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Critical Care: Common Poisons

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CRITICAL CARE: COMMON POISONS

INTRODUCTION

Emergency department and intensive care unit (ICU) doctors commonly encounter patients who have:

- taken an overdose of a therapeutic drug
- abused an illicit drug
- **OR** been exposed to a toxic agent.

These can be intentional with suicide attempts/drug abuse or unintentional. This booklet aims to review the epidemiology of poisoning, the clinical findings and laboratory data that may assist the clinician in recognizing a toxidrome (symptom complex of specific poisoning) or identify the specific cause, as well as describe a rational and systematic approach to the poisoned patient.

I will then go into detail of the pathophysiology and specific management of topical poisons that are commonly encountered in a critical care setting. The spectrum of poisonings is too wide and vast to possibly cover all of the drugs and toxins in one booklet. Illicit drugs have recently been covered in an UKZN FMM and therefore is not within the scope of this booklet.

DEFINITION

Overdose: when a patient takes more than the therapeutic dose of a drug. (4)

Self-poisoning: self-exposure of a patient (either by ingestion or inhalation) to enough of a substance that has the significant potential to cause harm. Self-poisoning episodes are intentional or unintentional, and are further classified as fatal or nonfatal. (5)

Parasuicide: occurs with intentional self-poisoning, which is nonfatal. The World Health Organization's (WHO) definition of parasuicide is “An act with nonfatal outcome, in which an individual deliberately initiates a nonhabitual behaviour that, without intervention from others, will cause self-harm, or deliberately ingests a substance in excess of the prescribed or generally recognized therapeutic dosage and which is aimed at realizing changes which the subject desired via the actual or expected physical consequences”. (5)

Suicide: same as the parasuicide definition, except that death has occurred from the event. (5)

Poisons: a substance that cause harm to organisms when an adequate amount is absorbed, inhaled or ingested. (6)

Toxin: a natural type of poison that is produced within living cells or organisms. However, in some scientific research, toxins is used to describe any poison, and then toxins produced by a living source are called ‘biotoxins’ or ‘natural toxins’. (6)

EPIDEMIOLOGY

Poisoning is a common cause for morbidity and mortality globally. The 2012 WHO data revealed that approximately 190 000 people died globally from unintentional poisoning. More than 80% of these deaths took place in low- and middle-income countries (LMICs). In 2012, the unintentional poisoning caused the loss of more than 10.7 million years of healthy life (disability adjusted life years, DALYs). (7) The mortality rate for unintentional poisoning in 2020 for South Africa according to the WHO, is 1.5 deaths/ 100 000 population. (8)

Suicide is a global phenomenon and it in indicated that for each adult who died by suicide, there may have been > 20 others attempting suicide. (9) Suicide was the 18th leading cause of all deaths worldwide in 2016 at 1.4%, 79% of the suicides occurred in LMICs. Chemicals account for a substantial number of these deaths, with a significant quantity of deaths thought to be due to intentional self-poisoning with pesticides, up to 370 000 deaths each year. Pesticide related suicides predominantly occur in the rural areas of LMICs. (7) During 2019 the self-harm category made it into the 10th position of the top 10 causes of death in South Africa for both sexes and all ages, with 23.5 deaths/ 100 000 population. (10) Intentional poisoning cases, as part of self-harm, are on the rise in South Africa. Paracetamol is the most commonly ingested drug in intentional self-poisoning. (11)

GENERAL APPROACH

Due to the variation of the presentations of toxidromes, it is difficult to summarise a single uniform method of assessing patients suspected of having one of these conditions. Still, there are common fundamentals in the history, physical examination, and laboratory investigations of the patient suspected of having an overdose or toxin exposure.

Key factors in shared management include:

- Need to stabilise and correct abnormal physiology
- Recognise what the toxic substance is based on history and signs of toxidrome
- Prevent further adverse effects from toxin by decreasing absorption, increasing elimination and administer antidote if possible when indicated.

HISTORY

The patients may not be forthcoming with their presentation history, either because the patient is not willing to volunteer information or due to their decreased level of consciousness. In these scenarios, collateral history may assist with establishing the ingested toxin, although the ingestion may have been unwitnessed. (2)

When witnessed or volunteered intentional ingestion occurs, it is important to estimate the volume of ingestion and the concentration of the substance in order to determine the ingested dose. However, the precision of such estimations is extremely poor. The average volume of a mouthful tends to vary with age and gender, this appears to have wide confidence intervals. (2) The number of tablets ingested, and the drug formulation, in terms of whether that tablet is an extended-release formulation, is also important. (12)

EXAMINATION

If the patient doesn't present with a classic toxidrome, patients should be allocated into different categories based on vital signs, ocular findings, mental status, and muscle tone. This can help to determine the drug or toxin class. (13)

Table 1: Common Toxidromes (13)

Toxidrome	Features	Drug/Toxins	Treatment
Anti-cholinergic	Mydriasis (dilated pupil) Blurred vision Pyrexia Dry skin Flushing Ileus Urinary retention Tachycardia Hypertension Psychosis/Delirium Coma Seizures Myoclonus	Antihistamines Atropine Baclofen Benztropine Phenothiazines Propantheline Scopolamine Tricyclic antidepressants (TCA)	Physostigmine (for critical events) - do not use in TCA overdose because of potential worsening of conduction disturbances TCA overdose: Sodium bicarbonate
Cholinergic "SLUDGE"	***S***alivation ***L***acrimation ***U***rination ***D***iarrhoea ***G***I cramps ***E***mesis Diaphoresis Muscle fasciculations Hypothermia Bronchorrhea Respiratory depression Pulmonary oedema Wheezing Bradycardia Arrhythmias Miosis (constricted pupil) Blurred vision Headache Dizziness Decreased level of consciousness	Carbamate Organophosphates Physostigmine Pilocarpine	Atropine Pralidoxime for organophosphates
Serotonin	Irritability Hyperreflexia Flushing Diarrhoea Diaphoresis Pyrexia Trismus Tremor Myoclonus	Fluoxetine Meperidine Paroxetine Sertraline Trazodone Clomipramine	Benzodiazepine Withdrawal of drug Cyproheptadine
Uncoupling of oxidative phosphorylation	Pyrexia Tachycardia Metabolic acidosis	Aluminium phosphide Salicylates 2,4-Dichlorophenol Dinitrophenol Glyphosate Phosphorus Pentachlorophenol Zinc phosphide	Sodium bicarbonate for severe metabolic acidosis. Patient cooling. Avoid atropine and salicylates. Haemodialysis in refractory acidosis.

INVESTIGATIONS

Routine investigations include arterial blood gas (which reveals pH, anion gap, lactate, ionised calcium, glucose), serum osmolality, renal function, liver function tests (LFT's), full blood count and coagulation profile. Urine dipsticks can reveal urinary pH and presence of ketones. (2, 14) An electrocardiogram (ECG) should be done is any drugs with cardiac toxicity are suspected. (12, 13)

Toxicology screening might confirm the toxin exposure, but it seldom changes the management and the availability of results in LMICs are usually delayed. However, blood concentration of certain toxins is useful, such as (13):

- paracetamol
- salicylate
- phenobarbital
- theophylline
- digoxin
- iron
- lithium

One might consider testing for other common drugs if co-ingestion is suspected. (13) In countries that have the necessary resources, it seems acceptable to institute universal screening for intentional paracetamol overdose patients, especially since the test is relatively low cost. If the test is not done, there is high-risk to the patient in terms of hepatic failure, and possible mortality, if paracetamol toxicity is not discovered. (13, 15) In resource-poor countries, an individualised approach and preventative public health strategies might be more conscientious use of resources. (15)

Three gaps are important in toxicology: the anion gap, osmolar gap, and oxygen saturation gap. (13) Due to multiple causes of deranged anion and osmolar gaps, it is important that the other causes are excluded by appropriate investigations such as blood glucose, blood salicylate concentrations and urinalysis for ketones.(2)

A normal **anion gap** (AG) does not exclude intoxication, because most toxins do not elevate the AG **or** there may be a coexisting diagnosis that decreases the gap. (13)
The AG is primarily used to detect the presence of unmeasured anions in the evaluation of metabolic acidosis. The normal AG depends on serum phosphate and albumin concentrations. (13, 14) Albumin contributes almost the complete value of the AG as the major unmeasured anion. (13)

AG = Na+ – (Cl- + HCO3-)

Normal range = 4 to 12mmol/L. If the AG is 20-29, then a ⅓ won't have a metabolic acidosis and if it is > 30, metabolic acidosis is definitely present. (13, 14)

The K+ can be added to Na+ in the formula, but offers minor benefit. (14) Hypoalbuminaemia, which is common in ICU patients, may cause a falsely normal AG. In hypoalbuminaemic patients, the corrected AG can be used which is (13, 14):
AG + (0.25 X (40-albumin) expressed in g/L

HAGMA results from accumulation of organic acids or impaired H+ excretion.
Causes mnemonic LTKR ("left total knee replacement") (13, 14):

- Lactate
- Toxins
- Ketones
- Renal failure

Toxin causes that are relevant include (2, 14, 16):

- Methanol, Paracetamol, Ethylene glycol, Salicylates, Sympathomimetics

The **osmolar gap** (OG) must be cautiously interpreted due to different ways of measurements of osmolality being done. Measurement by **vapor pressure osmometry** detects ethylene glycol, but doesn't detect ethanol and methanol. The commonest method, **freezing point depression osmometry**, measures all of these solutes. Therefore, the doctors should be aware of the method used by their available laboratory. (13)

