Acute exogenous poisonings. Principles of intensive care in carbon monoxide, cyanide, organophosphate, paracetamol, salicylate, mushroom poisonings

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Definition

Carbon monoxide (CO) poisoning occurs by accidental or voluntary inhalation, caused by incomplete combustion of gases and solids

Carbon monoxide is:

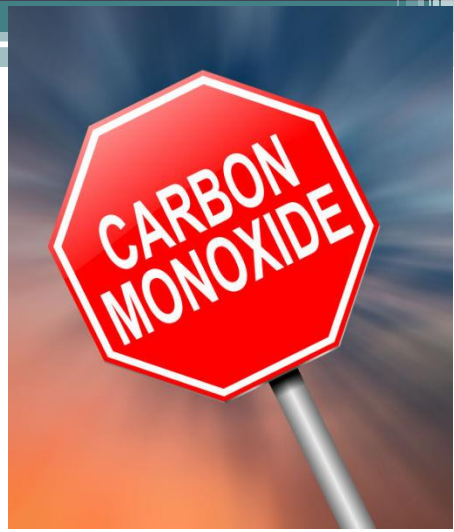
- Very diffuse gas, colorless, odorless, does not irritate the airways (make it undetectable sensory)
- With density equal to air (approx. 0.46)
- From the incomplete combustion of materials used in heating devices, defective apartment buildings or used without complying with the rules of installation and operation
- In 20-25% CO poisoning is fatal

Circumstances of CO intoxication

It is installed in case of incomplete combustion of carbon-containing substances:

- Fire
- Heating sources (natural gas stoves, wood fires, kerosene installations)
- Exhaust gases from motor vehicles
- Criminal act

Epidemiology



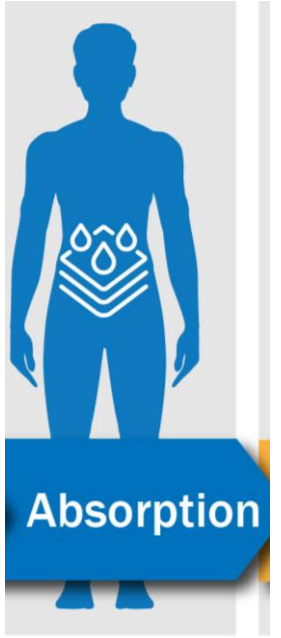
- Globally, it is the most common cause of accidental lethal poisoning in the world
- According to WHO, over 50,000 deaths annually
- In Europe, the incidence is 0.5-2 cases/100,000 persons per year
- In the Republic of Moldova, approximately 200 cases of acute CO poisoning, of which approximately 10 deaths
- During the period 2020-2023, approximately 800 cases and 42 deaths

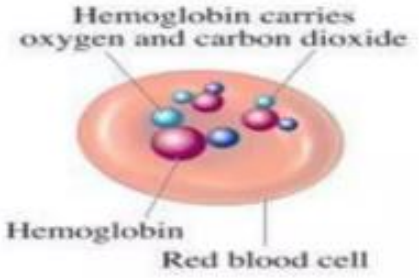
Hampson NB. Carbon monoxide poisoning mortality in the United States from 2015-2021. Clin Toxicol (Phila). 2023 Jul;61(7):483-491.

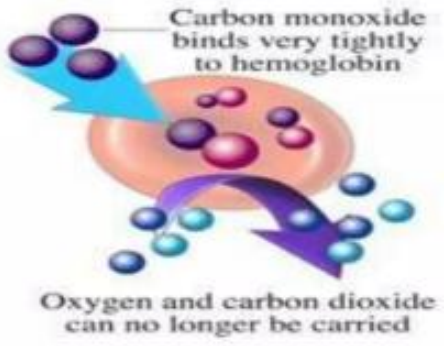
Toxicokinetics of carbon monoxide

1. **Absorption**

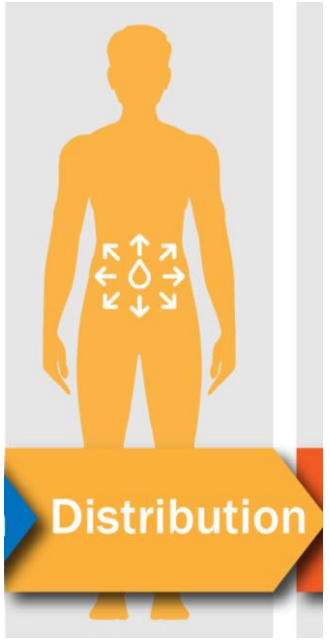
- CO is absorbed exclusively by inhalation
- Diffuses rapidly through the alveoli into capillary blood, does not require metabolism for activation
- Absorption is directly proportional to the concentration of CO in the air and the duration of exposure







Toxicokinetics of carbon monoxide



2. **Distribution**

- CO has an affinity of approximately 200/250 times greater for hemoglobin than oxygen → forms carboxyhemoglobin (COHb)
- COHb → reduces the oxygen transport capacity and modifies its release to tissues (the Hb dissociation curve shifts to the left)
- CO binds to:

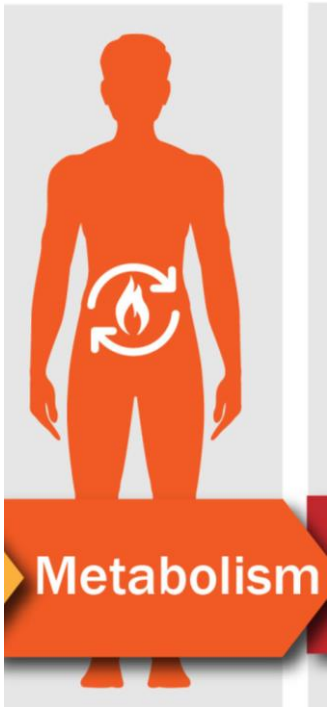
➢ Myoglobin (in muscle and heart) → cardiac damage

➢ Cytochromes → inhibition of the mitochondrial respiratory chain

Toxicokinetics of carbon monoxide

3. **Metabolism**

- CO is not actively metabolized
- It is an inherently toxic gas, excreted unchanged



Toxicokinetics of carbon monoxide

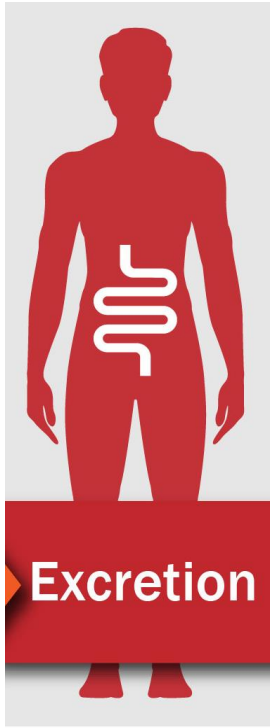
4. **Elimination**

- It is eliminated exclusively through the lungs (in exhalation)
- Biological half-life of COHb:

✓4-6 hours in atmospheric air

✓1-2 hours with 100% O2

✓20-30 min in hyperbaric oxygen therapy

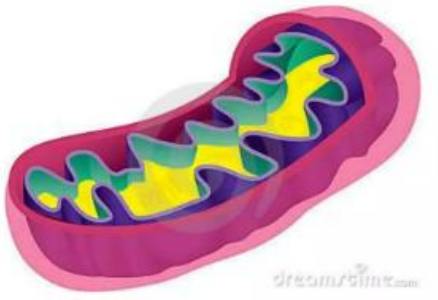


Pathophysiology and toxicity of CO

- Inhibition of cellular respiration
  - CO binds to myoglobin → with cardiac muscle damage
  - Cytochrome a3 (mitochondrial complex IV) → inhibition of the respiratory chain
- Systemic involvement
  - Brain and heart are most sensitive to hypoxia

CNS → confusion, coma, seizures

Cord → arrhythmias, myocardial ischemia



- Oxidative stress and inflammation
  - Reperfusion after hypoxia generates free radicals → delayed neuronal damage with the appearance of late neurological symptoms
  - Vasodilation due to increased nitric oxide release; worsening tissue perfusion

Severity of intoxication

- Mild – carboxyhemoglobin level 20-30%
- Moderate – carboxyhemoglobin level 30-50%
- Severe – carboxyhemoglobin level 50-60%
- Fatal – carboxyhemoglobin level >60%

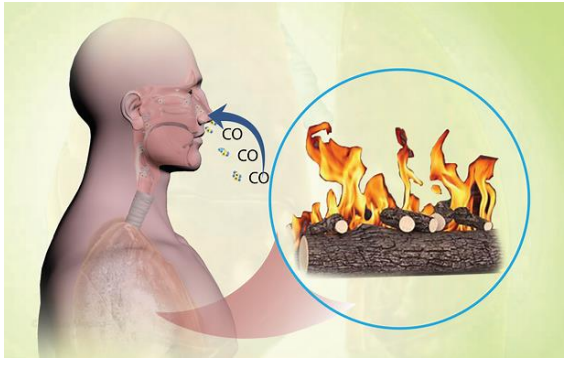
Clinical manifestations

- *Neurological* – headache, dizziness, blurred vision, altered mental status, cognitive impairment, seizures, coma
- *Cardiovascular* – sinus tachycardia, hypotension, collapse. ECG – normal or with ischemic-type disorders, arrhythmias
- *Pulmonary* – tachypnea, dyspnea, acute respiratory failure, pulmonary edema
- *Cutaneous-mucosal* – raspberry-pink face, cyanosis, erythematous plaques
- *Ocular* – “flame” retinal hemorrhages, very rarely blindness, decreased visual acuity, cortical blindness, retrobulbar neuritis, papillary edema

Clinical manifestations

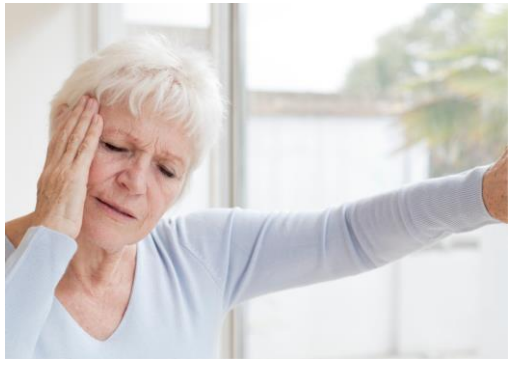
- *Gastrointestinal* – vomiting, diarrhea, hepatic necrosis, hematemesis, melena
- *Hematologic* – disseminated intravascular coagulation, thrombocytopenic purpura, leukocytosis
- *Muscular* – rhabdomyolysis, myonecrosis, compartment syndrome
- *Renal* – acute renal failure secondary to myoglobinuria, proteinuria
- *Metabolic* – lactic acidosis, non-pancreatic hyperamylasemia, diabetes insipidus

Phases of CO poisoning



Impregnation phase (onset of intoxication)

- Preserved consciousness
- Increasing frontotemporal headache, vertigo, hallucinations, vomiting



State phase

- Muscular hypotonia of the lower limbs

Coma

- Coma is calm, with muscular hypotonia
- Progress into irreversible coma with generalized hypotonia

Brutal death

- By anoxemia, total and sudden

Diagnosis of CO poisoning

1. **Clinical diagnosis**

Suggestive history:

- ✓ Exposure in a closed, poorly ventilated space
- ✓ Several members of the same family affected simultaneously
- ✓ Possible sources: stoves, central heating, cars running in the garage

Non-specific symptoms, but associated with exposure: headache, dizziness, nausea, confusion, loss of consciousness

Diagnosis of CO poisoning

2. **Laboratory confirmation**

Carboxyhemoglobin dosage

It is made from venous or arterial blood, values

< 3%	normal
3-10%	smoker
10%	mild intoxication
25%	sever
50%	potentially lethal

- Pulse oximetry may be falsely normal

Diagnosis of CO poisoning

3. **Arterial blood gas analysis**

- Normal PaO2 (does not exclude intoxication)
- Metabolic acidosis with elevated lactate

Diagnosis of CO poisoning

4. **Imaging investigations**

- ECG – signs of ischemia and arrhythmias
- CT/MRI – useful in case of coma or persistent neurological symptoms

The diagnosis is often clinical plus confirmed by COHb values, not the opposite!!

Antitoxin treatment

- **Oxygen** - is considered the antidote to carbon monoxide poisoning, it is administered via mask or oro-tracheal tube

NB! The only therapeutic means is oxygen therapy with 100% oxygen, which ensures the release of oxygen to the tissues and decreases the T1/2 of HbCO from 4-5 to 1.5 hours.

Antitoxin treatment

Hyperbaric oxygen therapy (1.5-2 atm)
Initiation will be done only after stabilization of the patient
Purpose: increase PaO_2, accelerate CO elimination and correct tissue hypoxia

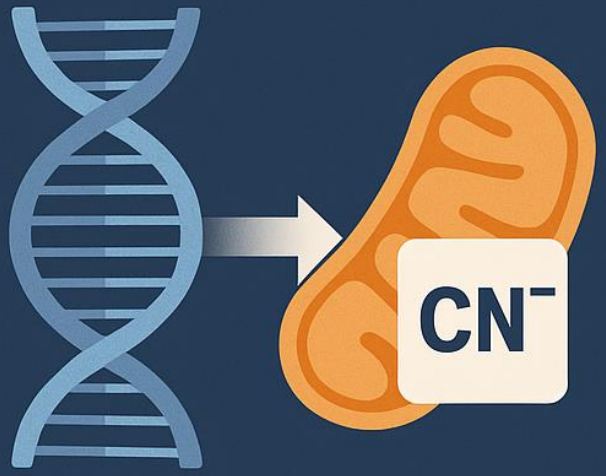
Indications
- Severe intoxication
- Extreme age
- Neurological complications
- ECG changes – myocardial ischemia
- Severe metabolic acidosis
- Pregnancy

Contraindications
- Unresolved barotrauma
- Pneumothorax
- Severe claustrophobia (relative)

Symptomatic treatment

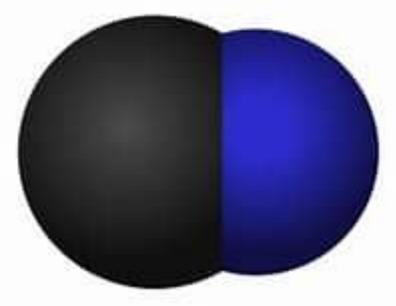
- Acute pulmonary edema
- Cardio-respiratory failure
- Cardiac rhythm disorders
- Metabolic acidosis
- Seizures, coma

Cyanide poisoning



Cyanide poisoning

Cyanides are toxic compounds containing the CN group



Sources: hydrocyanic acid (HCN), cyanide salts (KCN, NACN), combustion products (e.g. fire flue)

Cyanide poisoning

Cyanide toxicity is a rare but often fatal poisoning that occurs through ingestion, inhalation, dermal absorption, or injection.

