Poisoning & Drug Overdose

Def'n: ***overdose***: exposure to an amount of a substance likely to produce untoward effects in the individual

1. ~ 20% of overdoses are at any significant risk
2. ≥ 50% of suicidal overdoses are ***mixed***, frequently including ***ethanol***

- ***Age Distribution***

a. 25% < 5 years → usually accidental

b. 50% ~ 5-30 years → F:M > 2:1

c. 25% > 30 years

NB: ***overall mortality*** **~ 0.5%** **1:200**

- ***General Principals***

NB: three basic management principles

1. ***resuscitation*** - ABC
2. ***diagnosis***
   - i. history and examination
   - ii. investigation
     - E,C&U, FBE, AGA's, osmolality & osmolar gap
     - blood & urine drug screening
     - CXR
   - iii. gastric lavage *if appropriate
3. ***treatment***
   - i. drug manipulation
     - general - emetics, lavage, cathartics
       - dilution
       - activated charcoal
     - specific - antidotes
       - forced diuresis ± pH modification
       - altered drug metabolism (methanol/ethanol)
       - haemoperfusion, dialysis, plasmapheresis
   - ii. complications - airway obstruction, respiratory failure
     - hypoglycaemia, metabolic derangement
     - seizures
     - arrhythmias, hypotension
     - NB: CVS, CNS, RS, temperature

ICU Admission Criteria

1. requirement for intubation
   i. ventilatory failure
   ii. airway protection / maintenance
   iii. therapy → induced hypocapnia/alkalosis
2. CNS
   i. uncontrolled seizures
   ii. coma, GCS < 9
3. CVS
   i. arrhythmias
   ii. AV block, prolonged QRS
   iii. hypotension requiring CVS support
4. large ingested dose
   - ± high blood levels predictive of poor outcome

Serum Levels Predictive of Outcome	
Essential	Useful
• paracetamol • theophylline • salicylates • alcohols	• lithium • barbiturates • phencyclidine • phenytoin • iron

Drug Removal General

▪ *Emetics*

• Ipecac syrup 10-30 ml, apomorphine, pharyngeal stimulation
• must have ***awake*** patient with gag reflex present
• use is controversial, there being ***no direct evidence*** that these agents improve morbidity or mortality associated with drug overdosage
• ***absolute contraindications***

1. unprotected airway
2. strong acids / alkalis
3. petroleum derivatives

NB: generally ***not recommended*** as impedes the subsequent use of activated charcoal, which has been shown to improve clearance

▪ *Gastric Lavage*

• exchange volumes £ **1 ml/kg** *greater volumes promoting gastric emptying
• useful early after ingestion £ **1 hr**
• doubtful efficacy after this but may be useful for slow release preparations and slowly absorbed agents, eg. tricyclics
• ***indications*** where large dose within 24 hours,

1. analgesics - paracetamol, aspirin, dextropropoxyphene
2. antidepressants - tricyclics
3. alcohols - methanol, ethylene glycol
4. others - theophylline, digoxin

• ***contraindications***

1. unprotected airway
2. strong acids / alkalis → risk of ***oesophageal perforation***
3. petroleum derivatives
   - most of these are relatively ***nontoxic*** following ingestion
   - aspiration of volumes ~ 1 ml may produce ***severe pneumonitis***

Activated Charcoal

- 50-100g immediately following lavage, then 50g q4h
- repeated doses ***effective*** for,

1. benzodiazepines, barbiturates, narcotics
2. tricyclics, phenothiazines
3. salicylates
4. theophylline
5. digoxin, digitoxin
6. atropine
7. some heavy metals

- relatively ***ineffective*** for,

1. most heavy metals - Li^{+}, Fe^{++}, boron
2. pesticides - organophosphonates, DDT, carbamates
3. alcohols - ethanol, methanol, ethylene glycol, isopropyl alcohol
4. cyanide
5. strong acids/alkalis

- ***contraindications***

1. unprotected airway
2. strong acids / alkalis
3. petroleum derivatives

Cathartics

- sorbitol 70% with charcoal
- use with first dose, subsequent use doubtful

Drug Removal Specific

1. forced diuresis - acid or alkaline
2. altered drug metabolism - N-acetylcysteine, thiosulphate, ethanol
3. antidotes - chelating agents, antibodies
4. extracorporeal techniques - haemodyalisis, haemoperfusion
   - plasmapheresis, exchange transfusion

Activated Charcoal

a. non-specific absorbent - drugs, toxins, gases
   - especially ***alkaloids*** and other ***bases***

b. fine black powder, odourless, tasteless

c. insoluble in water or lipids

d. large surface area & absorptive capability

- prepared from vegetable matter, eg. sawdust, peat, coconut shells
- treated with "activators", CO_2, steam, strong acids
- contains 15% H_2O, therefore stored airtight
- absorptive capacity,

a. per gram charcoal ~ 100-1000 mg (ie. ~ 10-100% by weight)

b. optimal charcoal:toxin ratio **~ 8:1** (calculated for ***salicylates***)

- increases systemic clearance of drugs through the GIT,

1. interrupted enterohepatic circulation
2. enteric "dialysis"

Repeated doses ***effective***	Charcoal is ***ineffective***
• benzodiazepines, barbiturates • opioids • tricyclics, phenothiazines • salicylates • theophylline • digoxin, digitoxin • atropine • some heavy metals	• alcohols - ethanol, methanol - ethylene glycol, isopropyl • pesticides - organophosphates - DDT, carbamates • heavy metals - Li, Fe, Hg - Cu, Au, Bo • cyanide • strong acids & bases • paraquat[1]

[1] one study showing equally efficacious to Fuller's earth

- ***contraindications*** include,

a. inability to protect the airway

b. strong acids & bases (caustics)
   - risk of oesophageal perforation with passage of the gastric tube

c. petroleum derivatives
   - risk of aspiration & severe chemical pneumonitis

- ***Fuller's Earth***

• specific antidote for ***paraquat***, also used in chemical warfare decontamination
• paraquat neutralised by contact with soil & only 5-10% absorbed in 24 hrs

1. initial dose ~ 30% solution, 300 g/l
   + 200 ml of 20% mannitol
2. subsequently q2h ~ 15% solution, 150 g/l
   + mannitol q4h

Enhanced Elimination

- ***Forced Diuresis***

a. ***acid diuresis*** → phencyclidine and amphetamine overdose
b. ***alkaline diuresis*** → salicylate and barbiturate overdose

• unless managed carefully, potential for fluid overload & electrolyte abnormalities
• sedation is preferred for the former, haemodialysis for salicylates and repeat charcoal for barbiturates

pH Dependent Renal Excretion	
Weak Bases	Weak Acids
• amphetamine	• sulphonamides
• ephedrine	• salicylates
• phencyclidine	• phenobarbitone
• quinidine	
• tricyclics	
optimal urine pH ≤ 5.5	optimal urine pH ≥ 7.5
• ascorbic acid 0.5-2.0 g ó/IV • NH_4Cl 0.1 g ó/IV	• bicarbonate 1-2 mmol/kg • acetazolamide 500 mg

- ***Peritoneal Dialysis***

• effectively no place in management of drug overdose

Haemodialysis

• indications for use include ***severe*** poisoning with,

1. salicylate
2. lithium
3. alcohols - isopropranolol, methanol, ethylene glycol
4. phenobarbitone

▪ ***Charcoal Haemoperfusion***

NB: largely ***unproven*** form of therapy, \ rarely recommended

• filter composed of activated charcoal granules covered with ***cellulose*** or ***cellophane***
• large active surface area ~ 1000 m^2/g
• effective for ***lipid soluble*** molecules, where plasma clearance may approach circuit plasma flow
• duration for drug overdose is ~ 4-8 hrs, or until symptoms are controlled
• for hepatic failure ~ 4-8 hrs/day
• recently developed ***polystyrene resins*** (Amberlite XAD-4) also have high affinity for lipid soluble compounds and have a clearance ~ **2x** charcoal