OG = Osmolality (measured) – Osmolarity (calculated)
Normal OG = < 10
Osmolality unit**:** mOsm/**kg**. Osmolarity unit: mOsm/**L**

Calculated osmolarity = (2 x [Na+]) + [glucose] + [urea]
Units: mmol/L

Normal range of osmolality: 285 to 295. (13, 17) Potential pitfalls of interpreting OG are the variation in normal ranges, some state it as -5 to 9 mOsm, but some cohorts of patients have a range as wide as -10 to 20 mOsm. (17) There is also a propensity for false negatives and the clinician might underestimate the severity of ingestion of the toxin. Therefore, OG should not be regarded as a guaranteed screening tool. (2) Elevated OG results from accumulation of an abnormal solute (2, 17):

- mannitol
- ethanol/methanol
- ethylene glycol
- sorbitol
- renal failure
- sepsis or shock
- diabetic ketoacidosis
- hyperglycaemia

If the ethanol levels are known, it can be added to the formula as an additional contributor to the OG. The relative contribution of ethylene glycol to the OG is less than other alcohols, due to its smaller molecular weight. (2, 17)

Calculated osmolarity = (2 x [Na+]) + [glucose] + [urea] + [ethanol]
Units: mmol/L

An **oxygen saturation gap** occurs when there is > 5% difference between the saturation calculated from an arterial blood gas and the saturation measured by co-oximetry. Co-oximetry determines oxygen saturation (SaO2), ratio of oxygenated haemoglobin to total haemoglobin (including non-functional or non-oxygen carrying haemoglobin) by detecting the absorption of four different wavelengths, which enables it to directly measure levels of four types of haemoglobin (13):

- oxyhaemoglobin
- reduced haemoglobin
- carboxyhaemoglobin
- methaemoglobin

The calculated oxygen saturation of the blood gas is from the measured oxygen tension using an assumed standard oxygen-haemoglobin dissociation curve. High oxygen saturation gap causes include (13):

- carbon monoxide
- methaemoglobinaemia
- cyanide
- hydrogen sulphide

TREATMENT

<u>Stabilisation</u>
All poisoned patients may present in a life threatening condition and initial stabilisation must be instituted following the advanced cardiac life support (ACLS) guidelines, before directed possible treatments can be employed. (18)

It is not evidence based, but the clinician might consider administering enough sodium bicarbonate to correct a significant metabolic acidosis, especially if it is contributing to depression of cardiac contractility and blood pressure. (18)

Once intravenous (IV) access if achieved in a patient who is unconscious, some institutes give a “coma cocktail” of thiamine (100mg), dextrose (50g), and naloxone (0.2 – 0.4mg). This treatment cocktail can be both therapeutic and diagnostic, but this strategy is not well supported by the available evidence. Thiamine use is safe and inexpensive, and dextrose administration to hyperglycaemic patients is not likely to cause harm. Naloxone can rapidly reverse depressed level of consciousness, respiratory depression, and hypotension induced by opioids, but its administration can lead to acute pulmonary oedema, opioid withdrawal, and seizures. Flumazenil should be used in suspected benzodiazepine overdose cases, an initial 0.2mg of IV flumazenil over 30s, an additional dose of 0.3mg can be given if indicated. (13)

Contact Poison Information Centre

In the event of a confirmed or suspected case of poisoning, the clinician is urged to contact the regional Poison Information Centre for drug information and to help guide management in confirmed cases. (13, 18) The South African centre provides a 24/7 telephonic toxicology consultation service. (19)

Contact number: (0861) 555 777.

Gastric Decontamination

The majority of toxin exposures and poisonings that are managed by ICU occur by ingestion. There are three methods of gastrointestinal tract (GIT) decontamination including two mechanical approaches (emesis, gastric lavage) and the use of activated charcoal.

Emesis (ipecac induced) and **Gastric lavage** (via orogastric tube) are both only useful in patients who present within 1 hour of ingestion and who are fully conscious. (13, 18) Contraindications to emesis and gastric lavage include ingestion of corrosives and petroleum products. Gastric lavage in patients who present within an hour should not be performed if they have vomited extensively or have taken a substance that is rapidly absorbed. Gastric lavage may potentiate material being propelled into the duodenum, thereby increasing the risk of drug absorption. It is suggested that the time limit of gastric lavage may be increased to 12h when the ingested drugs are known to delay gastric emptying (tricyclic antidepressants, opioids, or salicylates), but this is controversial. (13)

Activated Charcoal is a powerful, inert, nontoxic, and nonspecific adsorbent that irreversibly binds intraluminal drugs and interferes with their absorption. It is most effective in binding high-molecular-weight substances. Activated charcoal is usually administered as the sole GIT decontaminating agent. It also is contraindicated in decreased LOC patients and is most beneficial if administered within 1 hour of ingestion. The ideal dose should give a charcoal: drug ratio of 10:1, but the quantity of drug ingested is commonly unknown. (13) Therefore, the typical dose of activated charcoal is 50g in adults and 1 g/kg in children, administered as an aqueous solution. (13, 18)

It can cause significant constipation, so it can be co-administered with a cathartic, a drug that speeds up defaecation. In theory it has the added benefit of facilitating evacuation of the toxic substance, but evidence has not shown a significant decrease in the percentage of drug absorbed. Cathartics are usually magnesium or sorbitol based, and are given with the first dose of activated charcoal to avoid adverse effects (hypernatraemia, hypokalaemia, hypermagnesaemia). (13)

Table 2. Toxins and Drugs not adsorbed by Activated Charcoal (13)	
• Alcohols • Hydrocarbons • Organophosphates & Carbamates • Dichloro diphenyl trichloroethane	• Acids & Alkali • Potassium • Iron • Lithium

Inhibition of Metabolism

Antidote is a substance which raises the limit of the mean lethal dose of a toxin, or that reverses/ minimises the negative effects of a poison. This is the main mechanism of inhibiting metabolism. Some antidotes can be toxic themselves, with significant adverse effects, therefore it should only be used when indicated. (13) The specific antidotes will be discussed under each particular drug sections.

Promote Elimination

Multiple-dose activated charcoal (MDAC) can be a useful way to promote the elimination of toxins that have already been absorbed. It binds drugs that are transported back into the gut lumen from the circulation via the enterohepatic/ enterogastric circulation of drugs. It has limited application to very specific toxins, and could enhances drug elimination significantly. Multiple dosing should be used cautiously in patients with signs of bowel obstruction and an intact or protected airway is essential. It is indicated in patients with a significant ingestion of, phenobarbital, quinine, carbamazepine, dapsone or theophylline. (13)

Haemodialysis is clinically indicated when the projected clearance is expected to be insufficient due to organ dysfunction, the metabolism produces toxic metabolites, or there is delayed toxicity as a characteristic of the intoxication. Haemodialysis is useful for substances that have a low molecular weight, are water soluble, with low protein binding (<70%) and a small volume of distribution (<1 L/kg). It also functions in the correction of associated metabolic acidosis and electrolyte abnormality. Haemodialysis is useful in the early stages post-ingestion of (13, 20):

- methanol
- ethylene glycol
- boric acid
- salicylates
- lithium
- paracetamol (extreme overdose)

SPECIFIC POISON TOXIDROMES

ETHYLENE GLYCOL (EG)

EG poisoning is uncommon, but it remains clinically relevant due to its significant potential for morbidity and mortality. (2, 18) This substance depresses the freezing point of water, and is most commonly used as a de-icing solution or as antifreeze in coolant systems. It is used as a solvent and found in brake and hydraulic fluid, and in household cleaners, such as window cleaner. (2, 18)

Ingestion is the commonest route of exposure for EG and all systemic toxicity and fatalities occur by this route. (21) It is a colourless, viscous liquid with a sweet taste. A bittering agent was added to products that contain more than 10% concentration of EG (or more than 4% methanol), in 1991, in an effort to reduce accidental ingestion (occurs mostly in children). (2, 21) Unintentional and intentional ingestion of products containing EG and methanol is relevant in Africa. The use of home brewed alcohols for entertainment and social purposes is common in the indigenous South African and other African population, the brews may be mixed with EG and methanol to improve their potency and palatability.

(16) An increase of home brewed alcohol preparations occurred in South Africa following the alcohol ban instated as a result of the COVID 19 national lockdown.

