Severe intoxications (2)
Anion gap

\[ \text{Na}^+ + (\text{K}^+) - (\text{Cl}^- + \text{HCO}_3^-) \]

< 10% of all acute ethanol intoxications → ketoacidosis
Ingested ethanol, fatty acids, and acetic acid lead to Acetyl-CoA, which can form through various processes including:

- Long chain fatty acids
- ATP
- Insulin

Additionally, ADP can influence these processes. The final step involves the formation of H+ and ketoacid anions.
Ibuprofen

- > 400 mg/kg potentially toxic

- Intoxication usually asymptomatic or mild GI symptoms with lethargy, headache, nystagmus

- AKI, acidosis and coma rare

- Usually distal tubular acidosis (hyperchloremic) sometimes with life-threatening hyperkalemia

- Extremely rare: anion gap MA (proprionic acid)
Salicylates

- Uncouples oxidative phosphorylation (500 - 800 mg/L) → increases glucose and oxygen consumption due to ATP deficiency
- Fever, tinnitus and deafness
- Hypoglycemia with ketoacidosis and lactic acidosis
- Respiratory alkalosis
- Seizures, AKI, pulmonary edema, coma

Hemodialysis with end organ failure and salicylate > 1000 mg/L

Urine alkalinization if hemodialysis is deemed unnecessary
Isoniazid intoxication

- Results in pyridoxine and GABA deficiency
- Altered mental changes or seizures (30 min - 2 hrs after ingestion)
- Complications: rhabdomyolysis
- Treatment: symptomatic + pyridoxine supplementation (1 gram/gram INH - otherwise 5 gr)
GHB

- [Peak] 40 minutes after oral ingestion
- $T^{1/2}$ 20-30 minutes
- Coma after 40 - 60 mg/kg
- Coma, myoclonus, hypoventilation and bradycardia
- Supportive therapy
Cocaine

- Re-uptake inhibition of NE, dopamine, serotonin

- Effects may occur minutes after ingestion - T1/2 60 minutes

- Signs and symptoms of sympathetic overdrive
  - Hypertension, tachycardia, hyperthermia, cardiac arrhythmia, stroke, seizures
  - Rhabdomyolysis

- Symptomatic treatment (benzodiazepines, β + α-blocker)
Do you really need that emergency drug screen?

- Usually urine (preferably immune assay) - cannot test for all drugs involved and does not tell you that symptoms are explained by the drug

- Turn around time sometimes high and treatment usually symptomatic
Do you really need that emergency drug screen?

- Adults: 7 retrospective case series (N=1405), 1 prospective case series (N=196), 1 RCT (N=117)
- Children: 3 retrospective case series (N=694)
- Multiple trauma: 3 retrospective case series (N=3509)

< 5% CHANGE IN THERAPY

Tenenbein M. Toxicology 2009;47:286-291
Osmol gap

Osmol gap = measured osmolality - calculated osmolality (2 × Na⁺ + Gluc + BUN)

Osmol gap 0.7 - 4.5 mmol/l

Heavens KR. Am J Clin Nutr 2014;100:1252-1256
Ipecac sirup

• Emetic for patients with ingested poisons

• Contraindications: compromised airway protective reflexes, hydrocarbon ingestion with high aspiration potential, corrosive substances and debilitated elderly patients

The routine administration of ipecac at the site of ingestion or in the emergency department should definitely be avoided. Ipecac may delay the administration or reduce the effectiveness of activated charcoal, oral antidotes, and whole bowel irrigation. There is not sufficient evidence to warrant any change in the previous ipecac position papers. There are, however, insufficient data to support or exclude ipecac administration soon after ingestion of some specific poisons in rare situations.

Höjer J. Clinical Toxicology 2013;51:134-139
Lithium intoxication

• Relatively narrow therapeutic index (effective dose range 0.6 - 1.0 mmol/l with toxicity in chronic use starting at 1.2 mmol/l)

• Alkali metal with rapid distribution over total body water

• Acute intoxication: GI symptoms, cardiotoxic effects and late developing neurologic signs (no compartment saturation - rapid decrease in levels)

• Chronic: neurologic effects - confusion, myoclonus seizures (compartment saturation)
Lithium intoxication

Acute and acute-on-chronic intoxication
- Gastrointestinal symptoms (nausea, vomiting, diarrhea)
- Cardiac symptoms (ECG changes, arrhythmias, prolonged QTc intervals, bradycardia)
- Neurological symptoms (late-developing: Syndrome of irreversible lithium effectuated neurotoxicity SILENT)