It is a very dangerous toxin, being included on the list of the most dangerous poisonings for humans because the lethal dose of cyanide is extremely small.

Historically, cyanide toxicity has been used in mass suicides, individual murders, and chemical warfare.

The lethal dose of cyanide is 1.1 mg/kg for intravenous administration and 100 mg/kg for dermal exposure.

The role of cyanide in history and famous crimes

- Herman Goring's suicide (Nazi): swallowed a cyanide capsule before execution
- Jonestown (1978) – over 900 people died by ingesting a mixture of juice and cyanide (largest mass suicide)
- Used by spies and secret agents: cyanide pills in case of capture (e.g. CIA, KGB)

Epidemiology

- According to the National Poisoning Data System, 853 cases were reported between 2019 and 2023, with 14 deaths and a mortality rate of 1.6%.
- Adults accounted for 86.5%, while 4.2% occurred in children under 5 years.
- 7.6% of cases were intentional poisoning attempts, and 68.2% were accidental exposures.

Gummin DD, et al. 2019 Annual Report of the American Association of Poison Control Centers' National Poison Data System (NPDS): 37th Annual Report. Clin Toxicol (Phila). 2020 Dec;58(12):1360-1541.

Sources of cyanide

Cyanide poisoning is generally occupational, occurring in:

- industrial areas (especially burning in these areas)
- metallurgical industry
- mining (gold extraction by dissolving tailings in cyanide)
- jewelry manufacturing and radiological film.

Cyanide is released from the burning of synthetic materials:

- Polyurethane
- Plastic
- Chemically treated wool

Circumstances of cyanide poisoning

<u>Homicide</u>

- introduction into food
- war gas used during First World War

<u>Suicide</u>

- cyanide capsules used by terrorists

<u>Accidental</u>

- those working in electroplating, gold planting, rubber industry, laboratory workers.
- Fires (especially in enclosed spaces)
- Natural: fruit pits (bitter almonds, apricot pits, peach pits – in large quantities)

Mechanism of action

1. Target: Cyanide binds to **cytochrome c oxidase**, an essential enzyme in the electron transport chain in mitochondria, also responsible for the final transfer of electrons to oxygen (forming water) and the generation of energy (ATP)
2. Lethal inhibition

- By binding to the ferric group (Fe3+) in the active center of the enzyme, cyanide completely blocks its activity.
- Oxygen is no longer used at the cellular level → **histotoxic hypoxia**

3. Metabolic consequences

- Blockage of oxidative phosphorylation → cessation of ATP synthesis
- Cell switches to anaerobic metabolism → accumulation of lactate → severe metabolic acidosis

Routes of entry of the toxic

- Inhalation of cyanide gas

- Ingestion

✓ Usually KCN

✓ Combines with stomach acid to release hydrogen cyanide gas

- Skin absorption

✓ In case of injury

✓ In case of skin being moist due to sweating

Clinical manifestations

Symptoms vary from patient to patient:

- **Rapid onset**, dose-dependent
- **Neurological symptoms** reflecting progressive hypoxia: headache, dizziness, vertigo, confusion, generalized seizures, coma
- **Gastrointestinal symptoms**: abdominal pain, nausea, vomiting
- **Cardiopulmonary symptoms:** dyspnea, retrosternal pain, apnea.
- **Typical sign**: bitter almond odor (perceived by few)

Diagnosis

1. *Clinical* (especially in emergencies)
2. Laboratory analysis (if is available) *Plasma cyanide concentration*
3. *Carboxyhemoglobin level* should be analyzed in patients poisoned with cyanid by inhalation because they may be poisoned simultaneously with carbon monoxide.
4. *Methemoglobin level* is useful in monitoring treatment after the use of antidotes that induce an increase in methemoglobin levels such as sodium nitrite.
5. *Acid-base balance* – metabolic acidosis, increased lactate (> 8-10 mmol/L)
6. The *electrocardiogram* may show nonspecific changes in the electrical activity of the heart such as: atrioventricular blocks, supraventricular arrhythmias, ventricular arrhythmias, ischemic electrocardiographic changes and possibly asystolia.

Treatment

1. ABCs Resuscitation
2. Removal from the source
3. Antidote Therapy:

- Hydroxycobalamin 5 g i/v over 15 min (may be repeated once). This binds to cyanide to form cyanocobalamin (vitamin B12), a non-toxic compound that is eliminated renally.
- Nitrites (amyl nitrile, sodium nitrite): induce methemoglobinemia, 300 mg i/v slowly
- Sodium thiosulfate 12.5 g i/v, increases the conversion of cyanide to thiocyanate which is excreted renally
- Activated charcoal in case of oral ingestion
- Administer 100% oxygen
- Advanced life support

Treatment

Antidote kit:

- Sodium nitrite/amyl nitrite
- Sodium thiosulfate
- Hydroxycobalamin

Prognosis

- Depends on the dose and and how quickly does the treatment begin
- Without treatment → death within minutes
- With rapid treatment → good prognosis

Organophosphorus poisoning

Organophosphate Poisoning

- Insecticides
- Herbicides
- Nerve Gases
- Industrial chemicals

Emergency Medicine

Organophosphorus poisoning

- Organophosphorus compounds were synthesized in 1800 by Lassaigne through the reaction between alcohol and phosphoric acid.
- Initially they were proposed as toxic substances for warf (sarin, tabun), currently they are chemicals used in agriculture and households
- Very toxic to humans

Organophosphorus poisoning

- It begins to manifest itself after 30-60 min and becomes maximum after 2-8 hours
- The frequency of poisoning is due to both their widespread use and their improper storage

Epidemiology

Globally (according to WHO)

- Approximately 3 million cases of pesticide poisoning each year
- Of these, over 200,000 deaths/year from pesticide poisoning, most caused by organophosphates
- 95% of these deaths occur in low- and middle-income countries
- Most common cause: suicide with agricultural pesticides
- In the Republic of Moldova between 2016-2021: 655 cases of pesticide poisoning with 24 deaths

OMS – Public health impact of pesticides used in agriculture
FAO/WHO – codex on pesticide management