The symptoms of poisoning along with the elevated drug concentrations occur 20–30 min following ingestion, whilst the EG concentration peaks at 1–4 h. The highest morbidity effects develop from the metabolites of EG, and not from the actual parent drug. (2, 18, 22)

PHARMACOKINETICS

Ethylene glycol is highly water soluble and not protein bound, distributing evenly throughout the body tissues with a volume of distribution of 0.5–0.8 L/kg. (2, 18) Hepatic metabolism is responsible for 80% of the elimination of EG, while the remainder is eliminated unchanged through renal excretion. Major metabolites are organic acids which are responsible for cellular injury and cause a raised AG. (2, 18)

The metabolic steps leading to the accumulation of glycolic acid (GA) and hence the development of HAGMA, are demonstrated in figure 1. (2, 18) Due to the 3 – 8 hour elimination half-life of EG, the development of HAGMA occurs more than 3 hours following ingestion, and as a result of preferential hepatic metabolism of ethanol, can be even further delayed should co-ingestion occur. (2)

A small amount of glyoxylic acid is converted to oxalate which then precipitates as calcium oxalate crystals. (2)

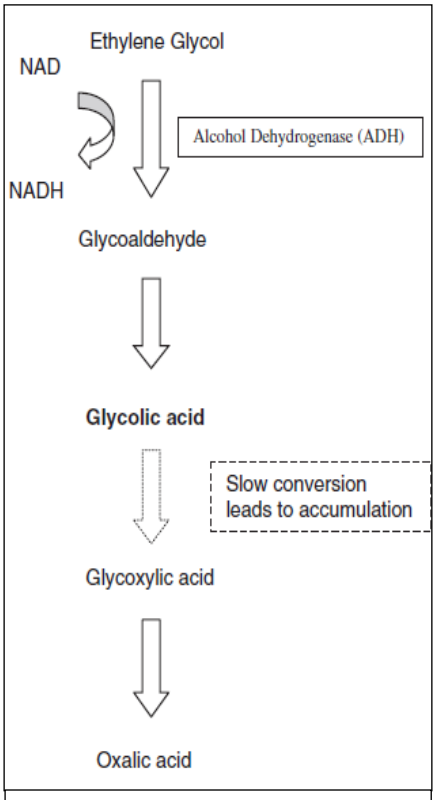

Figure 1: Hepatic metabolism of EG. McQuade et al 2014 (2)

HISTORY

The clinical presentation varies depending on co-ingestion with other toxins and the time delay from ingestion to presentation. The co-ingestion of ethanol may delay the signs and symptoms; and may confuse the interpretation of tests such as the OG. (2) If there is an extended delay between ingestion and presentation to hospital, there is a greater likelihood that more EG would have been metabolized to GA, which would result in severe metabolic acidosis; and therefore, a higher risk of morbidity. (22)

EXAMINATION

The toxicity features are caused by the major metabolites of EG and prompt recognition will expedite lifesaving management. The presentation of EG toxicity is described in three phases, and the phases can overlap (2, 18):

Table 3. Ethylene Glycol Clinical Presentation Phases (2, 18)		
Phase 1	**Phase 2**	**Phase 3**
Central nervous system (CNS)	**Cardiovascular system (CVS)**	**Renal**
0.5 – 12h	**12 – 36h**	**24 – 72h**
• euphoria • slurred speech • ataxia • nausea and vomiting • increased drowsiness • seizures and myoclonic jerks • coma	• tachycardia • hypertension followed by hypotension • tachypnoea • Kussmaul's respirations • congestive heart failure • pulmonary oedema	• progressive renal injury from tubular necrosis • renal failure • haematuria • proteinuria • flank pain • oligo-anuria

INVESTIGATIONS

During the first few hours after ingestion the **OG** is significantly raised. (2, 13) As EG metabolism begins, the OG may decline to near normal, while an HAGMA manifests (Figure 2). To our diagnostic detriment, rare cases have existed where both the OG and the AG have been normal in known EG toxicity patients. (2)

Arterial **blood gas** reveals the HAGMA, and allows for identification of lactic acidosis. Lactic acidosis may distract from a diagnosis of EG poisoning, as it may be misinterpreted as the cause for HAGMA. (4)

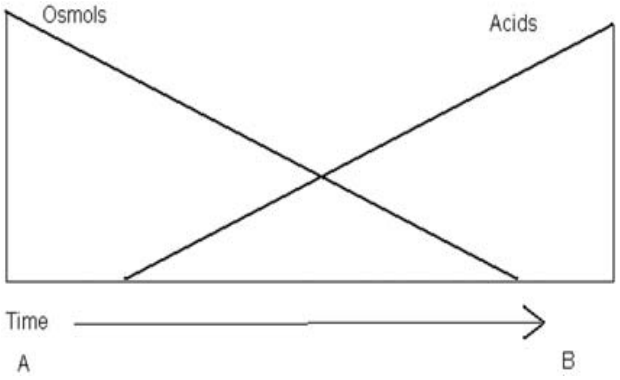

Figure 2: Visual illustration of relationship between OG and AG in EG poisoning. McQuade et al 2014 (2)

The 3 possible mechanisms for an increased lactate are (2):
1.) Metabolites of EG
2.) Concurrent cause, such as tissue hypoxia.
3.) The lactate assay may be falsely increased due to interference from GA, which has a structural similarity with lactate. Certain blood gas machines have shown this effect, such as the GEM Premier 4000 and the Radiometer ABL series.

A decreased **ionized calcium concentration** found on the blood gas may suggest EG poisoning due to the formation of a complex from the oxalic acid and calcium, which occurs > 6h post-ingestion, and can assist in differentiating EG toxicity from methanol toxicity. (2)

Glycolic acid concentration measurement is useful in patients with a delayed presentation, with the likelihood that all of the EG has been metabolized. (2) The GA concentration relates better to the clinical severity, when compared to the EG concentration. (22)

Urine fluorescence should not be used as a screening test, due to its many pitfalls. (2)

Calcium oxalate crystals on urinalysis can be detected in the urine within 4–8 h of ingestion. Detection of these crystals is not specific, but it could support the diagnosis of EG toxicity with other positive investigation results. (2)

The **direct testing** gold standard is gas chromatography, but even in first world countries like the United Kingdom, it is only available at centralized laboratories due to the high expense involved and poor validity of an infrequently executed test. (2) Toxic alcohol analysis is not often carried out by the majority of South African laboratory services in, and if performed, results are only accessible a few days later. (16)

Table 4. Criteria to assist with the presumptive diagnosis of EG poisoning. (18)
A) A history or suspicion of ingesting EG plus any 2 of the following: Arterial pH < 7.3 Serum bicarbonate of < 20 mmol/L OG > 10 mOsm/L Presence of urinary oxalate crystals ***OR***
B) A history or suspicion of EG ingestion within the last 1 hour and OG > 10 mOsm/L

TREATMENT

Stabilisation

Mild to moderate acidosis should be primarily managed by the administration of the antidote. Significant hypocalcaemia may lead to seizures; therefore, levels of ionised calcium should be determined immediately and calcium replaced if necessary. Calcium should only be given intravenously to replace serious calcium deficits, as excessive calcium administration may promote calcium oxalate formation. (18)

Gastric Decontamination

Due to its rapid absorption for the GIT and associated decreased LOC, induced emesis is not recommended. Aspiration or lavage of gastric contents using a nasogastric tube, is only useful if it is done a short while after ingestion. It is questionable whether activated charcoal can absorb EG and it is likely to be of little advantage clinically, but it should be given when it is likely that there is a toxic dose of a co-ingestant. (18)

Inhibition of Metabolism

After initiation of the of supportive strategies, the next important step in the management of this poisoning by the inhibition of metabolism. There are 2 known antidotes, both of these work by inhibiting ADH. (18) The antidote is required when the EG concentration is > 3 mmol/L or an OG > 10 mOsm/L. Some centres use a higher upper limit cut off for the OG reference interval, this has demonstrated a decreased incidence of false-positive results. (2) Antidote administration is also advised for patients with the qualifying criteria in table 4. (16, 18)

Fomepizole is the only antidote for EG poisoning approved by the US Food and Drug Administration (FDA), and due to its high efficacy as an antidote, it is considered standard of care by the Practice Guidelines by the American Academy of Clinical Toxicology. Fomepizole is a potent inhibitor of ADH. The IV loading dose of fomepizole is 15mg/kg, diluted to at least 100ml of normal saline or 5% dextrose and infused over 30 minutes. This next step is initiating an IV maintenance dose of 10 mg/kg every 12 hours for 4 doses. During haemodialysis, the maintenance dosing interval should be decreased to 4 hourly, as fomepizole is dialysable.(18)

Ethanol is a competitive substrate for ADH and has a much higher affinity for ADH than methanol or EG, up to 10 times higher. (16, 18) The endpoint of ethanol administration is to succeed in obtaining a serum ethanol concentration of 10 – 12.5 mg/L (21.7 – 27.1 mmol/L). This concentration is thought to saturate the ADH enzyme, therefore preventing

further metabolism of EG. The loading dose of ethanol is generally 0.6 to 0.7 g/kg. A maintenance infusion must be carefully adjusted based on repeated serum ethanol concentrations (every 1 – 2h). (18) The maintenance infusion will range from 66 to 154 mg/kg/hour. During haemodialysis the dose should be increased up to 3-fold, as ethanol is dialysable. Pharmaceutical grade ethanol can be administered IV as a 10% solution in 5% dextrose. Ethanol can also be given orally; pharmaceutical grade ethanol or alcoholic spirit beverage should be diluted to 20% first in any liquid before administration. Once ethanol treatment is considered, these patients should be admitted and kept in ICU and they may require dialysis more frequently. (18)

Thiamine is administered to prevent the oxalic acid formation by promoting the conversion of glyoxylic acid to α-hydroxy-β-ketoadipic acid, which is a harmless metabolite. The standard dosing is a 100mg thiamine IV given 6-hourly. (18)

Pyridoxine is administered to prevent the oxalic acid formation by converting glyoxylic acid to non-toxic hippuric acid and glycine metabolites. Whether pyridoxine has this effect with EG poisoning is not clear. The standard dosing is 50mg pyridoxine IV given 6-hourly, up to a maximum of 4 doses (or 24h). Excessive doses of pyridoxine given rapidly can cause a toxicity related sensory peripheral neuropathy. (18)

Promote Elimination

A key feature of the treatment protocol is improving the elimination of the unmetabolised EG and of the GA metabolite. (18) **Haemodialysis** is extremely effective in clearing both substances from the blood and the additional benefit of correcting any other metabolic abnormalities. It is indicated in the presence of severe electrolyte imbalance, severe metabolic acidosis (pH 7.25–7.30), renal failure, or significant deterioration of the patient's clinical condition despite best supportive strategies. (18, 22)

In our setting we predominantly use peritoneal dialysis and IV or oral ethanol, due to the limited access to haemodialysis and no supply of fomepizole, due to our resource constraints. (16)