▪ ***Clinical Uses***

a. hepatic failure, encephalopathy
   - randomised studies from King's group → no additional benefit in ***survival***

b. drug overdose
   - often recommended for
     - theophylline
     - methotrexate
     - disopyramide
   - other drugs
     - barbiturates
     - ethanol, methanol
     - lithium
     - paraquat
     - salicylates (dialysis better)

   i. ***theophylline***
      - acute ≥ 500 µmol/l ≥ 100 µg/ml
      - chronic ≥ 200-300 µmol/l ≥ 40-60 µg/ml
      - severe refractory seizures, arrhythmias
      - severe cardiac, respiratory, or hepatic disease ≥ 40 µg/ml

   ii. ***salicylates*** ≥ 0.5-1.0 mg/ml
      - severe intoxication and unable to promote diuresis and alkalinisation

- ***Complications***

a. those of central line insertion
b. those of anticoagulation
c. thrombocytopaenia
d. haemolysis
e. electrolyte disturbances
f. pyrogenic reactions
g. time delay for commencement - severe toxicity of paraquat
h. hyperglycaemia - primed with dextrose

Toxicological Screens

a. spot urine tests
   - colour tests
   - rapid < 2 hrs, cheap
   - qualitative, non-specific
   - not for initial assay
   - use to confirm prior to more sensitive/specific assay

b. thin layer chromatography
   - rapid ~ 2-4 hrs, qualitative
   - interference common
   - urine or plasma
   - not useful for volatiles, alcohols, metals, salicylates, cyanide

c. gas and high pressure chromatography
   - useful for any specimen
   - not useful for initial screen
   - more specific & quantitative

d. emzyme immunoassay
   - measures rate of conversion NAD/NADH with photometry
   - more expensive & specific
   - useful for conformation

e. mass spectometry
   - highly specific/sensitive
   - qualitative & quantitative
   - expensive

Alcohols

- the various alcohols are metabolised by ***alcohol dehydrogenase*** and ***aldehyde dehydrogenase***

	alcohol dehydrogenase		**aldehyde dehydrogenase**	
Ethanol	⟶	Acetaldehyde	⟶	Acetate
Methanol	⟶	***Formaldehyde***	⟶	Formate
Ethylene Glycol	⟶	Glycoaldehyde	⟶	Glycolate
Isopropranolol	⟶	Acetone	⟶	
Paraldehyde	⟶	Acetaldehyde Formaldehyde	⟶	Acetate Formate

▪ ***Ethanol***

- hepatocyte alcohol dehydrogenase metabolises ETOH at a constant rate **~ 7-8 g/hr**
- this reduces $NAD^+ \rightarrow NADH + H^+$ and increases the lactate:pyruvate ratio
- clinical effects correlate with blood levels,
  a. 0.5-1.5 g/l → ataxia, slurring of speech, drowsiness
  b. 1.5-3.0 g/l → stupor
  c. > 3.0 g/l → coma
  d. fatal dose ~ 320 g, which may produce blood levels ≤ 7.6 g/l
- management is largely supportive

▪ ***Methanol***

- methanol itself is non-toxic, however its metabolite ***formic acid*** produces,
  1. profound metabolic acidosis
  2. inhibits cytochrome oxidase → ***lactic acidosis***
  3. retinal damage ± blindness
- as little as 4 ml may lead to ***blindness***, 30-250 ml may be fatal
- the clinical features of formaldehyde poisoning are essentially identical
- not reproducible in animal models as most readily metabolise formate to CO_2 & H_2O
- later discovered this pathway is also present in humans but requires ↑ ***folinic acid***
- ∴ in suspected methanol O/D → Rx with folinic acid, then folate

- clinical features,
    1. often asymptomatic for 12-24 hrs
    2. nausea, vomiting, abdominal pain
    3. headaches, disorientation, vertigo
    4. blurring of vision, blindness > 24-72 hrs
       - may be permanent
    5. fixed, dilated pupils, coma death

- biochemistry,
    1. profound ***metabolic acidosis***
        - often severe for clinical appearance
    2. high ***osmolar gap***
    3. raised serum methanol

- ***ineffective therapy*** includes,
    1. gastric lavage - absorption is rapid & usually complete by presentation
    2. activated charcoal

- specific therapy includes,
    1. ***haemodialysis***
        - indicated if > 30 ml ingested
          - serum methanol > 0.3 g/l (**0.03%**)
          - severe metabolic acidosis
        - high levels may be seen in chronic alcoholics (≥ 1.6 g/l) without signs of intoxication, due to ethanol inhibition of methanol metabolism
        - dialysis should be continued until plasma levels < 0.1 g/l
    2. ***IV ethanol***
        - alcohol dehydrogenase has ~ **20x** the affinity for ethanol cf. methanol
        - acts as a ***competitive substrate*** at plasma levels ≥ 1.5 g/l
    3. 4-methylpyrazone
        - inhibits action of alcohol dehydrogenase, ∴ formate production
        - 10 mg/kg / 250 ml N.Saline over 45 mins, q12h
    4. folinic acid
        - theoretically may increase the metabolism of formic acid, however doses required for significant effects are > 2000x normal plasma levels
    5. fluids & electrolytes
        i. acid-base status, osmolar gap
        ii. hyperkalaemia
        - monitor q2h early in treatment & treat in standard manner

Ethylene Glycol

- metabolised to glycolic acid → glyoxylic acid & oxalic acid
- the former is converted to ***glycine*** and enters the citric acid cycle, with ***thiamine*** as a cofactor
- the later is excreted through the kidney as ***calcium oxalate***
- this may precipitate in the proximal tubules and produce acute renal failure
- clinical features,

1. often asymptomatic for 8-12 hrs
2. nausea and vomiting
3. headache, visual blurring, nystagmus
4. stupor, seizures & coma
5. pulmonary oedema
6. cardiac arrhythmias
7. acute renal failure > 48 hrs post-ingestion

- biochemical findings,

1. high anion gap metabolic acidosis
2. high osmolar gap
3. ***hypocalcaemia***
4. hyperoxaluria, calcium oxalate crystals in the urine

- management,

1. fluids & electrolytes
   i. acid-base status, osmolar gap
   ii. hyperkalaemia
   iii. hyponatraemia
2. ***alkaline diuresis***
   - theoretically to reduce ***calcium oxalate*** precipitation and ARF
   - N.Saline + mannitol ± bicarbonate
     ± acetazolamide
3. ***haemodialysis***
4. IV ethanol
   - effective at levels ~ 1.3-2.0 g/l
   - increases the elimination half-life from 3 hrs to ~ 17 hrs
   - recommended with > 0.5 g/l serum level
     > 0.25 g/l in symptomatic patients
5. 4-methylpyrazone
   - 10 mg/kg / 250 ml N.Saline over 45 mins, q12h
   - inhibition of alcohol dehydrogenase

Antihistamines

- produce a mixture of,
    1. CNS excitatory & depressant effects
        - central ***anticholinergic*** action - see later
    2. myocardial depression
        - ***quinidine***-like effects

- clinical features,
    1. nausea, vomiting, dry mouth
    2. headache, drowsiness
    3. agitation, tremors, ataxia, delerium, halucinations
    4. seizures, coma
    5. hyperthermia
    6. tachycardia, hypotension, pulmonary oedema, shock

- management,
    1. ABC
    2. IVT
    3. gastric lavage
    4. repeated oral ***charcoal***
    5. physostigmine
        - may reverse CNS effects, however use is controversial
    6. cooling if hyperthermic

Carbamazepine

- structurally related to tricyclics, however toxicity is not similar
-

Carbon Monoxide Poisoning

- ***Toxicity***

  a. avid binding of CO to Hb ~ **250x** that for O_2 → L.shift of HbO_2 curve

  b. vasodilatation

  c. stimulation of chemoreceptors

  d. cellular hypoxia
     - CO also binds to ***cytochrome oxidase***, however affinity of O_2 ~ 8x that of CO

  NB: complete clinical picture ***not*** explained by above,
  effects may result from action as a ***cellular messenger*** cf. NO

