METALS AND INHALANTS

ARSENIC:

ACUTE INGESTION IS FOLLOWED BY SEVERE GASTROENTERITIS WITH *CHARACTERISTIC, SEQUENTIAL MULTI-ORGAN FAILURE*

RISK ASSESSMENT:

- Ingestion >1mg/kg potentially lethal
- Chronic poisoning usually occurs secondary to long term-drinking of contaminated artesian water

TOXIC MECHANISM:

- Binds to numerous cellular enzymes, interfering with cellular respiration and DNA replication and repair
- Substitutes for phosphate in ATP
- Produces reactive oxygen intermediates → lipid peroxidation

TOXICOKINETICS:

- ABSORPTION OCCURS VIA DERMAL, RESPIRAOTRY AND GIT
- Elimination half life is 3-5 days following acute ingestion, distributing to liver and kidneys

CLINICAL FEATURES:

- **ACUTE TOXICITY:**
  - Rapid onset of rice water diarrhoea/vomiting
  - GI haemorrhage can occur
  - Encephalopathy, seizures and CV collapse within hours
  - HYPERSALIVATION WITH GARLIC ODOUR IS CHARACTERISTIC
  - Acute cardiomyopathy with ECG changes/dysrhythmias have been described
  - ARDS, renal and hepatic failure follow
  - Bone marrow depression within 24-72 hours in survivors → nadir at ~3 weeks
  - Alopecia
  - Peripheral neuropathy (ascending motor neuropathy mimicking GBS)
- CHRONIC:
  - Insidious onset over years → constitutional symptoms, cutaneous lesions (hyperkeratosis of soles/palms), painful peripheral neuropathy and malignancies of skin/bladder

INVESTIGATIONS AND MANAGEMENT:

- Spot urinary arsenic confirms ingestion but 24-HOUR urinary arsenic is a better reflection of body burden
- Immediate threat to life early is HYPOVOLAEMIC SHOCK due to GI losses → mandates aggressive fluid resuscitation
- Activated charcoal DOES NOT BIND ARSENIC → whole bowel irrigation if arsenic trioxide ingestion confirmed

- ANTIDOTES:
  - Chelation is indicated where there are objective clinical features of acute arsenic intoxication
  - SUCCIMER IS THE AGENT OF CHOICE IF ORAL ADMINISTRATION POSSIBLE:
    - ORALLY ACTIVE METAL CHELATOR, aka DMSA
    - Used in mercury, lead, copper poisoning as well
    - It is a water-soluble analogue of DIMERCAPROL (see below), that binds to heavy metal ions via sulfhydryl groups, which then are excreted in the urine as complexes
    - 10mg/kg tds for five days then bd for 14 days.
    - GI upset is very common, transient LFT upset
  - DIMERCAPROL:
    - Given IM, but is the most toxic of all chelating agents and is reserved for treatment of lead, inorganic arsenic and mercury poisoning (severe)
    - Binds metal ions to form stable dimercapttides, which then can be excreted in the urine
    - Formulated in peanut oil, only suitable for IM
    - Conjugates can be removed by dialysis
    - Extremely high adverse event rate → pain and sterile abscess, fever, chest pain/↑BP/↑HR, peripheral paraesthesiae, intravascular haemolysis in G6PD deficiency, NEPHROTOXICITY IF URINE ACIDIC (ALKALINISE FIRST TO PREVENT DISSOCIATION OF COMPLEXES)
  - Do not delay chelation therapy pending confirmatory levels

CARBON MONOXIDE:

COMMON CAUSES OF POISONING DEATH → usually pre-hospital

ACUTE EFFECTS ARE DUE TO TISSUE HYPOXIA

RISK ASSESSMENT:

- Acute deliberate self-poisoning by exhaust fumes usually involves exposure to high concentrations, but are lower risk of long-term problems
- HIGH RISK FEATURES:
    - Significant loss of consciousness/coma
    - Persistent confusion/neurological impairment
    - Abnormal cerebellar examination
    - Metabolic acidosis
    - Myocardial ischaemia
    - Age >55
    - PREGNANCY → foetal haemoglobin binds CO more avidely, thus the foetuus is more susceptible to injury
        - Outcome is POORLY CORRELATED WITH CARBOXYHAEMOGLOBIN LEVEL

