in the alveolar space, cause direct injury to pulmonary alveoli and inhibit surfactant function leading to alveolar instability.

Certain HCs cause euphoria, disinhibition, confusion, and obtundation. Inhalation of these substances allows the patients to avoid hepatic first-pass metabolism and generate high concentrations in the CNS. Chronic use of inhaled HCs can cause peripheral neuropathy, cerebellar degeneration, neuropsychiatric disorders, chronic encephalopathy, and dementia. HCs can cause sudden death, especially after physical activity. They produce myocardial sensitization of endogenous and exogenous catecholamine causing ventricular dysrhythmias and myocardial dysfunction. This is particularly true of halogenated and aromatic HCs.

Toluene may induce renal tubular necrosis while benzene may induce bone marrow toxicity. As for Methylene chloride it may induce carbon monoxide poisoning. Chlorinated HC may induce centrilobular hepatic necrosis and renal failure. Direct skin exposure can cause extensive chemical burns.

Diagnostic Strategies

Prehospital care providers should bring a patient to the ED. All patients with HC exposure should have a CXR. Radiographic changes can occur within 30 min Thorough medical examination is required to exclude other medical problems. ABG's and continuous pulse oximetry may also be helpful.

Management

Because of sudden decompensation risk all patients should be on a cardiac monitor and continuous pulse ox in a well-observed area. In severe aspiration early intubation and positive airway pressure is recommended to minimize aspiration risk and prevent HC induced alveoli collapse. High frequency jet ventilation and extracorporeal membrane oxygenation (ECMO) is used to treat respiratory failure induced by aspiration. Corticosteroids and antibiotics have not been shown to be beneficial in HC aspiration.

Epinephrine and isoproterenol should be avoided unless required for cardiac resuscitation. Patients are recommended to be sedated if necessary to prevent excess catecholamine release. Dermal exposures of HC should be decontaminated immediately. Skin must be washed with soap and water. GI decontamination should be avoided. Risk of aspiration outweighs the benefits. In specific cases GI decontamination is indicated because of inherent toxicity or toxicity of additives to the HC.

MUSHROOMS

Exposures occur in three types of situations:

1. Accidental ingestion of wild mushrooms by young children playing outdoors
2. Mistaken selection of poisonous mushrooms for edible wild mushrooms intended for a meal
3. Abuse of certain mushrooms for their mind-altering potential.

Despite the potential for severe toxicity and death, most exposures are relatively benign. If a specimen is available, store it in a paper bag at room temperature. Vomitus can be collected, because some mushroom parts may still be recovered. The species is unknown in > 90 % of ingestions. However, Amanita species are responsible for the vast majority of deaths.

Mushroom Poisoning. Early Onset of Symptoms

GI symptoms of N/V/D and abdominal cramps are common. Treatment is supportive, with good outcome expected. The CNS effects are associated with two groups of mushrooms, ibotenic acid & muscimol, and psilocybin. Similar to LSD, hallucinations and the CNS effects are prominent. Lethargy, hallucinations, seizures, or severe agitation begin within 1 to 2 h after ingestion. Treat for seizures and use supportive care. The cholinergic toxidrome is associated with muscarine-containing mushrooms. Symptoms include salivation, lacrimation, urination, defecation, gastroenteritis, and emesis (SLUDGE). Atropine can be used for severe symptoms.

Mushroom Poisoning. Late Onset of Symptoms

Three groups of mushrooms containing cyclopeptide, gyromitrin, and orelline/orellanine cause late onset of symptoms (> 6 h postingestion). The cy-

clopeptide group is responsible for the vast majority of mushroom-related deaths in the United States. Amanita phylloides is the most well-known cyclopeptide containing mushrooms. Initial manifestations such as severe nausea, vomiting, diarrhea, and abdominal cramping begin 6 to 24 h post-ingestion. Hydration and supportive care will often lead to symptoms relief.

Hepatic toxicity followed by other organ involvement may occur over the next several days to weeks. Progressive elevation of hepatic transaminases, jaundice, hepatic encephalopathy, and death can occur. Many cases are misdiagnosed as gastroenteritis. Repetitive administration of activated charcoal appears to be reasonable because of its ability to bind the toxins, availability, and relative safety.

Management

Treatment of Mushroom poisoning includes the following:

- Intensive care of acute intoxication according to the general principles;
- Treatment of gastrointestinal intoxication stage;
- Treatment of toxic hepatitis;
- Infusion therapy to perform rehydration, detoxication and parenteral nutrition;
- In severe cases (ARF, AHF) methods of efferent therapy — hemodialysis, plasmapheresis, are performed.

Disposition

Initial management is aimed at ruling out mushroom groups associated with early onset of symptoms. If the patient remains asymptomatic after a period of observation, discharge with instructions to return if any symptoms manifest over the next 72 h. The timing of initial symptoms and the assessment for associated symptoms is the most important information needed to make a differential diagnosis. A patient who has eaten or been exposed to a wild mushroom may have other medical conditions truly responsible for the symptoms.