- ***Severity***

  a. ***mild*** **< 30%** COHb
     - symptoms - headache, nausea, vomiting
     - signs - vasodilatation (>10%)
       - no neurologic or CVS dysfunction
     - R_X - admit if COHb > 20%
       - F_IO_2 = 100% until COHb < 5%
       - symptomatic therapy
       - CVS monitoring if pre-existing disease

  b. ***moderate*** **~ 30-40%** COHb
     - symptoms - headache, nausea, vomiting
       - fatigue, drowsiness, weakness
     - signs - vasodilatation
       - ***no*** neurologic or CVS dysfunction
       - dyspnoea on exertion
     - R_X - admit
       - F_IO_2 = 100% until COHb < 5%
       - symptomatic therapy
       - CVS & acid-base monitoring

  c. ***severe*** **> 40%** COHb or CVS/CNS dysfunction
     - symptoms - above plus dyspnoea, confusion
     - signs * neurologic ± CVS dysfunction
       - tachycardia, tachypnoea
       > 50% respiratory failure, seizures, coma
       > 70% rapidly fatal
     - R_X - F_IO_2 = 100%
       - ***hyperbaric*** $\mathbf{O_2}$ if available
       - CVS & acid-base monitoring

Blood COHb	Clinical Features
< 5%	• normal
5-10%	• smokers
10-20%	• headache, mild dyspnoea
20-30%	• increasing headache, dyspnoea • ***admit*** to hospital
30-40%	• further increasing headache, dyspnoea • irritability, confusion • nausea & vomiting
> 40%	• visual disturbance, severe headache • tachycardia, tachypnoea, dyspnoea
40-50%	• cerebral hypoxia, syncope
50-60%	• coma, convulsions, respiratory failure
70-80%	• rapidly fatal

- ***Delayed Complications***

1. diffuse cerebral demyelination
   - gradual neurological deterioration with ***polyneuropathy***
2. dementia
3. parkinsonism
4. late coma ~ 1-4 weeks following initial hypoxic insult

NB: frequency ~ 2-10% of patients
N-acetyl-cysteine, may reduce the frequency of late onset complications

- ***Management***

• the elimination ***half-life*** of COHb,

a. room air $t_{½\beta}$ ~ 4 hrs
b. F_IO_2 = 100% $t_{½\beta}$ ~ 40-90 min
c. hyperbaric O_2 $t_{½\beta}$ ~ 30 min (2.0 Atm.)

NB: if there is no impairment of ***consciousness***, then hyperbaric O_2 is not indicated

Central Anticholinergic Syndrome

NB: toxic dose for ***atropine*** child ~ 10 mg
adult ~ 100 mg * but wide variability

- commonly involved drugs,
  a. atropine
  b. hyoscine
  c. propantheline
  d. methylbromide
  e. benzhexol
  f. benztropine - eg. accidental ingestion
  g. anti-ACh effects of ***tricyclics***, or antihistamines

- ***Clinical Features***

a.	fixed ***dilated pupils***	- ↑ IOP
b.	dry mouth	
c.	flushed, dry skin	- unable to sweat
d.	cardiovascular	- tachycardia, tachyarrhythmias - hyper, then ***hypotension***
e.	CNS	- agitation, delerium, excitement - disorientation, hallucinations - ***hyperpyrexia***, disordered thermoregulation - seizures, coma
f.	GIT	- reflux, vomiting - gastric stasis, ileus
g.	GUS	- urinary retention
h.	respiratory	- tachypnoea, stertorous respiration

NB: ΔΔ use of ***cholinergic eyedrops*** for D_x no miosis → anti-ACh
miosis → neurologic

- ***Treatment***

  a. ABC - supportive
  b. physostigmine 1 mg in cases of coma (controversial)

Chloral Hydrate

- drug levels,
  a. therapeutic 20 mg/kg
  b. toxic 100-150 mg/kg
  c. lethal > 10 g

- a halogenated hydrocarbon → CCl_3 — $CH(OH)_2$
- rapid GIT absorption
- high first pass metabolism, rapidly metabolised to ***trichlorethanol***
- enzyme inducer, metabolism increased with ethanol use

NB: tolerance, dependence, and withdrawal syndromes are common

Features

a. cardiovascular - malignant and resistant ***ventricular arrhythmias***, SVT
   - hypotension
   - sensitization of the myocardium to catecholamines
   - ≤ 30% of severe cases have SVT or ventricular tachyarhythmias

b. neurological - profound respiratory depression
   ± coma

c. GIT - irritation
   - ***hepatitis***

Treatment

a. supportive

b. gastric aspiration and lavage

c. repeated ***charcoal*** administration ± mannitol NG
   - no data for repeated charcoal

d. b-***adrenergic blockade*** for arrhythmias
   - propranolol ~ 0.5 mg IV + 1-2 mg/hr
   - esmolol ~ 0.5 mg/kg stat, rpt x1
   - lignocaine
   - amiodarone

e. charcoal haemoperfusion

Colchicine Poisoning

- occurs within 3-6 hrs of toxic ingestion and may be fatal within 24 hrs
    a. toxic dose ≥ 6-10 mg
    b. fatal dose ≥ 20 mg

- side-effects of ***normal*** dosage include,
    a. nausea, vomiting, diarrhoea
    b. agranulocytosis, thrombocytopaenia
    c. impaired B_{12} metabolism

- ***Toxic Features***

a.	GIT	- mouth pain, sore throat, nausea, vomiting - profuse watery diarrhoea, abdominal pain - GIT haemorrhage, colic, tenesmus
b.	skin	- rashes, toxic epithelial necrolysis
c.	renal	- anuria, bladder spasm, ? toxic nephritis
d.	neurological	- ***peripheral neuritis***, ascending paralysis - convulsions, respiratory arrest
e.	cardiac	- hypotension

- ***Treatment***

    a. respiratory and cardiovascular support - ABC
    b. gastric lavage, repeated activated charcoal, and cathartics
    c. morphine for cramps, diarrhoea etc.
    d. ?? B_{12} / folinic acid

Cyanide Toxicity

• CN^- combines with cytochrome oxidase Fe^{+++} effectively paralysing cellular respiration
• lethal dose of hydrocyanic acid ~ 50 mg, cf. ingested cyanide salt ~ 250 mg
• poisoning may also occur with ***amygdalin*** toxicity, a cyanogenic glycoside found in the kernels of almonds, apricots, peaches & plums

a. large doses are associated with rapid death, usually within 1-15 mins
b. moderate doses usually result in death within 4 hrs

▪ *Clinical Features*

a. tachypnoea, high V_M
b. agitation, confusion, convulsions, coma
c. vomiting
d. hypotension, tachycardia
e. breath smells of "bitter almonds"

▪ *Metabolism*

• CN^- ions have 4 fates,

1. 60-70% ***enzymatically*** converted → ***thiocyanate***
   - catalyzed by ***rhodanese*** in the liver and kidneys
   - requires thiosulphate and B_{12} as cofactors
   - rate limiting factor is the availability of endogenous ***thiosulphate***
2. combination with MetHb → ***cyanmethaemoglobin***
3. combination with hydroxocobalamin → ***cyanocobalamin***
4. combination with tissue ***cytochrome oxidase*** → ***toxicity***

- ***Treatment***

• aimed at the formation of MetHb and detoxification of CN^-

1. supportive measures
   i. ***oxygen*** should be administered
   ii. potentiates the effectiveness of sodium nitrite & thiosulphate (? mechanism)
   iii. removal of contaminated clothing / washing skin
2. ***dicobalt edetate***
   - chelating agent with higher affinity for CN^- than cytochrome oxidase
   - give in 2 divided 300 mg doses, with 50 ml 50% dextrose between doses, due to risk of ***angioneurotic oedema***
   - only use if ***definite*** history of cyanide exposure
3. sodium thiosulphate ~ 150 mg/kg over 15 mins
   $\rightarrow SH^-$ ions necessary for the formation of ***thiocyanate***
4. sodium nitrite ~ 5 mg/kg over 3-4 mins
   - reduces HbO_2 to ***MetHb***
   - competes with cytochrome oxidase for CN^- ions
   aim **~ 25%** [metHb] is optimal for R_X
5. amyl nitrite inhalation - achieves ~ 5% MetHb which is inadequate
   - may however be used as interim measure in emergency
6. hydroxocobalamin ~ 5-10 mg slowly IV $\rightarrow$ ***cyanocobalamin***
   - LIGW states required dose ~ 50 mg/kg (~ 3000 ampoules)
   - not effective in acute toxicity cf. above agents