PARACETAMOL

Paracetamol is one of the most commonly used drugs associated with toxin related morbidity and mortality. The reported prevalence of intentional paracetamol overdose in four South African institutions is approximately 25% of intentional self-poisoning cases presenting to their emergency departments. (15, 23-25)

PHARMACOKINETICS

Paracetamol is rapidly absorbed by the GIT, achieves peak plasma levels 1 hour after oral ingestion and is fully absorbed by 4 hours. (3, 12) The immediate-release paracetamol drug preparations have an elimination half-life of 2 – 3h. The extended-release preparations have an increased elimination half-life of up to 12 h and an increased absorption phase. (12)

Hepatic metabolism is primarily responsible for the metabolism of paracetamol; however, the metabolic pathway can differ depending on the blood levels and the age of the patient. Up to 95% of the metabolites are harmless conjugates of glucuronide and sulphate. Glucuronidation is the primary route of metabolism in adults and sulphation is the primary route in young children. (3, 12)

The other 5% of metabolites are toxic, this is n-acetyl-p-benzoquinonimine (NAPQI), which is produced by the hepatic cytochrome P-450 (CYP450) enzymes. When the therapeutic dose of paracetamol is taken, the NAPQI is rapidly detoxified by irreversibly conjugating with the sulfhydryl group of glutathione and eliminated by kidney excretion as mercapturic acid and cysteine conjugates. (3, 12)

With an overdose scenario (right-hand side pathway of figure **3**), the glutathione supply is used up and NAPQI is not detoxified. The NAPQI then attaches to the macromolecules of the hepatocytes, this induces centrilobular hepatic necrosis with sparing of the periportal area. (3, 12) N-acetylcysteine (NAC) restores the glutathione supply, binds directly to NAPQI, and improves sulfate conjugation of paracetamol. (12)

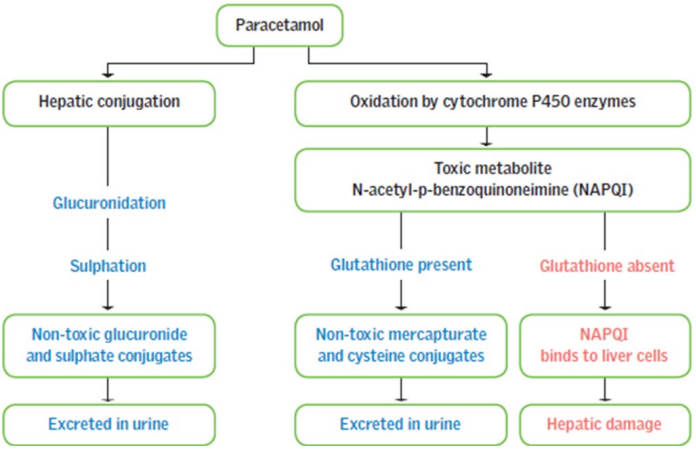

Figure 3: Paracetamol metabolism: therapeutic dose and overdose (3)

HISTORY

The dose of paracetamol with the potential to be hepatotoxic is 150 mg/kg or 7.5 to 10 g in adults and 200 mg/kg in children. However, 4 to 6 g/24 hours can cause injury in high risk patients. (12) The factors that contribute to being **high risk** are listed in table 5. (1, 12)

Table 5. Risk factors for severity in paracetamol overdose (1)

Decreased hepatic glutathione stores	Induction of cytochrome p450 enzymes
Anorexia nervosa	Phenytoin
Bulimia	Carbamazepine
HIV	Rifampicin
Cystic fibrosis	Phenobarbitone
Malnourishment	Chronic ethanol abuse

An **intentional overdose** in adults is done with the aim of self-harm and can be described as a total dose of paracetamol of > 4 g taken over a maximum of 4h. **Unintentional overdose** is an overdose taken without the intent of self-harm, this is commonly due to pain or accidental overdose during chemical intoxication. **Single overdose** (>4 g) is taken all at once, and a **staggered overdose** (cumulative dose of >4 g/24h) is consumption of two or more supratherapeutic paracetamol doses over more than 1-hour. (26)

Intentional overdose accounts for the majority of overdoses. Unintentional overdose patients are more likely to present with a staggered overdose history and to have overdosed on combination drugs (for e.g., paracetamol with codeine). Unintentional paracetamol overdose has a higher mortality compared to intentional overdose. This is due to (26):

- patients may present for the pain related diagnosis and not as an overdose, which will delay NAC treatment
- pattern of staggered overdose, association with older age and alcohol abuse

EXAMINATION

Paracetamol overdose has **four phases** of clinical presentation. (12)

Table 6. Paracetamol Clinical Presentation First Three Phases (12)		
Phase 1	**Phase 2**	**Phase 3**
1 – 24h	**24 – 48h**	**48 – 96h (3 – 5 days)**

• anorexia
• malaise
• pallor
• diaphoresis
• nausea & vomiting
	• Right-upper-quadrant pain
	• Deranged LFT's
	• This occurs despite some of phase 1 symptoms improving
		• Acute liver failure with:
		  ○ hypoglycaemia
		  ○ hepatic encephalopathy
		  ○ deranged LFT's peak: increased total bilirubin, transaminases and international normalized ratio (INR)
		  ○ coagulopathy – could lead to GIT haemorrhage
		• renal failure
		• multi-organ failure (rare: haemorrhagic pancreatitis & myocardial necrosis)
		• sepsis
		• cerebral oedema
		• death

Massive liver necrosis can occur in Phase 3 and leads to **acute liver failure (ALF)** with the associated symptoms. This could escalate to multi-organ failure which is associated with a high mortality rate. (12, 26) Paracetamol overdose is the commonest cause of ALF associated hospital admissions and emergency liver transplantation in the UK. (27) The increase in transaminases can be > 10 000, it tends to be much higher than the increase in total bilirubin, which may assist to differentiate between paracetamol-induced hepatotoxicity and other causes. **Acute renal failure** is secondary to acute tubular necrosis and usually occurs after the onset of ALF, treatment with NAC does not assist in its prevention. (12)

Sepsis risk is due to patients with ALF being immunosuppressed, with increased risk for bacterial and fungal infection. In paracetamol overdose sepsis is associated with worsening encephalopathy. The mortality rate for patients who develop septic shock is 98%. (28)

Encephalopathy begins with euphoria, anxiety, asterixis, then worsens to lethargy, somnolence, coma, and possible death. Encephalopathy and cerebral oedema combined is the most lethal combination of ALF, leading to uncal herniation and death. The encephalopathy should be graded using the West Haven grading system. Encephalopathy which does not progress past grades 1 or 2, has an excellent patient prognosis. The prognosis for liver recovery in patients with grades 3 is 40% and grade 4 is 20%. (28)

Table 7. West Haven criteria for grading mental state in hepatic encephalopathy. (28)	
Grade	**Features**
0	No signs or symptoms
1	Euphoria, anxiety, trivial lack of awareness, impaired performance, decreased attention span, mild asterixis
2	Lethargy, minimal personality changes, subtle personality change, inappropriate behaviour, asterixis
3	Somnolence, confusion, gross disorientation
4	Coma

Phase 4: 5 – 7 days: During this phase patients could fully recover (without chronic liver disease), undergo emergent liver transplantation or they could die. If they fully recover, the renal and liver function tests normalise within a few weeks. Improving transaminases levels may demonstrate recovery or massive hepatocellular necrosis. The massive hepatocellular necrosis will be associated with increased INR, high bilirubin levels and increased ammonia. (12)

INVESTIGATIONS

Hepatotoxicity directly contributes to significant metabolic acidosis, with a contribution from increased lactic acid secondary to global hypoperfusion. (28) A significantly increased lactate on arterial blood gas will assist in swiftly identifying patients who are likely to die from paracetamol-induced ALF. It also could hasten the selection of appropriate patients for liver transplantation. The hyperlactataemia can be due to increased production from multi-organ failure and hypoperfusion or decreased hepatic clearance secondary to significantly impaired hepatic function (> 50% reduction). (29)

Other than the arterial blood gas; bloods should be taken for renal function, LFTs, INR and the full blood count. Paracetamol concentration should be taken at least **four hours** post-ingestion, before four hours the concentration cannot be interpreted because absorption is not complete. (3) A point of care clotting profile might be beneficial, such as a thromboelastogram, especially if patient displays signs of coagulopathy. These include an increased INR, mild evidence of disseminated intravascular coagulation and presence of thrombocytopenia. (28)

TREATMENT

Stabilisation

Hepatic encephalopathy of grades 3 or 4 should be admitted to ICU and intubated for airway protection. As cerebral oedema worsens, the goal is to maintain cerebral perfusion pressure (CPP) above 40 mm Hg to prevent cerebral ischaemia. The intracerebral pressure (ICP) should be invasively monitored if possible and treatment of elevated ICP includes deep sedation and hyperosmolar therapy. (28)

Prophylactic administration of freeze-dried plasma (FDP) in absence of spontaneous bleeding is not advised due to fluid challenges with possible renal failure, and it might mask poor prognosis patients by artificially improving the INR. Proton pump inhibitors and/or H2 receptor antagonists should be commenced to reduce the risk of upper GIT haemorrhage. (28)

Gastric Decontamination

Gastric lavage is only useful if it is performed within 1h of ingestion. However, activated charcoal is the better option for gastric decontamination and is not likely to reduce the efficacy of oral NAC. Activated charcoal is useful beyond 1-hour post-ingestion and decreases the incidence of patients reaching toxic serum levels after ingesting > 10 g of paracetamol and presenting within 24 h. Additionally, activated charcoal can decrease the total amount of NAC that is required and shorten the length of hospital admission. (12)

Inhibition of Metabolism

Treatment with NAC inhibits metabolism into toxic metabolite. NAC is up to 100% effective when administered within the first 8 – 10h, although can be beneficial for up to 24 h post-ingestion and can continue even after ALF is diagnosed.