The role of organophosphorus compounds in history

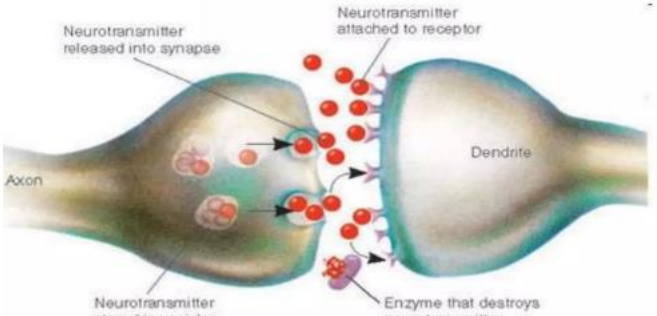
- In 1930, German chemist Gerhard Schrader, while searching for new insecticides, accidentally discovered the first nerve agent – Tabun
- Other substances created later: Sarin, Soman, VX used as chemical weapons
- In 1995, Tokyo: Aum Shinrikyo sect released Sarin gas in the subway – 13 dead, over 5,000 poisoned
- In 2013-2018, Syria: chemical weapons attacks (Sarin) were reported, resulting in hundreds of civilian victims.

Clinical manifestations

Toxicity is due to blockage of cholinesterases with accumulation of acetylcholine.

Three pharmacological actions produce the next symptoms

- **Muscarinic action** – miosis, salivation, profuse sweating, bronchial hypersecretion, digestive hypermotility, bradycardia, hypotension
- **Nicotinic action** – fasciculations progressing to muscle paralysis, muscle cramps
- **Central action** – confusion, coma, convulsions



Circumstances of intoxication

- Accidental poisoning (substance stored in unlabeled containers and packaging)
- Suicide attempt (common in adolescents)
- Criminal act
- Occupational exposure (more common in adults)

Routes of entry of the toxic

- Digestive tract by ingestion (voluntary or accidental)
- Skin route
- Respiratory route
- Through mucous membranes (conjunctiva of the eyes)

Diagnosis

- History of organophosphorus ingestion with specific symptoms
- Conclusive clinical signs:

✓ Altered mental status
✓ Miosis
✓ Bradycardia/tachycardia
✓ Diaphoresis
✓ Respiratory distress

- Bad breath with a pesticide or petroleum odor, which is identified after gastric lavage
- Therapeutic response to Atropine administration

Diagnosis

Laboratory investigations:

Low serum cholinesterase
Low erythrocyte cholinesterase (AChE) (where available)

Treatment

Stabilization of the patient

- At the place of the accident, airway realease, in the ICU, respiratory monitoring and, if necessary, endotracheal intubation and assisted ventilation
- Gastric lavage, administration of activated charcoal and substances that accelerate intestinal transit and increase the elimination of toxins
- Skin decontamination is mandatory, which is done with soap and water
- Stabilization of vital functions

Tratament

Specific treatment

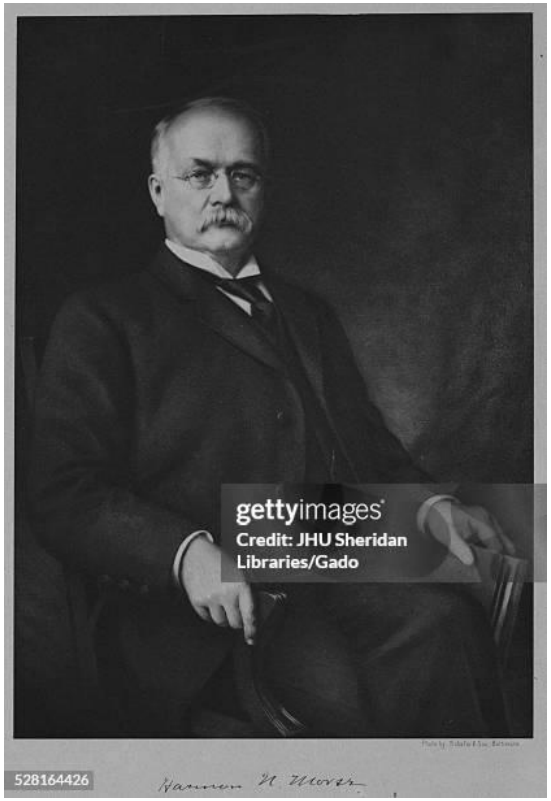
- Atropine 1-2 mg i/m or i/v repeated every 10 min, until signs of atropinization appear. Up to 10-30 mg are needed.
- Pralidoxime (regenerates cholinesterase by reversing phosphorylation) 1-2 g i/v in 5-10 min, repeated every hour, until an effective serum dose of 4 mg/l is achieved
- Diazepam for seizure control and neuroprotective effect

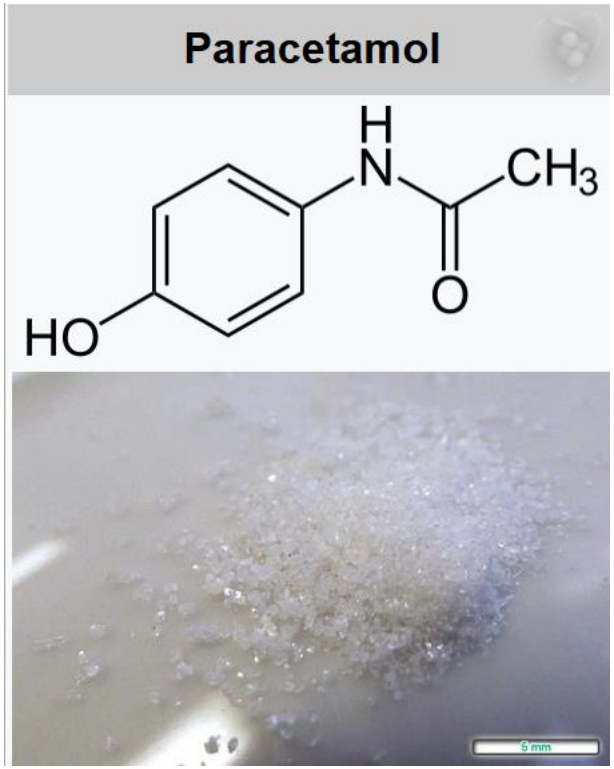
The therapeutic window is short (ideally within the first 24 hours)

Prognosis

- Without treatment → death by respiratory paralysis
- With rapid treatment → favorable outcome
- Risk of intermediate syndrome (muscle paralysis) and late neuropathy

Paracetamol poisoning





General data

- Acetaminophen is an analgesic, antipyretic and weak anti-inflammatory
- It is absorbed very rapidly in the gastrointestinal tract and is metabolized in the liver
- The recommended therapeutic dose is 650-1000 mg, every 4-6 hours for adults and 10-15 mg/kg every 4-6 hours for children
- Hepatic damage occurs at a dose > 10g