NB: normal metabolism will remove ~ 50% of CN^- within 1 hour

$\therefore$ if patient is stable, conscious & oriented, observation for 1-2 hrs is appropriate

Digoxin Toxicity

Def'n: toxic level ³ **2.6** nmol/l (> 2.0 µg/l)

- ***Predisposing Factors***

a. increased ***cardiac sensitivity***
   i. acute hypoxia
   ii. electrolyte disturbances
      - ↓ K^+, Mg^{++} → altered receptor binding
      - severe ↑ K^+, Ca^{++}
   iii. respiratory alkalosis
   iv. myocardial ischaemia & ? AMI
   v. increased sympathetic tone
   vi. elderly
   vii. DC cardioversion

b. toxic ***serum levels***
   i. overdose - accidental, iatrogenic
   ii. renal failure
   iii. drug interactions
      - quinidine, quinine
      - verapamil
      - amiodarone
      - diuretics - K^+-wasting
      - spironolactone
      - erythromycin, tetracycline - ↓'d bacterial metabolism

Clinical Features	
Acute Toxicity	Chronic Toxicity
• arrhythmias • nausea & vomiting • confusion, coma, seizures • hyperkalaemia	• arrhythmias • anorexia, nausea, vomiting • visual disturbance • confusion

• the incidence of arrhythmias is ***dose dependent***,

a. 2.2 nmol/l ~ 10%

b. 3.3 nmol/l ~ 50%

c. 4.4 nmol/l ~ 90%

NB: → ventricular ectopy, ventricular bigeminy
ventricular tachycardia, bidirectional ventricular tachycardia
increased atrial rate
conduction blockade, especially AV

■ ***Mechanism of Toxicity***

a. excessive Na^+/K^+-ATPase inhibition →
   - hyperkalaemia
   - increased ICF Ca^{++} → - conduction block
     - ***afterdepolarisations***
   - decreased ICF K^+

b. increase in central vagal & sympathetic tone

c. stimulation of ***area postrema*** → GIT effects

■ ***Management***

a. supportive measures are usually sufficient for - sinus bradycardia
   - PAT
   - junctional tachycardia

b. atropine or ventricular pacing for - SA or AV block
   - severe sinus bradycardia

c. phenytoin, lignocaine, or Fab fragments for - PVC's, ventricular bigeminy
   - bidirectional VT, VT, VF

d. glucose/insulin/HCO_3^- for - hyperkalaemia

e. Fab fragments
   - Fab dose (mg) ~ ingested dose (mg) x 67 *acute
   - Fab dose (mg) ~ serum level (nmol/l) x 3 x wt. *chronic
   - ingested dose ~ level (nmol/l) x wt. x 5.6(l/kg) x 0.0078

f. decreased GIT absorption
   i. ***activated charcoal*** or cholestyramine ↓ enterohepatic circulation
   ii. emesis, lavage for acute ingestion ? maybe

Digoxin Antibodies

- purified digoxin specific antibody derived from sheep, cost ~ $110 / 40 mg
- cleaved to leave the F_{ab} fragment → ***less immunogenic***
- rapid, extensive distribution into the ECF
- rapid renal elimination of Ab-digoxin complexes
- produces control of,

a.	GIT symptoms	~ immediate
b.	bradyarrhythmias	~ 30-60 min
c.	hyperkalaemia	~ 60 min
d.	tachyarrhythmias	~ 4 hrs

- criterea for use in digoxin toxicity,

1. life-threatening toxicity
2. failed conventional therapy
3. negative skin test for hypersensitivity to Ab

- complications occur ≤ 1% and include,

1. hypersensitivity
2. skin rash, urticaria
3. angioneurotic oedema
4. serum sickness

Heavy Metal Intoxication

▪ *Iron Poisoning*

• elemental iron content of principal preparations are,

a. gluconates ~ 12%
b. sulphates ~ 20%
c. fumarate ~ 33%

• ingestions are described as,

1. nontoxic < 20 mg/kg (< 1.5g / 70 kg elemental iron)
2. mild ~ 20-60 mg/kg
3. severe > 60 mg/kg

NB: serum levels > **60 µmol/l** are usually associated with toxicity (N: 13-32 µmol/l)

• poisoning occurs frequently in paediatric age groups
• clinical features relate to direct ***corrosive*** properties, and are divided into 4 stages

1. 0-6 hrs post-ingestion
   - nausea, vomiting, abdominal pain, diarrhoea
   - ***haemorrhagic gastritis***, intestinal necrosis, perforation & peritonitis
   - hypotension, hypovolaemia & haemoconcentration
2. 6-12 hrs post-ingestion
   - often clinically appear to be improving and severity of overdose underestimated
3. 12-24 hrs post-ingestion
   - ***systemic signs*** of toxicity appear
   - metabolic acidosis, hepatic failure, renal failure, shock
   - fever, seizures, coma
   - haemorrhagic complications
4. 1-2 weeks hrs post-ingestion
   - intestinal scarring & obstruction

• management,

1. supportive measures
2. ***desferrioxamine***
   - iron-specific chelating agent → 1g binds ~ 85 mg elemental iron
   - administered both ***enterally***, to reduce absorption, and ***parenterally*** to complex circulating iron, which is then excreted via the kidney
   - gastric lavage ~ 2g/l water + 5g / 50 ml post-lavage
   - IV dose for severe toxicity ~ 5 mg/kg/hr (350 mg/70 kg/hr) ≤ 80 mg/kg/day maximum

- ***Barium***

a. severe rapid ***hypokalaemia*** ± hypomagnesaemia
   - reduced membrane K-permeability by direct ***channel blockade***

b. GIT - nausea, vomiting & diarrhoea

c. NMJ / CNS - muscle ***fasciculations***
   - seizures, tremor, paralysis, coma
   - can initiate or potentiate synaptic transmission

d. CVS - arrhythmias, bradycardia, CCF

NB: R_X gastric aspiration and lavage
Dimercaprol
acid diuresis
haemodialysis for severe intoxication

- ***Copper***

a. GIT - profuse vomiting, diarrhoea
   - oesophagitis, gastritis, mucosal haemorrhage
   - hepatic necrosis, haemolysis

b. CNS - convulsions, coma

NB: R_X gastric aspiration and lavage
demulcent (milk, paraffin)
analgesics
Penicillamine 2g/day or Na^+/Ca^{++}-EDTA

- ***Gold***

a. skin - pruritis, rashes, contact dermatitis, photosensitivity, purpura

b. GIT - stomatitis, colitis, toxic hepatitis

c. Haem - thrombocytopaenia, aplastic anaemia, agranulocytosis

d. GUS - haematuria, proteinuria, nephrotic syndrome

e. CNS - peripheral neuritis, encephalitis

NB: R_X gastric aspiration and lavage
Dimercaprol 3-5mg/kg q4h IM
N-acetylcysteine IV (proven *in vitro* chelator)

- ***Lead***

a. GIT - thirst, metallic taste
- burning abdominal pain, V&D, melaena

b. CVS - hypotension, oliguria, shock

c. chronic - anaemia, *basophilic stipling of RBCs
- abdominal pain, constipation
- *blue gum line, *lead-line on XRays
- convulsions, encephalopathy, dementia, neuropathy

NB: R_X gastric aspiration and lavage
$NaHSO_4$ 30g, both cathartic and inactivator
chelators Dimercaprol 3-5mg/kg q4h IM
Penicillamine or Na^+/Ca^{++}-EDTA