These effects include (12):

- decreased incidence of hepatic encephalopathy
- enhanced oxygen transport and consumption, with the background of ALF

Table 8. NAC dosing			
Route	Drug preparation	Loading dose	Maintenance dose
Oral (12)	Diluted to a 5% solution in juice	140 mg/kg	70 mg/kg 4-hourly for 17 doses **OR** Until the serum paracetamol level was undetectable **If vomiting occurs:** doses should be repeated and anti-emetic administered
IV (30)	If oral NAC is given IV, a micropore filter is required	200 mg/kg over 4 h	100 mg/kg over 16 h

The IV administration of NAC is preferentially used in patients who cannot tolerate the oral route (due to vomiting), pregnant patients and late presentation of overdose. There is no clear evidence that the oral route is more effective than the IV route. The IV route adverse events include: angioedema, urticaria, bronchospasm and anaphylactoid reactions. (12)

If a single overdose of paracetamol is taken and at least 4 hours have passed since ingestion, NAC can be given according to the timed plasma concentration on or above a single treatment line on the nomogram. A value on or above the paracetamol treatment line indicates at increased likelihood of hepatotoxicity. (3) NAC can be discontinued if the initial plasma concentration is below the treatment line. (12)

NAC should be given despite the position on the nomogram in circumstances where the overdose is staggered or when the exact time of ingestion is unknown. (3) NAC is indicated if serum paracetamol level is > 5 mg/L and the precise time of ingestion is unknown, but it is known to be but less than 24h ago. (12)

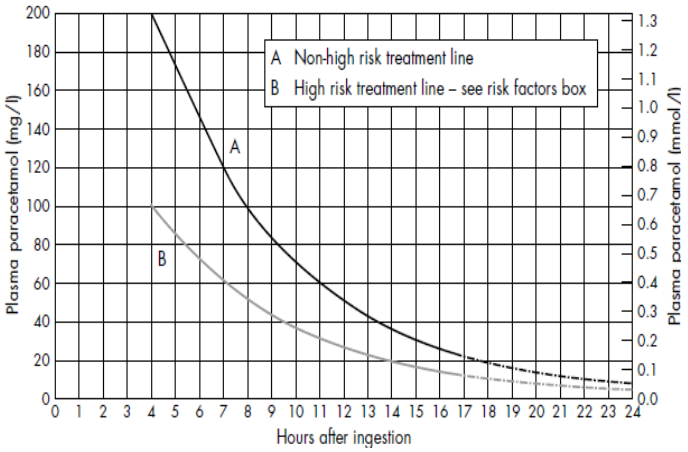

Figure 4. Prescott nomogram for paracetamol overdose treatment (1)

For extended-release ingestion serial paracetamol levels should be taken every 4 – 6 h post-ingestion and plotted on the nomogram. A complete course of NAC is required if any point is above or on the treatment line. NAC is also indicated when there are any signs of hepatotoxicity, even with paracetamol levels are below the treatment line. (12) For **high-risk** patients (discussed under history) NAC should be considered even if the serum paracetamol level falls below the non-high risk treatment line. (1, 12)

Pitfalls of nomogram use include (12):

- paracetamol levels taken < 4h post-ingestion
- late presentations could have lower than detectable concentrations in the blood, even though they may have ingested a lethal dose
- chronic ingestion
- overdose with an extended-release preparation
- inaccurate time of ingestion, even as small as a 1 – 2h difference, can shift the marginal patient above or below the treatment line

The dosing for adults and children should be weight-based and the duration of the loading IV dose should increase from 15min to 1-hour (to minimise adverse effects), some institutes now recommend initial dose to be given over 4 hours. (3, 30)

Patients who present more than 24h post-ingestion, that have symptoms or abnormal test results, should receive NAC for 48 h. With these late presentations, NAC had these benefits (11):

- decreased progression of ALF
- decreased onset cerebral oedema
- less vasopressor use indicated
- less haemodialysis indicated

Promote Elimination

Haemodialysis is indicated to remove paracetamol in patients with high concentrations of paracetamol (serum level >500mg/L OR ingested > 500mg/kg body weight), severe acidosis (metabolic and/or lactic) and decreased level of consciousness (with other causes excluded). This can be greatly beneficial, and with continued supportive care, the patient could fully recover without requiring a liver transplantation.(20, 31-33)

Both paracetamol and NAC are highly dialysable, therefore it is suggested that the NAC infusion rate be more than doubled during haemodialysis. This is considered to be enough to replace its loss during dialysis and achieve similar plasma concentrations to the standard NAC regimen. (32, 33)

Liver Transplant

Paracetamol induced ALF is one of the most common reasons for liver transplantation. A poor outcome is expected in patients with a delayed presentation, grade 3 or 4 hepatic encephalopathy, increased INR, severe acidosis (pH < 7.30), renal impairment, cerebral oedema, and/or presence of sepsis. An APACHE (acute physiology and chronic health evaluation) II score ≥ 15 provides an accurate risk of mortality and helped identify those who might require liver transplantation. The ICU staff may be more familiar with APACHE II, than with specialist liver scores, which may assist in more rapid transfers to liver units of appropriate patients. (12)

King's College criteria (KCC) is a specialist liver score used to determine patients who will most likely die without liver transplantation. Transplantation is considered in those who meet the KCC, while taking their medical condition and psychological assessment into consideration. (26, 28, 29) Most patients who meet the KCC do not undergo transplantation due to the organ not being available, they are too critically ill to undergo a transplantation or their clinical condition significantly deteriorates while waiting for an organ to become available. (29)

Table 9. King's college criteria for liver transplantation in paracetamol associated ALF (28)	
Arterial pH	< 7.3
Or all 3 • **INR** • **Creatinine** • **Encephalopathy**	 > 6.5 > 300 umol/L Grade 3 – 4

BETA BLOCKERS AND CALCIUM-CHANNEL BLOCKERS

PHARMACOKINETICS

Beta-blockers are competitive antagonists of beta-receptors and calcium-channel blockers (CCBs) selectively inhibit the movement of calcium ions through the membrane of cardiac and vascular smooth muscle. (12)

HISTORY

Beta-blocker and calcium-channel blocker overdoses may be the result of unintentional or intentional ingestions, medication errors, new onset renal failure or drug interactions. (34) Clinical features of the blocker overdoses depend on the type of drug, timing of ingestion to presentation, amount of drug taken, history of co-ingestion, and existing comorbidities. The risk of CVS morbidity increases another cardioactive drug is taken simultaneously. (12) The CVS toxicity that occurs with blocker overdoses leads to a high incidence of morbidity and mortality. (34) Most patients will develop toxicity within 4h of ingestion of overdose of beta-blocker and within 6h of CCB. In extended-release preparations toxicity may not be evident for up to 12h. (12)

In terms of the two drug classes, propranolol is the beta-blocker with the most overdoses (12) and amlodipine is the CCB with the most overdoses. (35) These agents can have different specific effects on the CVS. **Specific drug characteristics** (12)**:**

- Acebutolol, betaxolol, pindolol, and propranolol beta-blockers: myocardial membrane stabilizing properties that can cause QRS widening and decreased myocardial contractility
- Verapamil: more negative inotrope effect
- Verapamil and diltiazem: depress the sinus node and slows conduction through the atrioventricular (AV) node
- Nifedipine: more vasodilatory effect

EXAMINATION

Table 10. Clinical findings of Beta-blocker vs CCB overdose (12, 34-36)

System	Signs	Beta-blocker	CCB
CVS	**Hypotension**	Severe, due to decreased inotropy	Severe, due to vasodilation
	Bradycardia	Yes	Yes
	Negative Inotropy	Yes	Yes
	Conduction defects	Yes, AV blocks of different degrees	Yes
	Congestive cardiac failure (CCF)	Yes	No
	Cardiac arrest	Yes	Yes
Resp	**Bronchospasm**	**Yes**	No
	Pulmonary oedema	Yes	Yes
CNS	**Seizures**	Yes	Uncommon
	Lethargy, stupor, coma	Yes	Yes
GIT	**Ileus**	Yes	Yes
Renal	**Acute kidney injury**	Uncommon	Yes
Metabolic	**Hyperkalaemia**	Yes	No
	Hyper/ hypoglycaemia	**Hypoglycaemia**	**Hyperglycaemia**
	Metabolic acidosis	Yes	Yes

Hypo- or hyperglycaemia may be the only specific sign that assists in differentiating between the two types of drugs. (34)

INVESTIGATIONS

Drug blood levels can be measured, but they cannot predict the clinical severity of overdose, and the diagnosis is usually made based on clinical findings. (12) The routine bloods in the general approach are sufficient and an ECG to detect conduction abnormalities and arrhythmias.