The role of Paracetamol in history

- In the 19th century, German doctors noticed that certain patients treated for infections with a naphthalene derivative (acetanilide) and then phenacetin developed fever reductions.
- The discovery was accidental – they were receiving these substances as antiparasitics, but it was noted that the patients no longer had fever
- Paracetamol was first synthesized in 1877, but was ignored (Harmon Nothrop Morse)
- Reintroduced in the 1940s-1950s as a safer alternative to phenacetin
- Widely marketed in the US in 1955 under the name Tylenol

Epidemiology

- According to the Toxic Exposure Surveillance System, about 5% of all poisonings, as well as 23% of reported deaths, were caused by acetaminophen
- In the USA, UK, Australia and other developed countries, it is the No. 1 cause of drug-induced acute liver failure
- In the UK, out of 100,000 cases/year, over 40% involve paracetamol, of which 200 deaths annually
- In the Republic of Moldova, approx. 1,100 drug poisonings, including Paracetamol

Paracetamol (acetaminophen) poisoning

Nick Buckley [1,#], Michael Eddleston [2,#]

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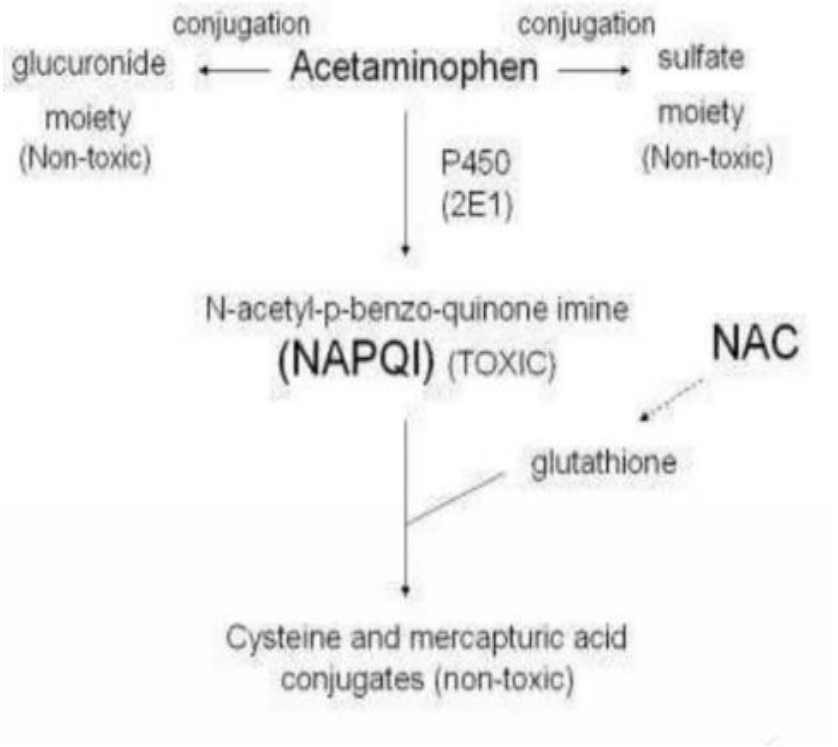
PMCID: PMC2943815 PMID: 19450343

Pharmacokinetics and metabolism

- ✓ After absorption, which is rapid and begins in the gastric mucosa, paracetamol undergoes a biotransformation process in the liver.
- ✓ 85% of the therapeutic dose is conjugated in the liver to form inactive metabolites excreted in the urine
- ✓ 5-8% is oxidized by cytochrome P450 to an intermediate product (N-acetyl-p-benzoquinonemine) that is conjugated with hepatic glutathione and excreted in the urine.
- ✓ At excessive doses of paracetamol, N-acetyl-p-benzoquinonemine (NAPQI) accumulates, covalently binds to macromolecules in hepatocytes and causes necrosis

Metabolism

- Metabolized in the liver into:
- Glucuronide conjugates (20-65%)
- Sulfoconjugates (20-40%)
- With the help of cytochrome P450 → NAPQI (5-15%)
- NAPQI – a toxic metabolite, detoxified by conjugation with glutathione
- In overdose, glutathione reserves are depleted → NAPQI accumulates → hepatocyte necrosis



Clinical manifestations

Can be classified into 4 stages:

Stage I – in the first 24 hours after ingestion may occur, nausea, vomiting, pale skin and malaise

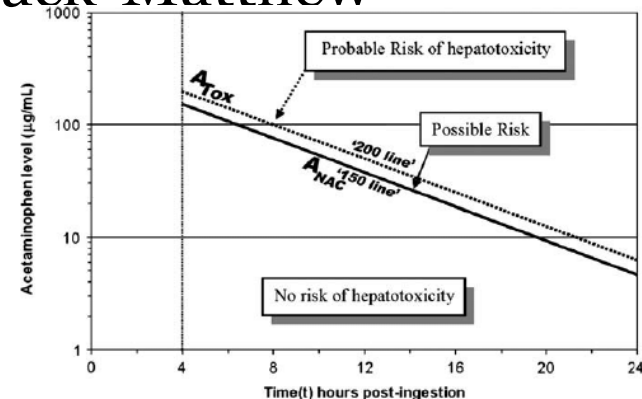
Stage II – in the first 2-3 days, appear signs of hepatotoxicity, manifested by abdominal pain, clinical and laboratory signs of liver and kidney toxicity. Transaminases and bilirubin are increased

Stage III – in the first 3-4 days, nausea and vomiting reappear, progress liver failure, metabolic acidosis, kidney failure and encephalopathy

Stage IV – in the first week, those who survive have a complete remission of liver dysfunction or die

Diagnosis

- Acetaminophen consumption more than 140-180 mg/kg/day or more than 7.5 g in 24 h
- Complete blood analysis, platelets, bleeding time
- Acid base balance
- Transaminases (ALT, AST) – increase suddenly and with rapid progression, dozens of times compared to normal value
- Bilirubin, Alkaline Phosphatase, Glutathione Transferase
- Urea, creatinine, blood sugar
- Serum acetaminophen level (using Rumack-Matthew nomogram) 4 hours after ingestion
- Urine screening



Treatment

- Rapid assessment and therapeutic approach with patient stabilization
- Gastrointestinal decontamination, activated charcoal if less than an hour has passed since ingestion
- Vascular access
- Increased toxin elimination
- Symptomatic treatment
- Early liver transplant

Treatment

Administration of the antidote

N-acetylcysteine:

Restores glutathione, neutralizes NAPQI

Attack dose of 150 mg/kg followed by an infusion at a rate of 12.5 mg/kg/hour for 4 hours, then the infusion rate is reduced to 6.25 mg/kg/hour.