- ***Arsenic***

a. GIT - severe gastroenteritis, NV&D which may be bloody
- severe abdominal pain
- hepatic failure at 1-3 days

b. CVS

i. acute - hypotension from hypovolaemia, fluid loss
- haemolysis

ii. chronic - CCF and arrhythmias

c. CNS

i. acute - seizures & coma

ii. chronic * predominant form in chronic toxicity
- headache, dizziness, cramps, paralysis

d. GUS - renal failure at 1-3 days

e. MSS - Mees' lines in nails, hyperpigmentation
- palmar/plantar hyperkeratosis, superficial BCC's

NB: R_X cf. lead intoxication

- ***Manganese***

a. lethargy

b. Parkinsonian features, coma

NB: R_X gastric aspiration and lavage
?? EDTA ?? Levodopa

- ***Mercury***

  a. rapidly absorbed through the skin and mucosa

  b. GIT - thirst, metallic taste
  - severe abdominal pain, vomiting, bloody diarrhoea, colitis
  - ashen discolouration of the mouth, stomatitis

  c. CVS - hypovolaemic shock

  d. chronic - GIT above & loose teeth, salivation, blue gums
  - tremor, weakness, mental change
  - dermatitis, acrodynia
  - anaemia
  - nephritis

  NB: R_X gastric aspiration and lavage
  Dimercaprol 5mg/kg in first 2 hrs, then 2.5mg/kg/d for 10/7
  Acetylpenicillamine 250 mg qid

- ***Silver***

  a. GIT - mouth pain, salivation, diarrhoea, vomiting

  b. CNS - convulsions, coma

  c. blue-black skin discolouration

  d. methaemoglobinaemia

  NB: R_X gastric aspiration and lavage
  $NaHSO_4$ 30g, both cathartic and inactivator

Antidotes to Heavy Metals	
Dimercaprol	• bismuth, gold, mercury, lead
Penicillamine	• copper
$NaHSO_4$	• barium, silver
Na^+/Ca^{++}-EDTA	• copper, lead

Heroin Overdose

1. CNS depression
2. respiratory depression
3. pulmonary oedema
   i. neurogenic
   ii. secondary to sepsis
   iii. quinine & other "cutting" substances
4. aspiration pneumonitis
5. acute cor pulmonale - talc pneumonitis
6. hypotension
7. ECG changes
   - ST/T wave changes
   - 1° HB
   - long QT syndrome
   - VT (?quinine)
8. acute cardiomyopathy
9. SBE
10. rhabdomyolysis
    i. pressure necrosis | compartment syndrome
    ii. direct drug | impurity toxicity
11. hyperkalaemia
12. acure renal failure
    - ATN
    - myoglobinuria
13. hepatitis B, C, D, HIV, CMV
14. opportunistic infections - CMV pneumonia, PCP, fungi, etc.

Lithium Toxicity

- peak serum concentrations occur **~ 2-4 hrs** post-ingestion
- long $t_{½\beta}$ ~ 8 hrs, with predominantly ***renal excretion***→
    1. ~ 30-60% is excreted after 12 hrs
    2. oliguria & dehydration potentiate toxicity

- therapeutic plasma levels ~ 0.6 - 1.2 mmol/l
    a. side-effects ≥ 1.5 mmol/l *ie. narrow safety margin
        i. nausea, malaise, fine tremor, weakness
        ii. polyuria, thirst - also with chronic toxicity
            - ***nephrogenic DI***, polyuria
        iii. ***hypothyroidism***, goitre
    b. minor toxicity < 2.0 mmol/l
        i. vomiting, diarrhoea
        ii. slurred speech, blurred vision, ataxia
        iii. coarse tremor, confusion & fasciculations
    c. severe toxicity ≥ 2.0 mmol/l
        i. nausea, vomiting, diarrhoea
        ii. ataxia, tremor, hyperreflexia, extensor spasms, confusion, seizures, coma
        iii. potentiation of sedatives and muscle relaxants
            - ***flaccid paralysis***, coma and cerebral oedema occur > 3.0 mmol/l
        iv. hypotension, syncope, cardiac failure, arrhythmias (? hypokalaemia)
            - refractory ventricular tachycardia, bradycardia or asystole
        v. nephrogenic DI, polyuric renal failure

    NB: ***chronic toxicity*** usually presents as ***thyroid*** or ***renal*** dysfunction,
    acute toxicity usually presents as ***neurologic*** or ***cardiac*** dysfunction

- ***Investigations***
    a. serum lithium level 0.5-1.0 mmol/l therapeutic
        1.3-2.0 mmol/l toxic
        2.0-3.0 mmol/l severe toxicity
    b. hyponatraemia
    c. hypokalaemia - may be "normokalaemic" with total body deficit
    d. ECG - T wave depression/inversion
        - VE's, sinus bradycardia

- ***Treatment***

a. gastric lavage

b. maintain ***euvolaemia***
   - saline loading & enhanced diuresis *per se* is of ***no value***
   - alkalinisation of urine - $NaHCO_3$, acetazolamide

c. indications for ***dialysis***
   i. plasma level > 4.0 mmol/l
   ii. plasma level ~ 2-4 mmol/l + deteriorating clinical status
   ~ 2-4 mmol/l + acute renal failure
   iii. extrapolated time to level < 0.6 mmol/l > 36 hrs
   - CVVHD effective but ***slow*** 2° to large V_{dSS}

d. β-adrenergic blockers for severe tremors

e. ***no*** useful effect from
   i. diuretics - frusemide (may worsen toxicity)
   - spironolactone
   ii. KCl
   iii. activated charcoal

Monoamine Oxidase Inhibitors

- ***tranylcypromine*** and ***phenylzene*** are the commonly used agents
- ***moclobamide*** is a more recently introduced agent
- selective for MAO_A and therefore has minimal pressor effect in conjunction with ***tyramine***

Clinical Features

a. fixed, widely ***dilated pupils***

b. excitement, agitation, delerium, ataxia, seizures

c. pyrexia, tachycardia, hypotension, diaphoresis

d. muscle rigidity, opisthotonus, trismus

e. metabolic acidosis, rhabdomyolysis

NB: these may be ***exacerbated*** by,

i. sympathomimetic amines
ii. pethidine *not other opioids
iii. theophylline
iv. tyramine containing foods/drugs

Management

1. supportive
2. gastric lavage
3. activated charcoal
4. β-blockade - providing hypovolaemia is not present
   - may require close monitoring
5. dantrolene ~ 2.5 mg/kg q6h for 24 hrs
   - has been used for muscle rigidity & hyperthermia

Mushroom Poisoning

- only ~ **50** of 2000 species are poisonous to man, 90% of these from the genus ***Amanita***
- milder poisoning occurs with varieties which contain either,
    a. atropine → narcosis, seizures, hallucinations
    b. muscarine alkaloids → excess secretions

- severe poisonings occur with,
    1. *Gryomitrin esculenta*
    2. *Amanita phalloides*

▪ ***Gryomitrin Esculenta***

a. N,V&D, often bloody diarrhoea, severe abdominal pain
b. liver failure
c. seizures, coma & death in 15-40% of severe cases
d. due to ***monomethylhydrazine***
e. management
    i. supportive
    ii. IV pyridoxine hydrochloride ~ 25 mg/kg

▪ ***Amanita Phalloides***

a. GIT irritability due to toxin ***phalloidin***
    - occurs 6-12 hrs post-ingestion
    - abdominal pain, N, V and watery diarrhoea
b. hepatic, renal and cerebral damage due to ***alpha-amanitin***
    - occurs 24-48 hrs post-ingestion, often after resolution of GIT symptoms
    - grossly elevated LFT's, prolonged INR
    - elevated creatinine / urea
    - ***encephalopathy*** follows progressive hepatic and renal failure
c. fatal in ~ 50% of cases with ingestion of 50 g (≥ ***3 mushrooms***)
d. management
    i. gastric lavage & repeated activated charcoal
    ii. ***penicillin G*** ≤ 10^6U/kg/d
        - specific ***antitoxin*** effect and enhances urinary excretion
    iii. ***plasmapheresis*** → ↓ mortality from 80% to 12%
        - α-amanatin is highly bound to plasma proteins
    iv. liver transplantation