Chronic intoxication
- Neurological symptoms (gradually developing: sluggishness, ataxia, confusion, agitation, tremor)
- Cardiac symptoms (see acute and acute-on-chronic intoxication)
- Renal symptoms (nephrogenic diabetes insipidus)

ACE inhibitors, NSAID's, Thiazide diuretics, hypovolemia increase lithium levels by increasing proximal tubular reabsorption

Lithium intoxication

- Immediate resuscitation (ABCDE)
- No antidote
- Placement of gastric tube/lavage (< 1 hour)
- No activated charcoal (cannot bind lithium)
- Whole body irrigation (polyethylene glycol) with sustained release tablets
ABC = airway, breathing, circulation

Hydration to maximize lithium clearance
(isotonic (0,9 %) saline depending on fluid status and cardiac function)

Gastrointestinal decontamination
(whole bowel irrigation with polyethylene glycol (PEG) solution in large acute or ingestion of sustained-release preparations, 2-4 hours after ingestion)
Lithium intoxication

- Hemodialysis - low molecular weight, water soluble, low distribution volume, insignificant protein binding

- In every patient with level > 4 mmol/l regardless of symptomatology and etiology

- > 2.5 mmol/l with signs of severe intoxication and with renal impairment

- Serial measurements necessary due to rebound phenomenon (every 2 - 4 hours)

- Continu HD sessions until levels are < 1 mmol/l for at least 6 - 8 hours
Lithium intoxication

<table>
<thead>
<tr>
<th>Hemodialysis?</th>
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<tbody>
<tr>
<td>when lithium level &gt; 4.0 mmol/l</td>
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<tr>
<td>- &gt; every patient</td>
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<tr>
<td>lithium level &gt; 2.5 mmol/l</td>
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<td>- &gt; renal insufficiency, severe intoxication, contraindication or aggressive fluid hydration (heart failure)</td>
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<tr>
<td>moderate to severe signs of intoxication when lithium level &lt; 2.5 mmol/l</td>
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<tr>
<td>- &gt; by-case decision</td>
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</table>
Theophylline intoxication

- Toxicity > 30 µg/mL
- 356 patients (mean 60 µg/mL - range 30 - 245 µg/mL)
- 20.8% cardiac arrhythmias, 8.2% seizures and 4.2% died
- Metabolic disturbances (hypokalemia, hyperglycemia and metabolic acidosis)
- Hemoperfusion (often with charcoal) in acute intoxications if > 80 - 100 µg/mL

Shannon M. Arch Intern Med 1999;159:989-994
Metformin

- Severe intoxication 1 - 5 cases/100,000 person years of metformin treatment

- Distribution volume 63 - 276 L and negligible plasma protein binding, excreted in unmetabolized form from the kidneys

- Intoxication usually in patients with renal insufficiency and cardiopulmonary instability

- Main problem lactic acidosis (increased conversion from glucose and reduced hepatic gluconeogenesis) with mortality > 20-40%

Hemodialysis if critically ill and pH < 7.1 and failure to improve with supportive care and AKI
Choline esterase inhibitor

- Cholinergic hyperstimulation
  - Muscarine receptor - exocrine secretion, mitosis, blurred vision
  - Nicotine receptor - muscle weakness, fasciculations, tachycardia, convulsions, coma
- Atropine (eg 2 mg/10 min) + pralidoxime (1 gr in 30 min) + benzodiazepines
Methylene blue

- NADH to NAD+
- Cytochrome b5 reductase
- Fe^{3+} to Fe^{2+}
- Methylene Blue
- NADPH to NADP+
- Glucose 6-phosphate dehydrogenase
- Glucose 6-phosphate to 6-phosphogluconate
Anti-cholinergic syndrome

- Flushing, dry skin and mucous membranes, mydriasis, altered mental status, fever, tachycardia, urine retention, ileus
- Antidote: physostigmine (crosses BB barrier)
- Contraindication: cardiac conduction disturbances and agitation/psychosis
Isoniazid intoxication

- Results in pyridoxine and GABA deficiency
- Altered mental changes or seizures (30 min - 2 hrs after ingestion)
- Complications: rhabdomyolysis
- Treatment: symptomatic + pyridoxine supplementation (1 gram/gram INH - otherwise 5 gr)
β-blocker intoxication

- Glucagon increases cAMP through adrenergic receptor independent pathways
- Bolus 5 - 10 mg iv - continuous infusion 1 - 5 mg/h