Effective in the first 8 hours → ideally < 4 hours

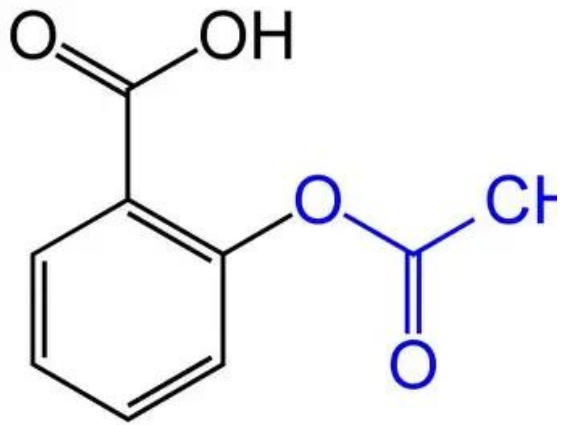
Prognosis

Clinical situation	Estimated survival
Treatment < 8 h after ingestion	> 95 – 100%
Moderate liver damage	70 – 90 %
Severe liver failure without transplantation	< 20 %
With liver transplant	60 – 70 %

Prognosis depends on:

- Time since initiation of antidote treatment
- Dose ingested and patient age
- Presence of liver pathologies, alcoholism and malnutrition
- Biological values at 48 – 72 hours (transaminases, INR, Creatinine, Glycemia, Ph)

Intoxicația cu salicilați



Salicylate poisoning most often consists of aspirin poisoning, which manifests itself in abdominal pain, fever, seizures, and cardiac arrest.

The salicylates group includes:

- Acetylsalicylic acid (Aspirin)
- Sodium salicylate
- Methyl salicylate
- Salicylamide

- ✓ Aspirin is widely used as an analgesic, antipyretic, anti-inflammatory, antiplatelet and antirheumatic.
- ✓ Intentional overdose with salicylate usually occurs in adolescents and young adults
- ✓ Overdoses in children are usually accidental and in the elderly as an error in administration
- ✓ Patients with severe toxicity die usually due to cardiovascular and central nervous system complications.
- ✓ In the US, approximately 15,000 cases are reported annually, with a mortality rate of approximately 1% for severe cases

The role of salicylates in history

- Salicylates originate from white willow bark, used for thousands of years as a remedy for pain and fever
- Hippocrates (5th century BC) mentioned the use of an infusion of willow bark for pain and fever
- The first chemical isolation was made by Johann Buchner – a German pharmacist – in 1828
- In 1897, chemist Felix Hoffman synthesized acetylsalicylic acid
- In 1899: Bayer introduces commercially Aspirin

Absorption:

- Rapidly absorbed by passive diffusion in the stomach
- After absorption it is de-acetylated

Distribution:

- 90% bound to blood albumin at a dose of 10 mg/dL
- Has a very short half-life (30 minutes)
- Reachs peak levels in 15-60 minutes

Elimination:

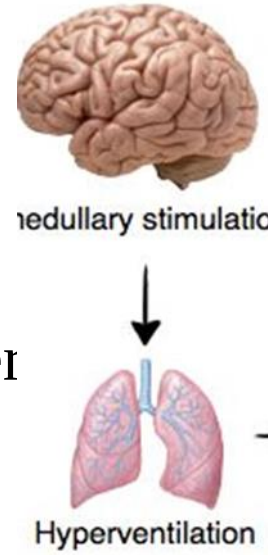
- 90% metabolized in the liver, 10% unchanged
- Salicylate is either metabolized to gentisic acid, bound to glycine or glucuronide, or eliminated as salicylate
- In the tubular fluid, unionized salicylate is reabsorbed.
- Ionized salicylate cannot be reabsorbed and is excreted in the urine (PH dependent).

Pathophysiology

<u>Stimulation of the respiratory center – early respiratory alkalosis</u>

Salicylates directly stimulate the respiratory center in the bulb → increase the frequency and amplitude of breathing → **hyperventilation** leading to:

- ↓ pCO_2
- Respiratory alkalosis (pH↑, HCO_3↓ compensatory)



! It frequently occurs within the first 3-6 hours after ingestion.

Pathophysiology

<u>Uncoupling of oxidative phosphorylation – metabolic acidosis</u>

Salicylates inhibit mitochondrial oxidative phosphorylation (uncouple the mitochondrial respiratory chain)

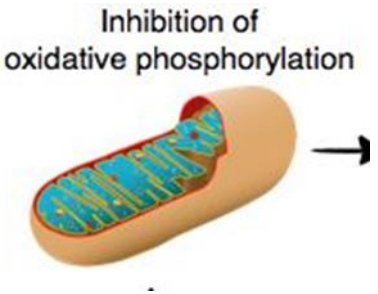
- Consequences:

✓↓ ATP synthesis

✓↓ cellular O2 consumption

✓↑ production of lactic acid and ketone bodies

Accumulation of anionic salicylate



The result is a metabolic acidosis with an increased anion gap.

Pathophysiology

Disorders of glucose metabolism

Although peripheral blood glucose may be normal, **functional hypoglycemia** may exist in the CNS.

- Reason: increased neuronal glucose consumption + inhibition of gluconeogenesis

Alteration of the state of consciousness

Pathophysiology

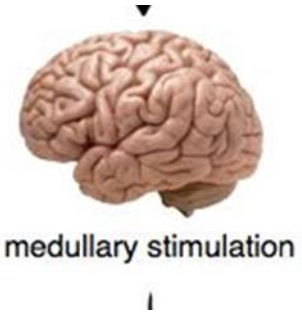
Fluid and electrolyte disturbances and thermoregulation

- **Severe dehydration** through vomiting, diaphoresis, hyperventilation, loss of sodium, potassium and water
- **Hyperthermia** through increased cellular metabolism (catabolic effect, massive oxygen consumption)
- **Hypokalemia** through respiratory alkalosis $^{+}$ urinary loss of K

Pathophysiology

Neurological and CNS effects

- Salicylates readily cross the blood-brain barrier
- Effects: confusion, agitation, delirium, convulsions, **cerebral edema**, coma



Pathophysiology

Effects on coagulation and renal toxicity

- Inhibits platelet aggregation → hemorrhagic potential
- In severe or chronic forms → may occur direct renal damage with oliguria and functional impairment

Clinical manifestations

Symptoms of poisoning depend on the ingested amount:

- at amounts less than or equal to 150 mg/kg body weight, symptoms occur mainly in children – dizziness, malaise, vomiting
- 150-300 mg/kg body weight – intoxication manifested by dizziness, vomiting, ringing in the ears, headaches, confusion, fever, hyperventilation, tachycardia
- 300-500 mg/kg body weight and more – hallucinations, convulsions, coma, cerebral edema, respiratory arrest, fever, severe dehydration, metabolic acidosis with respiratory alkalosis, renal failure

Diagnosis

A) **Laboratory tests:**

- Blood glucose levels – often low at CNS level, even if plasma levels are normal;
- Electrolytes – hypokalemia, hyponatremia, hypocalcemia;
- Blood gases – alkaline reserve, anion gap calculation (which is low), blood pH (metabolic acidosis);
- Creatinine, urea (repeated every 12 hours, until correction of hydro-electrolyte and acid-base imbalances is achieved);
- Liver tests – hepatic cytolysis (increased hepatic transaminases);
- Coagulogram (low prothrombin index, increased bleeding time).