METHODS OF EXTRACORPOREAL DETOXICATION

Some drugs in case of overdose with a dialysable drug or toxin are removed by renal replacement therapy (RRT) but some are not. As a general rule, drugs are cleared by RRT if they are water soluble and not highly protein bound (tabl. 6).

RRT encompasses peritoneal dialysis and renal transplantation. The most extensively used RRT forms in the intensive care setting are:

- Intermittent haemodialysis (IHD);
- Continuous renal replacement therapies (CRRT):
  a. Continuous venovenous haemofiltration (CVVH);
  b. Continuous venovenous haemodialysis (CVVHD);

c. Continuous venovenous haemodiafiltration (CVVHDF);
d. Slow continuous ultrafiltration (SCUF);
e. Continuous arteriovenous haemofiltration (CAVHD).

− **Hybrid therapies** e.g. Sustained low-efficiency dialysis (SLED).

Table 6

Examples of drugs/toxins removed or not removed by RRT

Removed	**Not removed**
Lithium	Digoxin
Methanol	Tricyclics
Ethylene glycol	Phenytoin
Salicylates	Gliclazide
Barbiturates	Beta-blockers (except atenolol)
Metformin	Benzodiazepines
Aminoglycosides, metronidazole, carbapenems, Macrolide and quinilone antibiotics	

The functional differences between the techniques listed above can be classified in terms of:

− The mechanism of solute removal (filtration versus dialysis).
− The duration of the treatment (continuous versus intermittent).

Haemodialysis involves blood being pumped through an extracorporeal system that contains a dialyser. Blood flows through the dialyser in one compartment, separated from crystalloid solution (dialysate) in a second compartment, by a semipermeable membrane (fig).

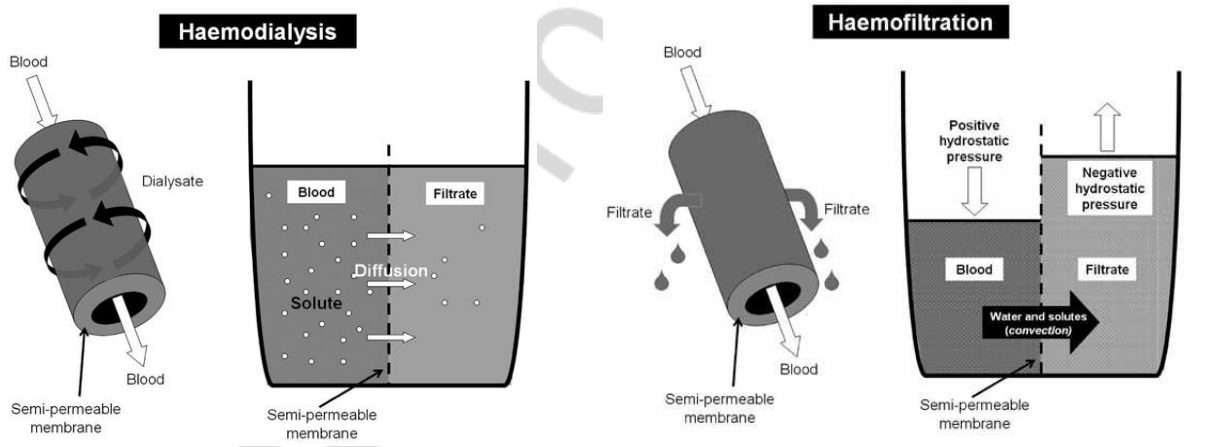

Fig. Schematic diagram comparing the different modes of solute removal in hemofiltration and haemodialysis

Solutes move across the membrane, down their concentration gradient (i.e. from high concentration to low) from one compartment of the dialyser to the other (Fick`s law of diffusion). For example, bicarbonate moves from dialysate to blood whereas urea and potassium move from blood to dialysate.

In order to maintain these essential concentration gradients and enhance the efficiency of the system the dialysate flows in the opposite direction to the flow of blood (countercurrent). When removal of water is required, the hydro-

static pressure on the blood side of the membrane is increased in order to force water molecules enter into the dialysate compartment.

Early hemodialysis in the toxigenic stage is indicated during intoxication with substances that may be dialyzed (barbiturates, organophosphates). A blood flow of ~250–300 ml/min is needed across the dialysis membrane. The equivalent clearance obtained is approximately 20 ml/min.

Vascular access may be obtained by fashioning an AV shunt via the radial artery, or more commonly Vascath, in case when venous rather than arterial blood is used. This involves cannulation of the internal jugular, subclavian, or femoral vein. Heparin is normally used for anti-coagulation. If contraindicated, e. g. recent hemorrhage, then prostacyclin may be used, but it may cause hypotension and abdominal cramps.

Patients with multi-organ failure commonly develop hypotension during hemodialysis. This may be ameliorated by high sodium dialysate, and priming the circuit with 4.5 % human albumin solution.

Complications of haemodialysis:

- Hypotension;
- Line infection;
- Dialysis disequilibrium;
- Dialysis reaction (allergy);
- Cramps;
- Air embolism;
- Haemorrhage.

Hypotension usually occurs within the first 15 minutes after commencing of the dialysis. It probably involves activation of circulating inflammatory cells by the membrane, osmotic shifts, and possibly loss of fluid. Treatment: cautious fluid replacement and inotropes (watch for pulmonary oedema if over-transfused).