TOXIC MECHANISM:

- CO has 210 times the affinity for Hb compared to oxygen, hence Hb oxygen transported is rendered far less efficient in the presence of CO → HYPOXIA
- Also initiates lipid peroxidation/tissue injury/inflammation that is probably responsible for long-term neurological sequelae

TOXIC MECHANISM:

- HALF-LIFE DETERMINED BY THE DISSOLVED OXYGEN TENSION
    - Room air → four hours
    - 100% oxygen → 90mins
    - 100% oxygen at three atmospheres (HYPERBARIC) → 23 minutes

CLINICAL FEATURES:

- Most patients present with headache and nausea
- CNS → headache, poor concentration, confusion, seizures/coma
- CVS → ischaemia/AMI, ↑BP, ↑HR
- Respiratory → non-cardiogenic pulmonary oedema
- Metabolic →lactic acidosis, rhabdomyolysis, ↑BSL
- Other → DIC
- Persistent neurological sequelae at 12 months in 6-10% → personality changes, poor concentration, dementia, parkinsonism, ataxia, psychosis

INVESTIGATIONS AND MANAGEMENT:

- **CARBOXYHAEMOGLOBIN:**
    - Dizziness/nausea/throbbing headache at 20%
    - Confusion, coma, seizures at 40%
    - CV/respiratory failure, death at 50%
        - Loose correlation with symptoms

- Serum lactate
- NEUROPSYCHIATRIC TESTING AT 3-12 MONTHS
- MANAGEMENT:
    - High-flow oxygen ASAP
    - Hyperbaric oxygen may be indicated in patients ≥1 risk factor listed above, but indications and effectiveness are controversial
    - Patients with persistent symptoms or evidence of ongoing end-organ ischaemia require HDU/ICU

CYANIDE:

RARE BUT DRAMATIC AND LETHAL

REMOVAL FROM THE SOURCE AND TIMELY ADMINSITRATION OF AN ANTIDOTE ARE CRUCIAL

RISK ASSESSMENT:

- Exposure occurs either by inhalation of hydrogen cyanide gas or by ingestion of cyanide salts → death is likely to occur prior to arrival at hospital. Those who arrive alive following inhalational exposure usually survive

TOXIC MECHANISM:

- Acts at several sites
- Binds to ferric iron of CYTOCHROME OXIDASE to inhibit oxidative metabolism → lactic acidosis
- Stimulates release of BIOGENIC AMINES → pulmonary and coronary vasoconstriction
- In CNS → ↑NMDA release → seizures

CLINICAL FEATURES:

- Acute inhalation leads to LOC within seconds to minutes, symptoms develop within 30-60 minutes after ingestion
- Progressive hypotension, bradycardia, tetany, coma/respiratory depression
- Delayed parkinsonism may occur weeks to months after surviving serious poisoning

INVESTIGATIONS AND MANAGEMENT:

- **ABG**
- Serum lactate strongly correlates with severity of intoxication whereas cyanide levels DO NOT aid management but confirm diagnosis in retrospect (take prior to antidotes)
- Multiple immediate life threats, and resuscitation takes priority over decontamination
- ANTIDOTES:
    - For those with suspected poisoning and serious sequelae (altered mental state, seizures, hypotension, acidosis)
    - HYDROXOCOBALAMIN:
        - Preferred if available as it has relatively benign adverse effects even if administered in ABSENCE OF CYANIDE POISONING
        - Vitamin B12 precursor and is effective chelator of cyanide at high doses
        - Has COBALT ion at its centre and it is COBALT THAT BINDS CYANIDE → forms CYANOCOBALAMIN which is non-toxic and prevents circulating cyanide from re-entering tissues and promotes reactivation of inhibited cytochrome oxidase by removing cyanide