Organophosphate Overdosage

- OGPs phosphorylate the ***esteratic site*** of the enzyme
- ***aging*** occurs over next 12 hrs & inactivation becomes ***irreversible***
- new enzyme synthesis requires 1-3 weeks
- ***carbamates*** combine reversibly at the anionic site, lasting up to 12 hrs for the insecticides

▪ *Clinical Features*

1. muscarinic
   - i. ***miosis***[§], lacrimation
   - ii. ***bradycardia***[§], junctional rhythm, peripheral vasodilatation, sweating
   - iii. bronchorrhoea, bronchospasm, pulmonary oedema
   - iv. salivation, colicky abdominal pains, diarrhoea
   - v. urinary incontinence
2. nicotinic
   - i. muscle ***fasciculation***[§], followed by ***paralysis***
   - ii. sympathetic ganglia stimulation
     - initially → ↑ HR/BP
     - later → ganglionic paralysis, exacerbating bradycardia/hypotension
3. mixed- CNS effects, anxiety, tremor, convulsions, coma

NB: ≡[T] cholinergic over-stimulation [§] most characteristic signs

▪ *Delayed Peripheral Polyneuropathy*

- due to CNS tissue esterase phosphorylation
- rapid onset of distal, symmetrical ***sensorimotor polyneuropathy***
- onset ~ 2-5 weeks post-exposure
- early onset motor paralysis developing 1-4 days post-exposure has also been described
- may require up to 18 days mechanical ventilation

▪ *Monitoring*

a. erythrocyte "true" cholinesterase - more sensitive for ***chronic*** OGP exposure

b. plasma "pseudo" cholinesterase - acute OGP or carbamate poisoning

- levels reduced markedly & usually < **30-50%** with onset of symptoms
- during recovery phase, may have return of muscle power with ≥ 20% enzyme activity
- RBC esterase levels return after ***5-7 weeks*** & pseudocholinesterase after 4-6 weeks

- ***Treatment***

1. ***decontamination***
   - treating staff must wear gloves ± respirators
   - discard clothing, wash skin with soap & water
   - gastric aspiration & lavage
2. supportive R_X - O_2, IPPV, IV fluids, etc.
3. ***atropine*** - 1-5 mg every 5 mins until control PNS → ***HR* > 60 bpm**
   - *failure to produce anti-ACh effects is diagnostic of poisoning
   - ***ineffective*** against neuromuscular paralysis
4. ***pralidoxime*** - 1-2 g slowly IV, within 24 hrs of poisoning
   ± infusion 0.5 g/hr (or 1-2 g q4h)
   - plasma levels better maintained by infusion, $t_{½\beta}$ ~ 1-2 hrs
   - more effective against ***nicotinic*** symptoms, not useful for ***carbamate*** poisoning
   - may actually ***worsen carbamate*** poisoning, due to weak anticholinesterase activity
   - does not cross the BBB, ∴no use in CNS symptoms
   - one large comparative study showing ***no improvement*** in outcome

- ***Classification***

a. latent poisoning
- plasma cholinesterase activity ≥ 50%
- no clinical manifestations

b. mild poisoning
- fatigue, headache, dizziness
- N,V&D, abdominal cramps
- sweating, salivation, chest tightness
- plasma cholinesterase activity ~ 20-50%
- PAM 1g IV, Atropine 1mg s/c
- good prognosis

c. moderate poisoning
- miosis, fasciculations
- generalized weakness, unable to walk, difficulty speaking
- plasma cholinesterase activity ~ 20-50%
- PAM 1g IV
- atropine 1-5mg IV q5m[§]

d. severe poisoning
- miosis, fasciculations, coma, flaccid paralysis, no light reflex
- profuse sweating, salivation and bronchorrhoea
- plasma cholinesterase activity ≤ 10%
- PAM 1-2g IV ± infusion 0.5g/hr
- atropine 1-5mg IV q5m[§]
- IPPV & CVS support
- fatal if untreated

NB: [§]***atropine*** until control of salivation / sweating, or, flushing & mydriasis occur, aim for ***HR > 60 bpm***

Paracetamol Poisoning

▪ ***Pathogenesis***

• principal route of metabolism in the liver ~ **85%**

a. glucuronidation ~ 55%

b. sulphation ~ 30% → both excreted by the kidney

c. P-450 MFO **~ 5-8%** → ***N-acetyl-p-benzoquinoneimine***
- normally conjugated with ***glutathione*** and then excreted by the kidney
- toxic intermediate, binds to sulphydrly containing proteins resulting in acute hepatic ***centrilobular necrosis***

• increased susceptibility to toxicity with,

1. overdose & saturation of normal conjugation
   - ≥ 140 mg/kg → ***zero order kinetics*** (≥ 10 g / 70 kg)
   - ≥ 25g / 70kg → usually fatal
2. hepatic glutathione depletion[§]
3. induction of P-450 MFO system[§]

NB: [§]both of the later occur in ***chronic alcoholism***
→ these patients may develop toxicity with chronic "normal" usage

▪ ***Clinical Features***

a. nausea & vomiting

b. abdominal pain & tenderness

c. pallor

d. coma - unusual, unless other drugs or late presentation

e. liver dysfunction * late, usually ≥ 24 hours
- ~ 60% of non-treated above "treatment line" show severe liver damage at 3-5 days
- **~ 5%** progress to ***hepatic failure***, encepalopathy, coma & death

f. uncommon complications
   i. renal failure - ATN ± papillary necrosis
   ii. cardiac failure
   iii. pancreatitis

- ***Treatment***

a. gastric lavage

b. activated charcoal (100g) & mannitol (500 ml 20%)

c. ***N-acetyl-cysteine***
   - dosage → 150 mg/kg/200 ml D_5W over 15 min, then
     50 mg/kg/500 ml D_5W over 4 hrs
     100 mg/kg/1000 ml D_5W over 16 hrs
   - total dose → ~ 300 mg/kg/24 hrs
   - actions → - increases ***glutathione*** levels
     - increases detoxification, "glutathione substitute"
     - antioxidant
   - in fulminant hepatic failure, dose ~ 150 mg/kg/24 hrs until encephalopathy resolves
   - this equates to 1 x 10g ampoule / day / 70kg patient

d. other therapies
   i. supportive therapy
   ii. l-methionine - substitiute for NAC
   - 2.5g q6h for 4 doses
   iii. haemoperfusion
   iv. liver transplantation

- ***N-Acetyl-Cysteine Indications***

a. paracetamol ingestion ≥ 150 mg/kg (10.5g/70kg)

b. plasma level

> 1300	µmol/l (200 µg/ml)	at 4 hrs
> 800	µmol/l (120 µg/ml)	at 10 hrs
> 300	µmol/l (50 µg/ml)	at 12 hrs
> 200	µmol/l (30 µg/ml)	at 15 hrs

c. within ***36 hrs*** of ingestion
   - most effective within 8-10 hrs of ingestion
   - even if given after onset of encephalopathy, still lowers ***mortality***

- ***Side Effects NAC***

- ADRAC records show 9 reactions over 30 yrs
- none of these had high risk blood levels → ***anaphylactic response***

1. rash, pruritis occur most commonly
2. angio-oedema, bronchospasm, hypotension, N & V (occur less commonly)

NB: 2° ***histamine*** release ~ 9%

- ***Prognosis With NAC***

a.	none	~ 75% severe liver damage ~ 60% mortality
b.	within 10 hrs	- low incidence of liver failure ~ 1% mortality
c.	between 10-36 hrs	- 50% liver damage - 40% mortality

NB: the degree of encephalopathy and coagulopathy show ***no correlation*** with the timing of the overdose and subsequent teatment

- ***Poor Prognosis***

1. drug levels in the high toxic range
2. late presentation
3. plasma bilirubin > 120 µmol/l at day 3-5
4. INR > 2.2