TREATMENT

Asymptomatic patients who have taken a potentially toxic dose of drug, defined as anything more than a single therapeutic dose, should be monitored in hospital (not in ICU per se) for at least 24h and gastric decontamination should be considered if they present within 1-hour of ingestion. (12, 36)

Stabilisation

They present with varying clinical severity (34, 36):

- **Asymptomatic:** See above management
- **Symptomatic requiring first line treatments**
  - Fluid resuscitation
  - IV calcium
  - Noradrenaline and/or adrenaline if shock is present
  - Glucagon
  - High-dose insulin therapy (not given as the first or sole treatment)
  - Atropine (for symptomatic bradycardia or conduction disturbances)
- **Refractory to first line therapy**
  - Incremental doses of high-dose insulin therapy (up to 10 U/kg/hr) if evidence of myocardial dysfunction is present
  - Pacemaker (for unstable bradycardia or high-grade AV block)
- **Refractory shock or peri-arrest:** IV lipid-emulsion therapy
- **Cardiac arrest:** Extra-corporeal membrane oxygenation

Calcium supplementation can be given IV after a baseline ionized calcium on arterial blood gas has been obtained. Calcium administration improves the inotropy and blood pressure. (12, 36) Monitor calcium every 2 hours and maintain ionized calcium at 1.25 – 1.75 mmol/L. (36) Beta-antagonism decreases intracellular calcium leading to smooth muscle relaxation and hypotension; calcium administration reverses this by increasing intracellular calcium levels. With CCB overdose the supplemented calcium overcomes inhibited calcium channels. (34) There are two formulations of IV calcium with distinct properties. The amount of elemental calcium is 8.9 mg/ml in a 10% calcium gluconate and 27.2 mg/ml in a 10% calcium chloride solution. The availability of calcium from calcium gluconate is limited until hepatically metabolised, therefore in any hypotensive patients with suspected poor liver perfusion, calcium chloride is preferred. (37)

Table 11. Calcium dosing for CCB overdose (36)

Route	Drug	Loading dose	Maintenance infusion
IV	10% Calcium Gluconate	3g IV over 20min	6 g/hour (24 grams per 1000 mL bag)
IV	10% Calcium Chloride	2 g IV over 20min	2 g/hour (8 grams per 250 mL bag)

Glucagon has a positive inotropic and chronotropic effect which is mediated through adenyl cyclase, increasing cyclic adenosine monophosphate (cAMP) and creating intracellular calcium influx. Clinical effects are noted after a few minutes and its use may preclude the indication for high-dose catecholamine infusion. The diluent of the glucagon

drug contains 2mg of phenol per 1 mg of glucagon and to prevent phenol toxicity, it should be diluted as per table 9. Phenol toxicity can induce hypotension and arrhythmias. (12) Glucagon can cause vomiting. (34)

Table 12. Glucagon dosing (12)			
Route	Drug preparation	Loading dose	Maintenance infusion
IV	Dilution of glucagon in saline or dextrose solution	5 to 10 mg over 1 min	1 – 10 mg/h

High-dose insulin (HDI) therapy has a low level of evidence to support its use, it is also known as an **insulin-glucose infusion** or **hyperinsulinemia-euglycemia therapy.** The evidence suggests a positive inotropic effect with a secondary increase in blood pressure, and a higher survival rate when used in blocker overdose patients, especially if myocardial dysfunction is present. (36)

There are 3 proposed mechanisms of effects of HDI in beta-blocker and CCB poisoning: (1) increased inotropy, (2) increased intracellular glucose transport, and (3) vascular dilatation. Intracellular glucose transport is enhanced by insulin in the myocardium and skeletal muscle, this is considered the mechanism for inotropic effect. Stressed myocardium primarily uses glucose as the preferred energy source, under normal conditions it prefers fatty acid oxidation. Insulin in high concentrations also affects several intracellular mechanisms that contribute to the inotropic effects, many of which involve calcium handling. These inotropic effects occur at the same time as an increasing coronary blood flow, but without an increasing oxygen requirement (unlike catecholamine agents). (34)

HDI is not a vasopressor, the blood pressure improves due to positive inotropic effect, insulin is a vasodilator of the systemic, coronary, and pulmonary vasculature. These vasodilatory effects are due to enhancement of endothelial nitric oxide synthase activity by its effects on a major insulin intracellular signalling pathway. (34) HDI may prove to be superior to glucagon alone in terms of reversal of refractory shock. (12)

Before initiating HDI, the glucose and potassium results must be checked. The potassium should be > 3.5 before commencing therapy. (36) The ease of access to HDI, affordability and minimal adverse effects supports its use. The adverse effects are logical and predictable, and are easily managed with glucose and potassium replacement. HDI has the greatest benefit is used early on in therapy, rather than as a rescue therapy. (34)

Table 13. HDI dosing (36)			
Route	Drug preparation	Loading dose	Maintenance infusion
IV	Regular insulin	1 U/kg	1 U/kg/hr
• Monitor glucose hourly and maintain euglycemia with a glucose infusion • Monitor serum potassium 4 hourly and replace as needed • If the patient is refractory to first line therapy (with myocardial dysfunction), the dose of insulin can be increased up to 10 U/kg/hr to improve inotropy			

The use of **IV lipid-emulsion therapy** has a low level of evidence to support its use when a patient is peri-arrest or has cardiac arrest, the evidence suggests possible haemodynamic improvement. The mechanism of action is believed to be that it mops up lipid soluble drugs from the plasma and therefore prevents further toxicity. Beta-blockers with high lipophilicity include propranolol and labetalol; the CCBs include amlodipine and verapamil. The dose is 1.5 mL/kg of 20% lipid emulsion administered as a bolus, repeated up to two times as required, until clinical stability is achieved, then a maintenance infusion of 0.25 mL/kg/min for 30–60 minutes. (36)

Gastric Decontamination

Induced emesis is not recommended due to the risk of sudden CVS collapse. Gastric lavage only beneficial is within an hour and up to 8h with extended-release drugs. Activated charcoal may be useful within an hour of ingestion. (12)

TRICYCLIC ANTIDEPRESSANTS (TCA)

It is reported that in the United States of America (USA), antidepressants were second commonest cause of overdose related death, analgesic overdose was the first. Most of the antidepressant fatalities were due to TCA overdose. TCAs are indicated is for depression, obsessive-compulsive disorder, migraines, chronic pain syndromes, anxiety and phobia disorders, eating disorders, insomnia, and peripheral neuropathies. Safer antidepressants are now available, such as the selective serotonin re-uptake inhibitors (SSRIs), and this has led to a decreased use of TCAs. TCA overdoses are more likely to cause significant toxicity requiring admission to the ICU, and possible death, when compared to SSRI overdose. (12)

PHARMACOKINETICS

The TCA's act by inhibiting presynaptic serotonin and norepinephrine uptake. They are rapidly absorbed in the GIT and obtain peak plasma concentrations within 2 – 8h. Due to their high lipid solubility, they have a high volume of distribution. They are also highly protein. They undergo hepatic metabolism. In an overdose, TCAs are able to block cardiac fast sodium channels and antagonize muscarinic acetylcholine receptors, peripheral alpha-adrenergic receptors, histamine H1 receptors, and central nervous system GABA A receptors. (1, 38) The sodium channel block is the main mechanism of mortality from TCA overdose. (1)

The clinical picture is worsened by the significant drug enterohepatic circulation and active metabolites of the drug metabolism. Drug kinetics are difficult to predict, even without an overdose, due to the effects of acidaemia, enzyme saturation, and decreased gut motility (anticholinergic effects) which help potentiate drug action. (38) Acidaemia causes unbinding of the drug from proteins, this increases the amount of free drug and contributes to increased toxicity. (12)

HISTORY

Patients who have taken a substantial overdose of TCAs will demonstrate clinical signs within 1-hour. If there are no signs or symptoms by 6 hours post-ingestion, they can be safely discharged. Severe clinical effects, like cardiac toxicity, typically resolve over a 24 – 48h period. Ingestion of a dose greater than 10 mg/kg of a TCA will lead to serious toxicity, while a 20–30 mg/kg dose can likely lead to death. Full neurological recoveries can occur with TCA overdose related cardiac arrest, even in the setting of extended resuscitation (up to 1-hour). (1)

The cluster on anti-cholinergic signs, that are typical with a TCA overdose, can help identify the causative agent in any patient with a depressed level of consciousness patient. The presence of conduction abnormalities on ECG and unconsciousness predict a more severe toxicity, than the cluster of anticholinergic signs alone. (1)

EXAMINATION

The CNS and CVS are the systems that are mostly affected by TCA toxicity. The CNS and CVS manifestations stem from inhibition of neural uptake of norepinephrine and/or serotonin, and the anticholinergic effects, The CVS signs are additionally caused by peripheral alpha-adrenergic blockade and membrane depressant effects of TCAs. (12) For full list of anticholinergic signs and symptoms, please see table 1.