        - 2.5g dissolved in 100mL NS infuse over 15 minutes and repeat → sufficient to bind 100mg cyanide
        - Can cause minor hypertension, orange urine/skin discolouration
        - Only the CYANOKIT provides sufficient dose → alternative preparation for pernicious anaemia only has ONE MILLIGRAM!
        - Do not mix with sodium thiosulfate as complexes will result
    - SODIUM THIOSULFATE:
        - Enhances endogenous cyanide detoxification capacity of the body
        - Should be used in conjunction with other antidotes in severe toxicity
        - LITTLE TOXICITY
        - Acts by being a SULPHUR DONOR TO RHODANESE (catalytic enzyme for enhanced conversion of cyanide to thiocyanate)
        - Give 12.5g over 10 minutes
    - DICOBALT EDETATE:
        - Acts by cobalt binding cyanide but has severe direct toxic effects when administered to a patient without cyanide poisoning
        - It is an inorganic cobalt salt, one mole of cobalt binds six moles of cyanide to form stable complexes
        - Toxicity includes convulsion, oedema of the face/larynx/neck, urticaria, chest pain, hypotension, vomiting

HYDROCARBONS:

WHETHER INGESTED OR INHALED, CAN CAUSE RAPID ONSET OF CNS DEPRESSION, SEIZURES OR ARRHYTHMIA (RARE)

ASPIRATION CAN LEAD TO CHEMICAL PNEUMONITIS

RISK ASSESSMENT:

- For most petroleum distillates, more than 1-2mL/kg are required to cause significant systemic toxicity
- Ingestion of as little as 10mL of eucalyptus oil may lead to CNS depression and seizures, always within 1-2 hours
- Large or prolonged inhalation exposure may also produce asphyxia

TOXIC MECHANISM:

- Disruption of lung surfactant produces a chemical pneumonitis,
- Mechanism of CNS effects is unclear
- Dysrhythmia secondary to myocardial sensitization to catecholamines
- Chlorinated hydrocarbons are metabolized to hepatotoxic metabolite

TOXICOKINETICS:

- Absorption following inhalation exposure is determined by concentration, duration of exposure and minute ventilation

CLINICAL FEATURES:

- RESPIRATORY → chemical pneumonitis → worsen over 24-72 hours and resolves within 5-7 days
- CVS → dysrhythmia occur early
- CNS → profound depression, coma, seizures in massive acute exposures
    - Chronic toluene abuse → ataxia, dementia and peripheral neuropathy
- Other → benzene associated with haemolysis and leukaemia and toluene is nephrotoxic (renal tubular acidosis with hypokalaemic hyperchloraemic NAGMA)

MANAGEMENT:

- In event of ventricular arrhythmia →ACLS, correct K/Mg, withhold catecholamines, IV beta-blockers
- Chemical pneumonitis is managed supportively (no role for prophylactic antibiotics)
- GI decontamination is CONTRAINDICATED → high risk of vomiting and aspiration

IRON:

POISONING CHARACTERISED BY LOCAL GI AND DOSE-RELATED SYSTEMIC TOXICITY→ SPECIFICALLY THE AMOUNT OF *ELEMENTAL IRON INGESTED*

IN LARGE OVERDOSE → SYSTEMIC TOXICITY CAN BE PREVENTED BY EARLY DECONTAMINATION AND ADMINISTRATION OF DESFERRIOXAMINE

RISK ASSESSMENT:

- Iron overdose is potentially lethal
- Assessment is based on ingested dose of ELEMENTAL IRON
- Refinement AXR and iron level at 4-6 hours
- Those presenting with established systemic toxicity have poor prognosis
- Anticipate systemic toxicity with ingestion over 60mg/kg, and doses >120mg/kg potentially lethal

TOXIC MECHANISM:

- LOCAL → direct corrosive effect on GI tract → V+D with large fluid losses. Systemic toxicity DOES NOT OCCUR in absence of GI symptoms
- SYSTEMIC → iron acts as a direct cellular toxin (CVS and liver are main targets). Severe lactic acidosis from hydration of free ferric ions with liberation of H+. Coagulopathy occurs. CNS toxicity due to CV instability/metabolic derangements

TOXICOKINETICS:

- Absorption of iron is usually finely regulated according to body needs, but these mechanisms are overwhelmed in overdose

CLINICAL FEATURES:

- Classical stages → better conceptualized by GI vs systemic phases:
    - EARLY → direct corrosive effects, GI losses/hypovolaemia
    - 6-12 hours → false hope due to resolution of some symptoms
    - 12-48 hours → disruption of cellular metabolism → shock (vasodilation/third space losses), AG MA, hepatorenal failure
    - 2-5 days → acute hepatic failure → rare but high mortality → jaundice/coma, ↓BSL, coagulopathy
    - 2-6 weeks → delayed cirrhosis, GI fibrosis/strictures

INVESTIGATIONS AND MANAGEMENT:

- Serum iron levels peak at 4-6 hours → take levels at this time, but they correlate poorly with toxicity
- ABG → anion gap acidosis useful marker of systemic toxicity
- EARLY PRIORITY → restoration of adequate circulating volume → fluid bolus
- IRON IS NOT ADSORBED TO ACTIVATED CHARCOAL, HENCE WHOLE BOWEL IRRIGATION IS THE DECONTAMINATION METHOD OF CHOICE → recommended for ingestions of >60mg/kg

- ANTIDOTES:
    - DESFERRIOXAMINE:
        - Indicated if systemic toxicity present → altered mental state, shock, lactic acidosis or predicted by serum iron of >90micromol/L
        - Binds avidly with free ferric ion in the plasma to form ferrioxiamine →highly water soluble and readily excreted in the urine → not able to remove iron outside the intravascular compartment
        - Hepatic metabolism produces multiple metabolites responsible for toxic effects → ARDS, retinopathy
        - Secondary infections as ferioxamine acts as a siderophore promoting yersinia and mucormycosis
        - 500mg/100mL at 15mg/kg/hour → ↑ to 40mg/kg/hour
        - Ideally administered before iron moves intracellularly and systemic toxicity develops
        - Six hours therapy usually sufficient
- Children who are suspected of ingesting <40mg/kg can be observed at home
- The foetus is relatively well protected unless maternal CV instability develops

LEAD:

ACUTE INTOXICATION USUALLY DUE TO INGESTION

RARE BUT POTENTIALLY LIFE-THREATENING

RISK ASSESSMENT:

- Acute/subacute intoxication associated with encephalopathy, cerebral oedema and death
- Chronic exposure leads to vague multi-system disorder with potential for permanent neurological/neuropsychiatric sequelae → RISK LOOSELY CORRELATES WITH BLOOD LEVEL

TOXIC MECHANISM:

- Lead has no physiological function
- Toxic effects through interference with intracellular functions → major target organs are nervous system, kidneys, reproductive and haematopoeitic systems

TOXICOKINETICS:

- Absorbed and bound by red cells then distributed widely throughout the body → bony skeleton acts as storage
- Easily crosses the placenta

CLINICAL FEATURES:

- ACUTE:
  - Abdominal pain, nausea, vomiting, ahemolytic anaemia and hepatitis
  - Cerebral oedema, encephalopathy, seizures and coma are PRE-TERMINAL
- CHRONIC:
  - Impaired concentration, anorexia, emotional lability, incoordination, impaired higher function

INVESTIGATIONS AND MANAGEMENT:

- Blood lead level predictive of chronic effects and loosely correlates with acute toxicity
- FREE-ERYTHROCYTE PROTOPORPHYRIN:
  - Surrogate marker of total bodyburden
- Acute resuscitation is rarely required → consider mannitol and dexamethasone if cerebral oedema is present
- DECONTAMINATION:
  - Endoscopic foreign body retrieval if proximal to gastrooesophageal junction → otherwise consider WBI
  - If shrapnel adjacent to synovium → surgical excision
- ANTIDOTES:
  - Chelation therapy indicated in symptomatic lead poisoning or if long-term neurological injury is anticipated
  - Can use DMSA/succimer (see arsenic)
  - SODIUM CALCIUM EDETATE:

        - IV chelator indicated for acute lead-induced encephalopathy or in the symptomatic patient with levels above 100micromol/L
        - Binds to divalent and trivalent metals, with calcium component being displaced and formation of water-soluble chelate → urinary excretion
        - Use in conjunction with dimercaprol and give sodium calcium edetate at dose of 50-75mg/kg in 500mL over 24 hours 4 hours after first dose dimercaprol
        - Can cause nephrotoxicity → ensure adequate urine output
- IF YOU IDENTIFY A CHRONIC LEAD TOXICITY CASE → INDEX CASE

MERCURY:

INTOXICATION RARE, MOST EXPOSURE FROM CONSUMPTION OF SEAFOOD

ACCIDENTAL INGESTION OF THERMOMETER MERCURY/AMALGAM PRESENTS MINIMAL RISK

RISK ASSESSMENT:

- Potentially serious presentations:
  - Inhalation of mercury aerosol or vapor → pneumonitis and non-cardiac pulmonary oedema
  - Ingestion of inorganic mercury salts → haemorrhagic gastroenteritis, ARF and shock, lethal dose 30-50mg/kg
  - Organic mercury ingestion → neurologic injury

TOXIC MECHANISM:

- **NO CELLULAR FUNCTION**
- Binds to sulfhydrl groups causing inhibition of enzymes and disruption of cellular membranes

TOXICOKINETICS:

- There is little absorption of elemental mercury through intact GIT, but it is well absorbed through respiratory tract
- Highly lipid solubility
- Half-life ~70 days

CLINICAL FEATURES:

- **ACUTE EXPOSURE TO ELEMENTAL MERCURY:**
  - Inhalation of vaporized mercury → headache, nausea/vomiting, can cause respiratory failure due to interstitial pneumonitis
- ACUTE EXPOSURE TO INORGANIC SALTS → severe haemorrhagic gastroenteritis within hours and local oropharyngeal pain. Massive fluid loss leads to hypotension, shock and ATN
- ACUTE EXPOSURE TO ORGANIC MERCURY→ acutely can cause respiratory distress/dermatitis, ECG changes, but chronically can cause cerebellar dysfunction, psychological issues, glove-stocking paraesthesiae, and motor weakness
- CHRONIC TOXICITY → insidious multi-system disorder with prominent neuropsychiatric symptoms

INVESTIGATION AND MANAGEMENT:

- Mercury levels confirms exposure but does not reflect total body burden
- Ingestion of inorganic salts requires aggressive fluid resuscitation and supportive care for multi-organ failure
- Decontamination is aimed at preventing further exposure at personal and environmental level
- ANTIDOTES:

- CHELATION THERAPY WITH DIMERCAPROL (see previous), PENICILLAMINE OR SUCCIMER
- Chelation is indicated when there are objective clinical features of mercury intoxication or if blood/urine levels indicate potential for harm. Only useful when further exposure to mercury is terminated.
- PENICILLAMINE:
    - Potent oral chelator for broad range of heavy metals
    - Poor side-effect profile and thus is indicated as agent of choice in limited circumstances
    - MAIN CHOICE IN COPPER TOXICITY (WILSON)
    - Second line for other heavy metals
    - Contraindicated in pregnancy, renal failure or in those with penicillin allergy
    - Binds to various metals and complex is excrete in urine
    - Administer 4-7mg/kg orally qid (to max 2g)
    - Monitor FBC fortnightly (marrow suppression)
    - Other issues → hypersensitivity, myasthenia gravis, nephrotoxicity (GN, nephrotic syndrome). Can cause Goodpastures, hepatotoxicity and pancreatitis
- DO NOT USE DIMERCAPROL → thought to ↑ distribution of mercury to CNS