B) The electrocardiogram (ECG) will show flattened T waves, the presence of U waves, and prolonged QT interval, reflecting hypokalemia, arrhythmias (ventricular tachycardia, ventricular fibrillation, ventricular extrasystole).

D) Imaging studies: chest X-ray in patients with severe forms of intoxication, pulmonary edema.

Diagnostic

D) Toxicological explorations:

- *Qualitative test* for identifying the presence of salicylates in urine (Trinder colorimetric method, based on the reaction of ferric ion with salicylate) or *ferric chloride test* – add 1-2 drops of 10% ferric chloride solution to 1 ml of urine; if the urine turns purple-red, the test is positive and signifies the presence of salicylates.
- More specific methods for quantitative determination of salicylates are s*pectrophotometric*, *gas chromatographic* and *liquid chromatographic* methods.

Treatment

1. Stabilization: oxygen therapy, IV hydration, correction of blood sugar level and correction of acid-base and hydro-electrolyte balance disorders
2. Decontamination: gastric lavage by administering activated charcoal that absorbs salicylates at the gastrointestinal level (effective even 1-2 hours after ingestion)
3. Urine alkalinization:

Sodium bicarbonate i/v → increases renal excretion of salicylates

- 1-2 mEq/kg in 5% glucose
- Target: urinary pH 7.5-8.0.

Treatament

1. Hemodialysis in severe forms:
- Salicylic acidemia exceeds 90-100 mg/100ml
- Refractory acidosis
- Cerebral edema, coma, convulsions
- Renal failure

2. Symptomatic treatment to maintain and stabilize vital functions.

THERE IS NO SPECIFIC TREATMENT (ANTIDOTE) FOR THIS INTOXICATION

Prognosis

- Mortality <1% with appropriate and prompt treatment
- Negativ prognostic factors: coma, severe alkalosis, treatment delays, undiagnosed chronic intoxication.
- Risk of permanent neurological complications in severe cases

Mushroom poisoning

- Acute mushroom poisoning represents the totality of symptoms characteristic of poisoning induced by the ingestion of inedible mushrooms
- They can be accidental or intentional
- They are often underestimated, but can lead to acute liver failure and death
- The most poisonous mushrooms resemble edible mushrooms at a certain stage of their development.
- The severity of poisoning depends on the species of mushrooms ingested, the quantity consumed and the age of the consumers.
- Children, the elderly and the chronically ill are more susceptible.
- They are seasonal (spring and autumn)
- It is sporadic and familial

Common causes of poisoning

- Confusion between edible and poisonous mushrooms
- Consumption of mushrooms picked from the forest by people without mycological knowledge
- Improper preservation and preparation

Classification by symptom latency

Type of intoxication	Latency time	Examples of toxins	Examples of mushrooms	Severity
Early	< 6 hours	Muscarine, gyromitrine, psilocybin, coprine	Inocybe, coprinus, psilocybe	Easier
Late	> 6 hours	Amatoxins, phallotoxins	Amanita phalloides, Galerina marginata	Severe (lethal)

Classification by type of toxin

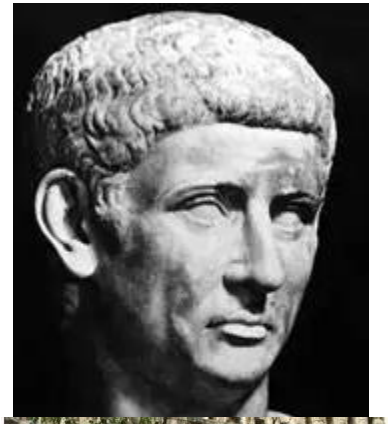
Type of toxin	Main mechanism	Examples of mushrooms
Amatoxins	Inhibits RNA polymerase II → hepatic necrosis	Amanita phalloides
Phallotoxins	Direct damage to hepatocytes	Amanita phalloides
Muscarine	Muscarinic cholinergic agonist	Inocybe, Clitocybe
Gyromitrina	Toxic hepatic și neurotoxic	Giromitra esculenta
Psilocibina	Serotonergic hallucinogen	Psilocybe spp.

Epidemiology

- Mushroom poisoning occurs worldwide, but is more common in rural areas or where mushrooms are eaten from the wild
- In Europe and the USA thousands of cases are reported annually, most accidental
- In the USA between 6000 – 8000 cases/year, most of which are non-lethal
- Amanita phalloides is responsible for over 90% of deaths from mushroom poisoning

The role of poisonous mushrooms in history

- Emperor Claudius (54 AD) would have been poisoned by his wife Agrippina, to provide the throne for her son Nero, with Amanita phalloides. After his death, he was ironically nicknamed the "Divine Mushroom".
- In Central America, the Mayan and Aztec civilizations used mushrooms such as Psilocybe spp. in religious rituals - called "flesh of the gods".
- In Europe, in the Middle Ages, accidental consumption of hallucinogenic mushrooms was considered a sign of possession.
- The first medical description of Amanita phalloides poisoning was made by Augustin Pyrame de Candolle in the 19th century. He described the progressive hepatotoxic effects, the symptomatology and severity of the disease.



Pathophysiology

- Inhibition of RNA polymerase, causing disruption of mRNA transcription.
- As a result, hepatocytes cannot synthesize key protein-coding genes, which leads to disintegration of nucleoli and pathological centrilobular hepatic necrosis.
- This leads to the insidious onset of liver failure over 48 hours.
- Late onset (more than six hours after ingestion) of vomiting and watery diarrhea occurs due to the second component, *phallotoxin*, which leads to damage to the membranes of enterocytes and hepatocytes

Clinical manifestations

Evaluate in 4 phases

1. Latency phase (6-12 hours) is asymptomatic
2. Aggression phase (from 6 to 24 hours) sudden onset, signs of gastroenteritis, abdominal pain, watery diarrhea, marked dehydration, hypotension, tachycardia, shock, anuria
3. Calm phase (24-48 hours) is characterized by apparent recovery, lasting 3-5 days.
4. Parenchymal or worsening phase (2-5 days) recurrence of digestive disorders associated with liver and kidney dysfunction, clinical signs of myocarditis appear, later may occur death

Diagnosis

Clinical diagnosis

- History taking with recent mushroom ingestion
- GI symptoms with hepatic/neurological depending on mushroom
- Latency of symptoms
- Affecting multiple persons

Diagnosis

Paraclinical diagnosis (repeat every 6 – 12 h)

Analysis	What does it indicate?
AST, ALT	Liver damage
Bilirubin	Liver damage
INR, PT, fibrinogen	Coagulopathy → hepatic severity
Glucose	Hypoglycemia → ↓ liver glycogen
Ureea, creatinine	Acute renal failure
Electrolytes (K, Na)	Electrolyte disturbances caused by vomiting, diarrhea
Lactate	Hypoperfusion, acidosis
Acid base balance	Severe metabolic acidosis