CVS (12):

- Anticholinergic effects
- Hypotension - due to venodilation and decreased myocardial contractility.
- Arrhythmias
- Pulmonary oedema
- Cardiac arrest

CNS (12):

- Anticholinergic effects
- Neurologic deterioration
- Seizures: may be temporary and self-limited, or prolonged and refractory to management

INVESTIGATIONS

An **ECG** will help detect common TCA overdose associated abnormalities (12)**:**

- sinus tachycardia
- prolongation of the QRS, QTc, and PR intervals
- ventricular tachycardia
- atrioventricular blocks
- right bundle-branch block

A limb-lead QRS interval > 0.10s predicts the likelihood of seizures and QRS interval > 0.16s is linked to ventricular arrhythmias. In any suspected poisoning patient with a prolonged QRS, TCA should be considered as the likely cause. ECG monitoring should be continued in symptomatic patients for 48 – 72 h. (12)

The **blood gas** will commonly reveal a metabolic acidosis. The **drug levels** are not required, because of the ability of the QRS duration to predict severity. (12)

TREATMENT

<u>Stabilisation</u>

The goals of initial supportive measures are to detect and manage life-threatening problems. Fluid resuscitation tends to not correct the associated hypotension; therefore, vasopressors are commonly commenced. Adrenaline and noradrenaline can potentially worsen the CVS toxicity, and should only be started after sodium bicarbonate has been given. (1, 12)

Sodium bicarbonate is the mainstay of therapy used to treat the CVS toxicity. (1, 12) The mechanism of action is due to the systemic alkalinisation and hypertonic sodium loading. (1) Serum alkalinisation decreases the fraction of free drug, by preventing it from unbinding from protein with metabolic acidosis. Artificial respiratory compensation of the

metabolic acidosis can be achieved by hyperventilating intubated patients, which would lead to a respiratory alkalosis and increase the pH in that manner. (12)

Table 14. Sodium bicarbonate dosing of 8.4% IV solution (1, 12)		
Route	Loading dose	Maintenance
IV	1–2 ml/kg	1–3 ml/kg every 3 – 5min titrated to clinical response
• Administer via a large peripheral vein, until central venous access is achieved. • Extravasation of sodium bicarbonate can cause significant tissue damage like necrosis, ulceration and/or sloughing at the infiltration site, secondary to chemical cellulitis. • Treatment continues until the QRS interval narrows or serum pH of 7.50 – 7.55 is achieved • Monitor for adverse effect of hypernatraemia, with a maximum acceptable goal of 155 mmol/L • Monitor for adverse effect of hypokalaemia, replace potassium as necessary		

If refractory ventricular arrhythmias occur, then **lignocaine** is the drug of choice. (12) Ventricular tachyarrhythmias resistant to treatment with sodium bicarbonate (with pH 7.50–7.55) should be managed with temporary ventricular overdrive **pacing** or with direct current **cardioversion**. (1)

Seizures should be treated with benzodiazepines and phenobarbital. (1, 12) Phenytoin should not be used primarily, due to its possible interaction with TCAs, so its use should be limited for refractory cases. TCAs can increase the phenytoin drug levels by inhibiting its elimination. Phenytoin has also been linked to increased arrhythmias in TCA overdose, although it is the same class on anti-arrhythmic as lignocaine. (12) Sodium bicarbonate can be used to treat seizures as well (same dosing goals as per table 14), as it limits the amount of TCA crossing into the CNS. Resistant seizures should be managed with deep anaesthetic sedation (propofol) with or without paralysis in ICU. (1) Continuous EEG monitoring is required to guide anti-seizure treatment if muscle paralysis is used. (12)

Limited low-level evidence available that suggests that **glucagon** may be beneficial in refractory cases. Physostigmine is useful for other drug overdoses that cause anti-cholinergic signs, but with TCA overdose there is the risk for seizures and asystole, and should therefore, be avoided. (12)

The use of **IV lipid-emulsion therapy** should sequester the ingested highly lipid soluble TCAs. The evidence is limited to multiple case reports that demonstrate significant clinical improvement in cases of severe TCA toxicity managed with supplementary intralipid administration in addition to the sodium bicarbonate infusion. (38)

All patients with signs of severe toxicity should be admitted to ICU and receive supportive care (including sedation). (1) These patients should remain admitted in the ICU until all therapeutic interventions have been discontinued for at least 12h, they should then be asymptomatic with a normal ECG and normal arterial pH before discharge. (12)

<u>Gastric Decontamination</u>
The preferential method of decontamination is gastric lavage (within 2 h of ingestion) followed by activated charcoal administration. Ipecac induced emesis is likely to cause rapid deterioration in mental status and possible seizures, so this practice should be avoided. (12)

<u>Promote Elimination</u>
There is no role for MDAC, especially due to the anticholinergic-induced ileus which increases the risk of charcoal-induced bowel obstruction. Haemodialysis is not effective due to high lipid solubility and protein binding. (12)

SALICYLATES

Salicylates are common ingredients in a variety of prescription and non-prescription preparations, such as aspirin (also known as acetylsalicylic acid). (12)

PHARMACOKINETICS

Aspirin is rapidly converted to salicylic acid once ingested, and salicylic acid is readily absorbed from the GIT. At **therapeutic doses**, salicylic acid is metabolized by the liver and is eliminated in 2 – 3h and the serum concentration levels are 100 to 300 mg/L. With **toxic doses**, the salicylates are metabolic poisons that negatively affect multiple organ systems by uncoupling oxidative phosphorylation and interfering with the Krebs cycle (also known as the citric acid cycle or the tricarboxylic acid cycle). (12) Uncoupling of oxidative phosphorylation produces metabolic acidosis. This acidosis predicts a more severe toxicity by two mechanisms, firstly, it results in an increase in the unionised salicylate concentration, which then gets transferred into the CNS more easily, this produces an increased CNS salicylate concentration, and leads to worsened CNS toxicity. The second mechanism, is that the acidosis causes decreased renal excretion of salicylates and therefore higher drug concentration in the blood. Salicylates are also known to produce respiratory alkalosis by stimulation of the respiratory centre, this is the more common presentation in adults. (1)

HISTORY

The lethal adult dose is approximately 10 to 30 g or > 35 tablets. With chronic ingestion the half-life of these drugs can be increased to > 20 h, therefore with chronic intoxication, toxicity occurs at lower drug dosage levels, especially in the elderly. The long-term use of these drugs and the use of enteric coated drugs are important. Clinical features of salicylate toxicity occur in most patients once their serum levels are > 400 mg/L. (12)

EXAMINATION

Table 15. Clinical features of different doses (1, 12)

Severity	Dose ingested	Clinical features
Mild	>150mg/ kg	Lethargy Nausea Vomiting Diarrhoea Tinnitus Dizziness Vertigo
Moderate	>250mg/ kg	Tachypnoea Hyperpyrexia Sweating Hypoglycaemia (children are more at risk) Dehydration Ataxia Peripheral vasodilatation Agitation Platelet dysfunction: petechiae, subconjunctival haemorrhage
Severe	>500mg/ kg	Hypotension Metabolic acidosis Renal failure Coagulation disorders with GIT bleeding Pulmonary oedema Coma Seizures Cardiovascular collapse

INVESTIGATIONS

Plasma **salicylate concentration** should be measured at least 4h post-ingestion (similar to paracetamol). With enteric coated tablet ingestion, the drug concentration will be an unreliable guide to the severity of poisoning, as the drug levels could only peak at 12–18 hours post-ingestion, in this scenario the concentration should be repeated every 4 hours until it peaks. (1)

A **blood gas** is an essential investigation and the anion gap should be calculated. Adults who present soon post-ingestion typically have a respiratory alkalosis that progresses to a mixed metabolic acidosis and respiratory alkalosis. Children tend to present with a metabolic acidosis only. (1, 12) Uncoupling of oxidative phosphorylation leads to a HAGMA with an increase in organic acids (including lactic acid and ketoacids). The contribution of salicylic acid to the measured anion gap is minimal. (12)

Renal function tests, coagulation studies and point of care clotting profiles should be done to detect some of the moderate and severe clinical features. (1, 12)

TREATMENT

Stabilisation

Adult patients with a severe metabolic acidosis (pH<7.3) should be given 50 ml 8.4% sodium bicarbonate solution IV. (1)

Table 16. Management based on severity (1)

Severity	Salicylate concentration	Management
Mild	Adults 300–600 mg/L Children/elderly 200 – 450 mg/L	MDAC until concentration peaks Oral or IV fluids
Moderate	Adults 600–800 mg/L Children/elderly 450 – 700 mg/L	MDAC IV fluids Urinary alkalinisation
Severe	Adults > 800 mg/L Children/elderly > 700 mg/L	MDAC IV fluids Haemodialysis

Gastric Decontamination

Patients who have ingested > 125 mg/kg of should be given activated charcoal. For patients that present within one hour of ingestion of more than 500mg/kg, gastric lavage should be considered. (1) Activated charcoal and gastric lavage only useful in acute ingestions, not chronic toxicity. (12)

Promote Elimination

Urinary alkalinisation is easy to achieve and it enhances the elimination of salicylates by **renal excretion**. Urine pH should be checked every 30 minutes with indicator paper with the pH goal of 7.5 – 8.5. Complications of this therapy include (1, 13):

- alkalaemia
- volume overload
- hypernatraemia
- hypokalaemia

The method of urinary alkalinisation in adults is achieved by administering a 1 litre of 1.26% sodium bicarbonate, with the addition of 20 – 40 mmol of potassium to the solution,

over three hours. This then promotes production of an alkaline urine, and the potassium prevents hypokalaemia from potassium loss once an alkaline diuresis is achieved. (1) Sodium bicarbonate given whilst there is a significant hypokalaemia, will not alkalinize the urine, as there will be potassium reabsorption in exchange for hydrogen ion taking place in the distal tubule of the kidney. (13) If the goal pH is not achieved, a bolus of 8.4% sodium bicarbonate may be necessary to achieve this. (1) Achieving an increase in urinary pH from 6.1 to 8.1 results in an > 18-fold increase in renal excretion of salicylates by avoiding non-ionic tubular back-diffusion. This decreases the elimination half-life from > 20h to < 8h. In patients that already have a significant alkalaemia due to their respiratory alkalosis, urinary alkalinization needs to used cautiously and might be contra-indicated, as it will increase the alkalaemia. (12)

The use of **MDAC** is controversial in salicylate poisoning, but it can be used until the plasma salicylate concentration has peaked to prevent delayed drug absorption. (1)

Haemodialysis is indicated in patients with severe signs of toxicity, such as (1):

- pulmonary oedema
- acute renal failure
- seizures
- coma
- refractory metabolic acidosis

Haemodialysis should also be considered in all patients with a drug concentration > 800 mg/l in adults or > 700 mg/l in children/ elderly patients. (1) In chronic toxicity, haemodialysis may be indicated for any symptomatic patient with a drug concentration > 600 mg/L. (12)