Paraquat Poisoning

▪ *Clinical Features*

• organs affected early include,

1. lung‡
2. liver‡ ‡also affected ***late***
3. kidney
4. adrenals
5. brain

• nausea, vomiting & abdominal pain occur early
• signs of ***renal & hepatic*** dysfunction develop within 1-3 days & are usually ***reversible***
• pulmonary oedema occurs within 24 hrs of ingestion
• followed after 1-2 weeks by progressive pulmonary fibrosis
• pulmonary effects are similar to those of O_2 toxicity → ***"fibrosing alveolitis"***
• this is ***non-reversible*** and is the common cause of death
• severe toxicity presents with multisystem failure → lung, kidney & hepatic
± cardiac, adrenal & cerebral

▪ *Metabolism*

• herbicide with rapid GIT absorption and slow ***renal excretion***, $t_{½}$ ~ 24 hrs
• during the first 24 hrs there is active & selective uptake by,

type II pneumocytes > type I pneumocytes > endothelial cells

• this occur even against a concentration gradient, and plasma levels fall reciprocally
• uptake is reduced by hypothermia and decreased VO_2
• mechanism of toxicity believed to be,

1. inhibition of ***superoxide dismutase***
   → ↑ O_2 free radicals and NADPH/NADH depletion
2. single electron, cyclic reduction-oxidation, forming ***superoxide radicals***
   - superoxide is nonenzymatically transformed to ***singlet oxygen***
   - produces ***lipid hydroperoxides***, which are unstable in the presence of ***trace metals***
   - these subsequently form lipid-free-radicals

• the reaction rate is enhanced by,

a. high paraquat levels
b. high F_IO_2
c. Fe^{++}
d. low NADPH states
e. high BMR or body temperature

- plasma levels ≥ 1.0 µg/ml are almost always fatal
- prevention is best achieved by,
    1. restricted sale
    2. adequate ***labelling*** and ***education***
    3. emetics may also be added to the formulation

Treatment

NB: without treatment, ***mortality*** **~ 85-100%**
∴treat ***all*** cases aggressively & early

1. gastric lavage
2. absorbents
    i. charcoal
        - one study showing equally efficacious to Fuller's earth

    ii. ***Fuller's earth***
        - specific binder, paraquat is inactivated on contact with soil
        - LIGW states only 5-10% of paraquat absorbed from GIT in 24 hrs
        - 1000 ml 30% solution, 300 g/l, followed by 200 ml 20% mannitol
        - definitely require ***laxative*** due to risk of constipation/obstruction
        - subsequently q2h - 15% solution, 150 g/l + mannitol q4h
        - monitor biochemistry for electrolyte disturbances
3. cathartics ~ 200 ml mannitol 20%
   ~ 100 ml sorbitol 70%
4. haemoperfusion[§] - limited to use within the first 12 hrs
   - may be some improvement if started early for severe cases
5. minimise lung injury
    - titrated to minimal F_IO_2
    - desferrioxamine - decreases Fe^{++}
    - steroids of ***no use***
    - ? hypothetical - 6-7 Å molecule to block lung uptake

NB: [§]LIGW states haemodialysis, haemoperfusion and peritoneal dialysis are ***ineffective*** for paraquat removal

Quinine / Quinidine Poisoning

• quini***d***ine is the ***d***extrostereoisomer of quinine, and has all of the pharmacological actions of this agent → antimalarial, antipyretic, oxytocic
• however, its actions on the ***myocardium*** are far more potent than quinine

NB: → ***cinchonism*** visual disturbance, headache, tinnitus/deafness
N&V, abdominal pain, rashes

i. toxic dose ³ **4g**
ii. fatal doses usually ³ **8g**

• quinine is frequently used to lace ***heroin*** → combined poisoning

a. CNS
- fever, headache, excitement, confusion
- vertigo, nystagmus, blindness, tinnitus, deafness
- convulsions, coma, respiratory failure

b. CVS
- hypotension (2° α-blockade), negative inotropy
- paradoxical ***rate rise*** with AF (vagolysis)
- occasional VT, torsade de pointes, cardiac arrest

ECG
- ↑ ***QRS prolongation*** proportional to dose
- SA/AV node blockade, bundle branch block
- polymorphic VT

c. skin
- rashes, purpura, dermatitis, erythema multiforme
- jaundice (G6PD deficiency)

d. eyes
- diplopia, toxic amblyopia, scotomata, tunnel vision
- photophobia, night blindness, distorted colour vision
- extraocular ophthalmoplegia
- mydriasis, retinal oedema, optic disc pallor

e. allergic
- Stevens-Johnson syndrome (erythema multiforme major)
- haemolytic anaemia, thrombocytopaenia
- angioneurotic oedema

- ***Treatment***

a. gastric lavage

b. repeated charcoal and purgatives

c. correct biochemistry * hyperkalaemia & hypocalcaemia potentiate toxicity

d. respiratory and cardiovascular support
   - may require PA catheter, pacing, rarely IABP

e. agents useful in the treatment of ***ventricular tachyarrhythmias*** caused by quinidine,
   i. sodium lactate
   ii. glucagon
   iii. catecholamines
   iv. magnesium sulphate

f. toxic amblyopia - Na-nitrite
   - nicotinamide
   - stellate ganglion blockade

Salicylate Overdose

- inhibits many enzymes including,
    a. cyclooxygenase - platelet > endothelial
    b. ***oxidative phosphorylation***
    c. Kreb's cycle - succinate dehydrogenase
       - α-ketogluarate dehydrogenase
    d. hyaluronidase

- the uncoupling in oxidative phosphorylation results in,
    a. increased heat production
    b. glycogenolysis → early hyperglycaemia
    c. increased energy requirement → late ***hypoglycaemia***
    d. increased ***lactate*** production, liberation of FFA's and ***ketogenesis***
       → ***metabolic acidosis***

- produces central respiratory stimulation, in addition to the ↑ VO_2 and CO_2 production
    → the net effect being a ***respiratory alkalosis***
- ***hyperpyrexia*** may occur if sweating decreases due to excessive dehydration

- the therapeutic level is 150 - 300 µg/ml (2200 µmol/l)
- toxicity and serum levels correlate ***poorly*** but usually ≥ 350-500 µg/ml
    1. maximal therapeutic doses ~ 4-6g/d
    2. toxic dose ≥ 10g
    3. fatal doses are usually ≥ 30g

- GIT absorption is usually rapid and within 1 hr
- large single doses may delay gastric emptying and prolong absorption for up to 24 hrs
- displays ***dose-dependent kinetics***, ie. half-life increases with larger doses,
    a. 300 mg → 2.5 hr
    b. 1000 mg → 5-7 hrs
    c. 4000 mg → **15-30 hrs**

- small changes in plasma pH significantly alter ***free fraction***,
    pH ~ 7.4 → 7.2 free fraction ↑ 2x

- ***Clinical Features***

a. neurological
- altered mental state, confusion
- agitation, tremor, seizures, coma (esp. children)
- tinnitus, deafness
- hyperthermia
- Kussmaul breathing

b. metabolic
- respiratory alkalosis
- metabolic acidosis
- ↑ anion gap ∝ ↑ lactate & ketones
- fluid & electrolyte loss, esp. K^+
- early hyperglycaemia, later hypoglycaemia

c. GIT
- nausea, vomiting and epigastric pain
- liver dysfunction, usually mild
- gastritis & haemorrhage

d. haematological
- platelet dysfunction → ↑ SBT
- ↓ Factor VII → ↑ INR

- ***Treatment***

a. gastric lavage - avoid alkalis

b. ***activated charcoal*** ~ 8g/g of salicylate
   - repeated q2h → * decreases $t_{½\beta}$ from 24-30 hrs to **< 4 hrs**

c. fluid & electrolyte replacement - glucose to avoid hypoglycaemia

d. hyperventilation & bicarbonate
   - aimed at correction of respiratory & metabolic acidoses respectively

e. Vit.K for coagulopathy

f. forced alkaline diuresis - $NaHCO_3$ ± acetazolamide → pH > 7.5
   - may worsen acidaemia & increase ***free fraction***, ∴ check AGA's
   - salicylate excretion is only marginally increased at urine pH > 7.5
   - excretion ***is not*** enhanced by the use of diuretics
   - complications of fluid overload, pulmonary oedema, electrolyte disturbance
   - really of marginal benefit

g. cooling measures

h. anticonvulsants prn

i. ***haemodialysis***
   i. clinically severe intoxication
      - coincident pulmonary oedema, acute renal failure, coma
      - acidosis unresponsive to R_X
   ii. salicylate level > 750 µg/ml (range: 500-1000 µg/ml)