Diagnosis

Specific toxicological tests

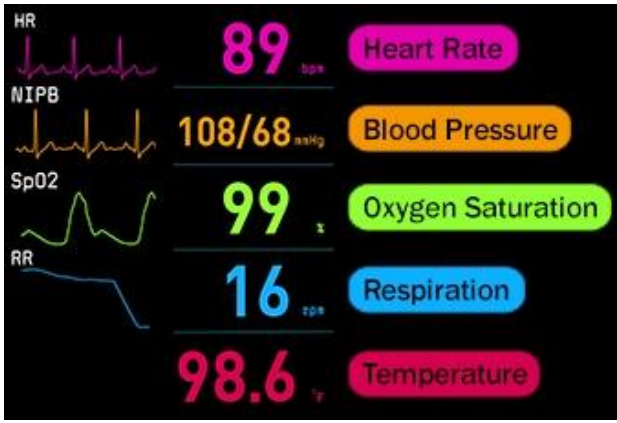
- Detection of amanitins in:

✓ Urine – within the first 24 – 48 hours

✓ Blood – less common, but useful in specialized centers

- Mycology (identification of fungi) from food scraps or vomitive masses

Patient stabilization



Maintaining vital functions and immediately correcting life-threatening disorders

A - airways: positioning, aspiration, ensuring airway permeability

B - respiration: administration of O2 by mask, nasal cannula, if necessary OTI with CMV

C - circulation: vascular access, volume resuscitation, symptomatic therapy

D - disability: assessment of the degree of consciousness disorder. Consciousness - dull, coma. Treatment of sezures.

E - exposure: thermometry

Treatment – elimination of the toxin

- Digestive decontamination: activated charcoal 1g/kg, repeated every 4 hours)
- Gastric lavage only if the patient presents < 1h after ingestion
- Saline purgatives
- Forced diuresis (2-4 ml/kg/min)
- Hemosorption/hemodialysis: in the first 24h, useful only in severe forms
- Plasmopheresis: optional, with variable results
- Periotoneal dialysis: not effective for amatoxin

Antitoxin treatment

- *Procaine benzylpenicillin* 1 million IU/kg/day, mechanism is competition for transport between penicillin and amatoxins, preventing amatoxins from binding to hepatocytes.
- *N-acetylcysteine*: IV dosage as in acetaminophen poisoning to treat potential liver damage and to provide glutathione.
- *Silymarin* inhibits hepatic absorption of amanitins. Doses are 1 g orally four times daily, or its purified alkaloid, *silibinin*, intravenously, 5 mg/kg IV over hour, followed by 20 mg/kg/day by constant infusion.

Symptomatic treatment

- Treatment of liver and kidney failure
- Correction of metabolic acidosis (Sodium bicarbonate solution)
- Correction of hypoglycemia (10% glucose solution)
- Correction of coagulopathy – administration of fresh frozen plasma
- Vitamin K
- Correction of dehydration – by administration of i/v fluids (Righer lactate solution, 0.9% sodium chloride solution)
- Treatment of cerebral edema
- Treatment of seizures
- Liver transplant

Prognosis

In the case of Amanita phalloides

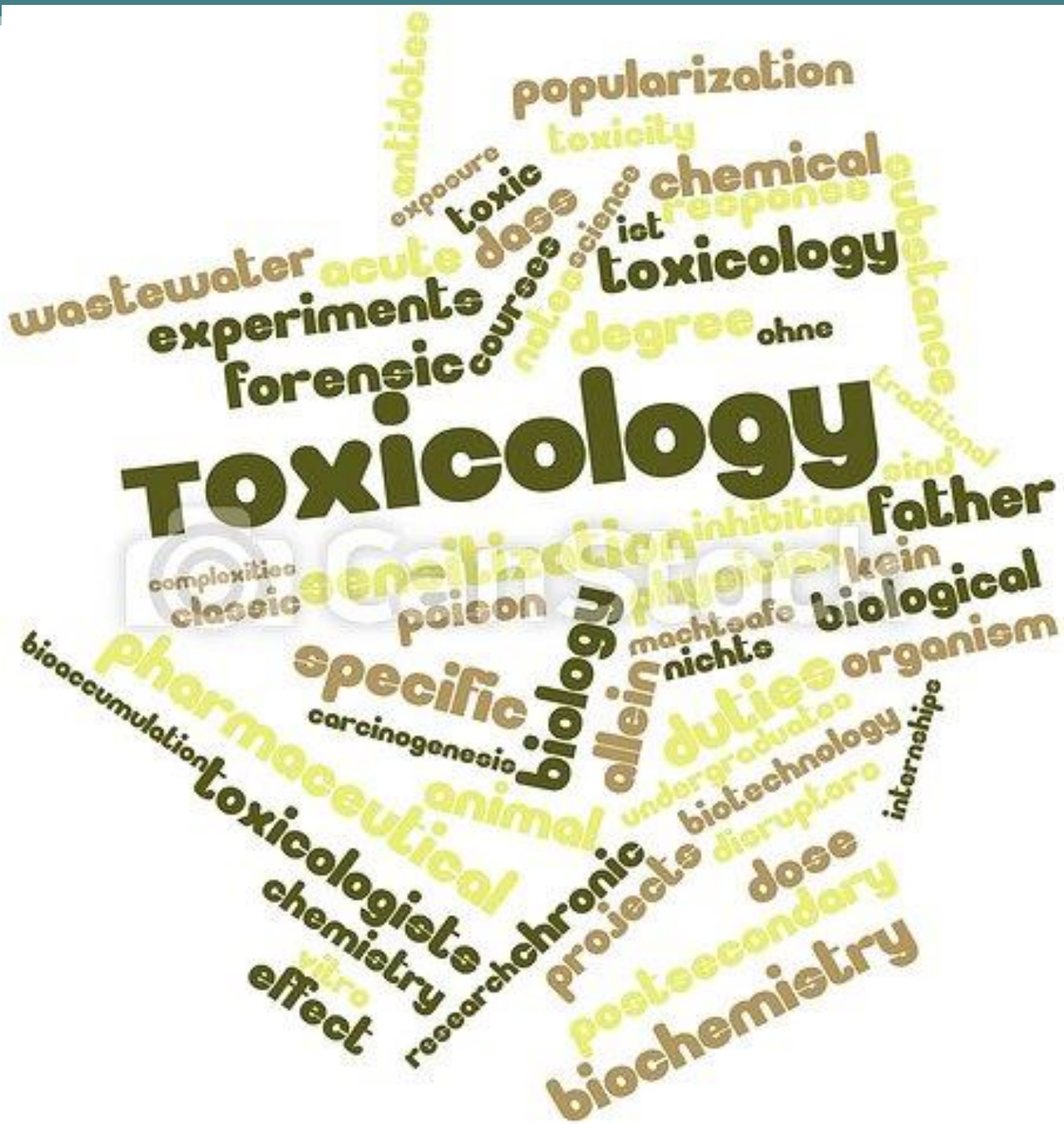
- Mortality up to 80 – 90% without treatment or transplant
- With early treatment: decreases to 10 – 30%

The prognosis depends on:

✓ Access to Sibilină or liver transplant

✓ Age (children and the elderly have more serious outcomes)

✓ Pre-existing liver comorbidities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