ORGANOPHOSPHATES

Organophosphates or carbamates are found in most insecticides. The commonest route of exposure is via ingestion, but the insecticides can also be absorbed through contact with the skin, conjunctiva, and respiratory tract. The emergency department staff can inadvertently become poisoned through contact with the organophosphate poisoned patients. Organophosphate poisoning causes significant morbidity and has a substantial risk of mortality associated with it. (12) Most of the deaths are related to intentional poisonings. The most potent pesticides with the highest risk of toxicity have been banned, this should decrease the associated mortality rate from self-harm associated with intentional ingestions and exposures. (39)

PHARMACOKINETICS

Organophosphates are rapidly absorbed and irreversibly inhibit cholinesterases. The two principal cholinesterases are **acetylcholinesterase** (also known as red blood cell [RBC] cholinesterase), which is found in the red blood cells and nerve endings synapses, and **pseudocholinesterase** (also known as plasma cholinesterase and butyrylcholinesterase), which is found in the serum and liver. Both of these cholinesterases are inhibited by organophosphates and carbamates poisoning. The clinical effects of their toxicity are due to the inhibition of acetylcholinesterase and the cholinergic syndrome which occurs due to the accumulation of acetylcholine (Ach). The clinical features of acute toxicity occur within 12 – 24 h of exposure. Organophosphates are lipophilic and easily cross the blood brain barrier into the CNS. (12)

Table 17. Differences between organophosphate and carbamate (12)		
	Organophosphate	Carbamate
Inhibits cholinesterase	Irreversible	Reversible
CNS toxicity	Yes	No
Extended treatment required	Yes	Not needed due to the rapid improvement of symptoms and the reversible nature of its enzyme inhibition

HISTORY

Finding out the exact type of insecticide that they were exposed to would be important in helping the clinician determine the likely severity and the reversibility of their clinical features. (39) The poison centre would be able to provide you with information about the specific substance.

EXAMINATION

Clinical features of organophosphate poisoning are due to overstimulation of muscarinic, nicotinic, and central receptors. (12) The features of cholinergic stimulation can be found in table 1.

Clinical features of specific receptor overstimulation (12):

- Muscarinic: Salivation, lacrimation, urination, vomiting, diarrhoea, abdominal cramps, miosis, blurred vision, bronchospasm, bronchorrhoea, bradycardia
- Nicotinic: hypertension, tachycardia, weakness, muscular fasciculations – which might progress to paresis and paralysis
- Central: ataxia, anxiety, confusion, psychosis and seizures

The most serious complications include respiratory failure, ventricular arrhythmias, decreased level of consciousness and seizures. (12) The respiratory failure can develop suddenly, even in patients with a normal level of consciousness and whilst appearing to recover from the cholinergic crisis, which is termed **intermediate syndrome** (also known as peripheral respiratory failure). This syndrome often leads to death in patients who have been successfully resuscitated and now appear stabilised after their admission to hospital. To help diagnose the risk of developing intermediate syndrome, the awake/alert patient's muscle strength should be assessed. This assessment can be done by asking them to lift their head off the bed and hold it up whilst you apply a downward pressure to their forehead, any sign of weakness indicates that they are at risk. (39)

INVESTIGATIONS

The measurement of cholinesterase activity in the blood can assist in the diagnosis of organophosphate poisoning. The test to quantify pseudocholinesterase activity is more readily available, but acetylcholinesterase activity is thought to be more specific. A falsely low pseudocholinesterase activity may be seen in patients with liver disease, pregnancy, anaemia, malnutrition and those with scoline apnoea. Normal levels of enzyme activity can occur despite poisoning due to multiple variations in what is constituted as normal. Therefore, the use of serial pseudocholinesterase levels can help confirm the diagnosis. In severe poisonings, the levels are 20 – 50% activity, but the level does not always correlate with the severity. These pitfalls are part of the reason that the diagnosis of organophosphate and carbamate poisoning is usually based on the clinical findings. (12) Treatment should be commenced without waiting for the results of the cholinesterase assays, as their results are not often available early enough to facilitate clinical decision making. (12, 39)

TREATMENT

Stabilisation

Management of organophosphate poisoning includes resuscitation according to ACLS principles, a muscarinic antagonist (usually atropine) and an acetylcholinesterase reactivator. During initial patient stabilization phase, the respiratory system should be closely monitored as the combination of bronchospasm, bronchorrhoea, muscle weakness and decreased level of consciousness increases the risk of respiratory failure, respiratory support should be given as necessary. (12, 39)

Atropine competitively blocks ACh at **muscarinic receptors,** but has no effect on nicotinic receptors. Symptomatic patients should immediately receive atropine. Atropine crosses into the CNS and the atropine related CNS toxicity, can be hard to differentiate from the organophosphate CNS toxicity. **Glycopyrrolate**, which does not cross the into CNS, provides the anticholinergic function without CNS toxicity effects. (12)

The goal of treatment is to achieve **atropinisation** (mydriasis, dry mouth, tachycardia). The endpoint for atropine is dried pulmonary secretions and sufficient oxygenation, the tachycardia and mydriasis should not be used to deter the repeat doses of atropine. (12) Before initiation of the first dose of atropine, the clinician should take note of the vitals, pupil size, presence of sweat, and chest auscultation findings. These same factors should be rechecked 5min after the first dose to assess for improvement, and if no improvement is detected, the original dose of atropine should be repeated at double the dose. (39) Atropine dosing has significant variation which depends on the amount of exposure and doses of up to 40 mg/d are not uncommon. The initial dose of atropine is repeated until adequate atropinisation has occurred. (12) Once there are improvements, then the dose doubling should cease and smaller doses can be used. (39)

The atropine associated CNS toxicity can present as an "**anticholinergic delirium",** especially in patients who have been given a very high dose. Treat the cause of the agitation by reviewing the atropine dose and benzodiazepine can be used as sedation. Physical restraint of agitated patients should be avoided as this can lead to severe hyperthermia; this is due to atropine related reduction in normal thermoregulatory mechanisms (like sweating). Therefore, adequate pharmacological sedation as restraints is essential. (39)

Pralidoxime reverses **muscarinic** and **nicotinic** effects of organophosphate poisoning by reactivating acetylcholinesterase by removal of the phosphate group, it also prevents further inhibition of the enzyme. (12, 39) It should be administered within 6h of the poisoning to ensure that it is prior to irreversible inactivation of cholinesterase and it is given along with atropine. However, it remains useful 24 – 48h post exposure, especially when the organophosphates that may have accumulated in fat are slowly released. The patient should be monitored for the detection of recurring cholinergic crises, secondary to this release from the fat stores. The cholinergic crises can occur for several days to weeks after ingestion of some organophosphorus. These crisis patients will need retreatment with atropine and oxime. (12)

If this treatment window of up to 48h is missed, the restoration of cholinesterase function requires regeneration of the enzyme, which can take weeks to complete. Pralidoxime helps to achieve more rapid atropinisation with smaller doses of atropine required. The dose of pralidoxime can be repeated if there is no improvement in muscle fasciculations or weakness within 1-hour, and then an infusion is commenced which can continue for > 24h.

(12) The pralidoxime infusion can be stopped when atropine has no longer been required for 12–24h and the patient has been extubated with no signs of recurring muscle weakness. (12, 39) An increasing activity noted on the pseudocholinesterase activity assay could inform the clinician about when to cease the pralidoxime treatment and when to actively wean the patient from a ventilator. However, that function is still under investigation. (39)

Table 18. Dosing of organophosphate treatment (12)

	Route	Initial dose	Repeated doses
Atropine	IV	2mg (6mg if life threatening)	2mg every 15min Consider doubling each subsequent dose for rapid control of patients in severe respiratory distress and until desired effect achieved of drying of pulmonary secretions and sufficient oxygenation. An infusion titrated to the above endpoints, can be continued until the patient's condition is stabilised.
Pralidoxime	IV	2g over 20min	2g after 1-hour Infusion titrated to effect, rate of 200 to 500 mg/h

Organophosphate poisoning patients can be admitted in ICU for up to two weeks, with more than half requiring require mechanical ventilation. (12)

New therapies

The evidence for these therapies is inconclusive. **Magnesium sulphate** prevents ACh release from pre-synaptic terminals and this could contribute to an improved function at neuromuscular junctions, and reduced CNS overstimulation. **Clonidine** theoretically causes a reduction in ACh synthesis and decreases its release from presynaptic terminals, but the effects in humans are unknown. (39)

Skin Decontamination

In farming related exposures, it is extremely important to remove all contaminated clothing as they act as a as a reservoir for continued exposure. cleanse the hair and skin thoroughly with nonabrasive soap and water to decrease skin absorption. These actions limit exposure for both the health care workers and the patient. (12, 13) Health care workers must also wear personal protection equipment (gloves and gowns) to protect themselves from accidental exposure. (12)

Gastric Decontamination

Gastric lavage may be useful if done immediately post-ingestion and activated charcoal is indicated to limit further drug absorption if administered within an hour. (12) However, it should only be considered once the patient fully resuscitated and stabilised. There is no evidence suggesting that patients benefit from treatment with activated charcoal. (39)

CONCLUSION

The scope of overdose and poisons is vast, and it is impossible to remember the features of specific substance overdose or exposure. I believe that our best bet is a clinical suspicion, excellent history taking and then pattern recognition as to what the most likely cause of the clinical features are. We need to remember to continuously monitor these patients as their clinical presentation evolves and they may quickly decompensate. The features of drugs that they have co-ingested may only be revealed once you commence treatment.

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