Strychnine

- fatal dose ~ 15-30 mg
- produces ***glycine*** receptor blockade on ***post-synaptic*** inhibitory neurones
- similar effects cf. ***tetanus*** (tetanospasmin TT)

→ prevents glycine release from ***presynaptic*** terminal

- ***Clinical Features***

a. increased muscle tone
b. extensor spasms
c. respiratory paralysis
d. seizures
e. lactic acidosis
f. hyperthermia
g. rhabdomyolysis

- ***Management***

1. support respiration
2. maintain CVS status
3. control spasms
4. prevent seizures

NB: normal excretion / detoxification is rapid, ∴***no*** specific therapy required
prognosis is good providing patient supported for 6-12 hrs

Theophylline Toxicity

- ***Clinical Effects***

a. GIT
- transient motility depression
- nausea and vomiting with toxicity

b. CNS
- general stimulation, increased arousal
- antagonism of benzodiazepine depression
- respiratory centre stimulation and ↑ V_M
- vasomotor stimulation, vasoconstriction, ↑ MAP and HR
- stimulation of ***vomiting centre***

c. CVS
- positive inotropic & chronotropic effect
- ↑ CO and $CMRO_2$
- direct vasodilatation ? reflex from baroreceptor stimulation
  → central effects predominate
- potentiates effects of β-adrenergic agonists

d. RS
- bronchodilatation (5-20 µg/ml)
- ↓ histamine release
- ↑ V_M

? improved mucociliary transport

e. renal
- ↑ RBF/GFR ∝ ↑ CO & MAP
- direct depression of tubular reabsorption → ***diuresis***

f. metabolic
- hyperglycaemia, hypercalcaemia
- hypokalaemia, hypomagnesaemia, hypophosphataemia
- ***lactic acidosis*** proportional to severity of toxicity
- respiratory alkalosis
- rhabdomyolysis

- toxic doses are usually ≥ 10 mg/kg
- in severe intoxication, the overall ***mortality* ~ 10%**
- hepatic clearance becomes saturated → ***zero order kinetics***
- effective plasma half-life, $t_{½β}$ ~ 8-30 hrs
- blocks both ***adenosine receptors*** and ***phosphodiesterase III***
- plasma levels and clinical features correlate reasonably well

Plasma Level		Clinical Features
µmol/l	µg/ml	
30-110	5-20	• therapeutic range
> 200	> 36	• tachyarrhythmias in chronic toxicity
> 500	> 90	• tachyarrhythmias in acute toxicity
> 500-800	> 90-145	• ***seizures***

- plasma levels should be monitored 2-4 hourly until level plateaus
- indications for ***ICU admission***,

a.	> 220 µmol/l	(**40 µg/ml**)	- chronic toxicity - elderly or child
b.	> 275 µmol/l	(**50 µg/ml**)	- adult with acute toxicity

▪ ***Treatment***

a. gastric aspiration and lavage

b. ***charcoal*** and mannitol via NG tube * repeat q2h

c. haemoperfusion
   - effective in removing systemic theophylline
   - ***no evidence*** that it reduces morbidity / mortality

d. plasmapheresis ? better than haemoperfusion

e. supportive therapy

i.	CVS	- verapamil, esmolol, propranolol
ii.	GIT	- ranitidine, metoclopramide * avoid cimetidine & phenothiazines (↓ Cl & epileptogenic)
iii.	CNS	- phenobarbitone * phenytoin is ***ineffective***

▪ ***Indications for Extracorporeal Techniques***

a.	severe clinical toxicity	- refractory arrhythmias - refractory seizures - refractory vomiting	
b.	serum level	> 350 µmol/l in acute > 220 µmol/l in chronic	(LIGW: > 550 µmol/l)

c. severe hepatic/cardiac/respiratory disease and level > 220 µmol/l

Tricyclic Overdose

NB: → ***hot*** as a hare
dry as a bone
red as a beet
blind as a bat
mad as a hatter

severe toxicity occurs at doses **> 1000 mg** (70 kg)

• most complications occur ***within 1 hour*** of admission and are almost never seen if patient remains alert with a normal ECG for over an hour
• however, complications may occur up to 6 days after ingestion (when severe)
• ***anticholinergic*** effects may slow GIT transit and absorption
• avid tissue binding → large V_{dSS} ~ 10-50 l/kg
• ***hypoalbuminaemia*** and ***acidaemia*** increase the free drug fraction & toxicity
• increasing plasma pH from 7.38 to 7.5 decreases free fraction by ~ 21%
• mechanism of effects includes,

1. ***anticholinergic*** effects
2. ***quinidine-like*** effects
3. blockade of ***catecholamine reuptake***

- ***Clinical Effects***

a. CVS
- postural hypotension
- prolonged QT_C and RAD
* some argue evidence for ↑ QT_C minimal
- tachyarrhythmias: AF, SVT, VEB's, VT, VF
- ↑ ***QRS duration***, ↑ PR interval, AV block
- ↓ ***VF threshold***
- acute congestive failure

b. CNS
* ***central anticholinergic syndrome***
- respiratory depression
- nystagmus, ataxia, dysarthria
- choreoathetosis, myoclonic jerks
- extensor plantars
- ***seizures***, coma

c. metabolic
- hypothermia | hyperthermia
- hypokalaemia, metabolic acidosis
- rhabdomyolysis

- ***Monitoring***

  a. blood levels correlate ***poorly*** with CNS / CVS toxicity

  b. if maximal limb lead QRS > 0.10s at 6 hrs then monitor for 24 hours
     - correlates with blood level > 3.7 µmol/l & severe intoxication

  c. seizures & ventricular arrhythmias may occur up to 6-24 hours post-ingestion

- ***Treatment***

  a. supportive therapy

  b. drug absorption / elimination
     i. gastric lavage (up to 24 hrs)
     ii. ***activated charcoal*** - repeated administration
     iii. sorbitol / mannitol

  c. CNS toxicity
     i. airway support / protection as required
     ii. control of seizures - diazepam or thiopentone
     + ***phenytoin***
     - seizures worsen acidaemia & CVS toxicity, ∴control promptly
     iii. physostigmine may reduce central depression
     - lasts ~ 30-60 min and has no effect on CVS toxicity
     - contraindicated if seizures or bradycardia are present

  d. CVS toxicity
     i. phenytoin, magnesium, or lignocaine for ventricular arrhythmias
     ii. ***alkalinisation*** may decrease cardiotoxicity
     - hyperventilation & bicarbonate
     iii. DCCV for VT - low energy (50J)
     iv. temporary pacing wire - torsade or CHB

  NB: dialysis is ***unhelpful*** due to large V_{dSS} and high lipid solubility
  repeated charcoal is of probable benefit

Specific Antidotes	
paracetamol	• N-acetylcysteine
methanol, ethylene glycol	• ethanol • 4-methylpyrazone
cyanide	• dicobalt EDTA • Na-thiosulphate • B_{12}
carbon monoxide	• 100% F_IO_2 • hyperbaric oxygen
organophosphates	• atropine • pralidoxime
paraquat	• Fuller's earth • activated charcoal • ? plasmapheresis
α-blockers	• α-agonists
β-blockers	• β-agonists • glucagon
calcium channel blockers	• $CaCl_2$
benzodiazepines	• flumazenil
opioids	• naloxone
warfarin	• vit.K, FFP
heparin	• protamine
digoxin	• Fab-digoxin fragments
Amanita phalloides	• penicillin