Risk or exacerbating factors for hypotension:

- Multi-organ failure;
- Autonomic neuropathy;
- Valvular lesions (e.g. mitral regurgitation, aortic stenosis);
- Arrhythmias;
- Pericardial tamponade;
- MI or poor LV function;
- Sepsis.

Haemofiltration involves blood being pumped through an extracorporeal system that contains a semi-permeable membrane (fig.). The hydrostatic pressure created on the blood-side of the filter drives plasma water across the filter. This process is referred to as ultrafiltration. Molecules that are small enough to pass through the membrane (< 50,000 Daltons) are dragged across the membrane with the water by the process of convection. The filtered fluid (ultrafil-

trate) is discarded and a replacement fluid is added in an adjustable fashion, according to the desired fluid balance (tabl. 7).

Table 7

How the choice of RRT can be determined by the aim of treatment

What do you want to remove?	Size of molecule (Daltons)	Example	Preferred type of RRT
Small molecules/ electrolytes	< 500	Urea, creatinine, K+, H+, lithium	Dialysis or filtration
Middle molecules	500–5 000	Large molecule size drugs, e. g. vancomycin	Filtration better than dialysis
Low molecular weight proteins	5000–50 000	Cytokines, complement	Filtration
Water	18		Filtration better than dialysis

Haemodiafiltration is a combination of filtration and dialysis (fig.). There is no evidence to suggest that Continuous venovenous haemodiafiltration (CVVDF) has a survival benefit when compared to Continuous venovenous haemofiltration (CVVH), but if may be a useful way of increasing clearance of small solutes. Slow continuous ultrafiltration is used when the only requirement is water removal. Application of CVVH with a low filtration rate is effective. It can remove up to 6 liters of fluid a day but solute removal is minimal.

Both of these methods cause less hemodynamic instability, and are particularly useful for patients with multi-organ failure.

Indications:

- Azotemia (uremia);
- Hyperkalemia;
- Anuria/oliguria; to make space for nutrition;
- Severe metabolic acidosis of non-tissue hypoperfusion origin;
- Fluid overload;
- Drug removal;
- Hypothermia/hyperthermia.

Complications:

- Disconnection leading to hemorrhage;
- Infection risk (sterile technique must be employed);
- Electrolyte, acid–base or fluid imbalance (excess input or removal);
- Hemorrhage (vascular access sites, peptic ulcers) related to anticoagulation therapy or consumption coagulopathy. Heparin-induced thrombocytopenia may rarely occur.

Acute peritoneal dialysis — is a slow form of dialysis, utilizing the peritoneum as the dialysis membrane. Slow correction of fluid and electrolyte disturbance may be better tolerated by critically ill patients and this technique does not require complex equipment. However, treatment is labor intensive and there is a considerable risk of peritoneal infection. It has been largely superseded by hemofiltration in most intensive care units (table 8).

Table 8

Relative benefits of peritoneal dialysis and haemofiltration

Peritoneal dialysis	Haemofiltration
Cheaper Biocompatible membrane Cardiovascular stability No need for vascular access No anticoagulation No specialized equipment or nursing required More rapid recovery of renal function than hemodialysis Easy transition to long term PD	More ablilities to control ultra-filtration rate Suitable for patients post lapa-rotomy

Peritoneal dialysis is effective during intoxications with salicylates, methanol and hydrocarbons. It is rarely used but does not require vascular access or anti-coagulation and provides insufficient dialysis for hypercatabolic patients. (the creatinine clearance rate of ~10ml/min may be achieved). This requires:

- a peritoneal dialysis catheter (may be inserted under LA on the ward)
- intact peritoneal cavity free of infection, hernia, adhesions.

Dialysis technique. Warmed peritoneal dialysate is infused into the peritoneum in a volume of 1–2 l at a time. During the acute phase, fluid is flushed in and drained continuously (i. e. with no dwell time). Once biochemical control is achieved it is usual to leave fluid in the peritoneal cavity for 4–6 h before draining.

Heparin (500 IU/l) may be added to the first 6 cycles to prevent fibrin catheter blockage. Thereafter, it is only necessary if there is blood or cloudiness in the drainage fluid. The commonest complication of CAPD is peritonitis. Infection occurs through the lumen of the catheter, along the catheter tract, transmurally from GIT, or haematogenously (rare).

Hemosorption. Sorption is absorption of gas molecules or solution by the surface of a solid substance (sorbent). During hemosorption toxic substances of high or medium size (which cannot be removed by dialysis) are withdrawn from the body. The main advantage of hemosorption is the high rate of detoxication. Hemosorption is used in intoxication with barbiturates, organophosphates, atropine and others. Plant sorbents and synthetic coal are most commonly used.

The overall effect of hemosorption is associated with removal of toxins and endogenous toxic substances from the blood, improvement of microcirculation. Venous or arterial blood via the perfusion pump is passed through the column with the rate from 50 to 250 ml/min. Possible complications of hemosorption include hypotension, immunosuppression. Contraindications include the following: hypotension, anemia, coagulation disorders.

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CONTENT

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