



MINISTRY OF HEALTH
SINGAPORE

Management of Poisoning

MOH Clinical Practice Guidelines Dec/2011



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Society

December 2011

Levels of evidence and grades of recommendation

Levels of evidence

Level	Type of Evidence
1 ⁺⁺	High quality meta-analyses, systematic reviews of randomised controlled trials (RCTs), or RCTs with a very low risk of bias
1 ⁺	Well-conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias
1 ⁻	Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias
2 ⁺⁺	High quality systematic reviews of case control or cohort studies. High quality case control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal
2 ⁺	Well conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal
2 ⁻	Case control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal
3	Non-analytic studies, e.g. case reports, case series
4	Expert opinion

Grades of recommendation

Grade	Recommendation
A	At least one meta-analysis, systematic review of RCTs, or RCT rated as 1 ⁺⁺ and directly applicable to the target population; or A body of evidence consisting principally of studies rated as 1 ⁺ , directly applicable to the target population, and demonstrating overall consistency of results
B	A body of evidence including studies rated as 2 ⁺⁺ , directly applicable to the target population, and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 1 ⁺⁺ or 1 ⁺
C	A body of evidence including studies rated as 2 ⁺ , directly applicable to the target population and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 2 ⁺⁺
D	Evidence level 3 or 4; or Extrapolated evidence from studies rated as 2 ⁺
GPP (good practice points)	Recommended best practice based on the clinical experience of the guideline development group

CLINICAL PRACTICE GUIDELINES

Management of Poisoning

MOH Clinical Practice Guidelines December/2011

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Statement of Intent

These guidelines are not intended to serve as a standard of medical care. Standards of medical care are determined on the basis of all clinical data available for an individual case and are subject to change as scientific knowledge advances and patterns of care evolve.

The contents of this publication are guidelines to clinical practice, based on the best available evidence at the time of development. Adherence to these guidelines may not ensure a successful outcome in every case, nor should they be construed as including all proper methods of care or excluding other acceptable methods of care. Each physician is ultimately responsible for the management of his/her unique patient in the light of the clinical data presented by the patient and the diagnostic and treatment options available.

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Foreword

It is estimated that 350,000 people died worldwide from unintentional poisoning in 2002.¹ In Singapore, injuries (including poisoning) ranked as the fifth leading cause of death and the leading cause of hospitalisation from 2007 to 2009. The pattern of poisoning has changed as the public is now exposed to other new drugs and chemicals. New antidotes and therapies have also been developed for the management of such poisoning, and are now available to health professionals.

The Ministry of Health released its first handbook on management of poisoning twenty years ago with the objective of providing a quick and reliable reference for the complex management of drug overdoses / poisoning. In 2000, a newer edition of the handbook was published to meet the changing needs.

This edition of the guideline updates the May 2000 guideline with a greater focus on the principles of emergency management of poisoning and the common toxins in the local context. A multidisciplinary expert workgroup reviewed the best available evidence from scientific literature and with their expertise in this area, has updated the guideline to assist healthcare professionals in the management of drug overdoses and poisoning.

I hope this set of recommendations will be useful for healthcare professionals, particularly physicians, pharmacists and clinicians who are involved in the management and care of patients with drug overdoses and poisoning.

PROFESSOR K SATKU
DIRECTOR OF MEDICAL SERVICES

¹ WHO Data: Poisoning Prevention and Management [Internet]. The International Programme on Chemical Safety (IPCS) [cited 5 September 2010]. Available from: <http://www.who.int/ipcs/poisons/en/>.

Executive summary of key recommendations

Details of recommendations can be found in the main text at the pages indicated.

Principles of management of acute poisoning – resuscitating the poisoned patient

GPP In a critically poisoned patient, measures beyond standard resuscitative protocol like those listed above need to be implemented and a specialist experienced in poisoning management should be consulted (pg 55).

GPP

D Prolonged resuscitation should be attempted in drug-induced cardiac arrest (pg 55).

Grade D, Level 3

C Titrated doses of naloxone, together with bag-valve-mask ventilation, should be administered for suspected opioid-induced coma, prior to intubation for respiratory insufficiency (pg 56).

Grade C, Level 2+

D In bradycardia due to calcium channel or beta-blocker toxicity that is refractory to conventional vasopressor therapy, intravenous calcium, glucagon or insulin should be used (pg 57).

Grade D, Level 3

B Patients with actual or potential life threatening cardiac arrhythmia, hyperkalaemia or rapidly progressive toxicity from digoxin poisoning should be treated with digoxin-specific antibodies (pg 57).

Grade B, Level 2++

B Titrated doses of benzodiazepine should be given in hyperadrenergic-induced tachycardia states resulting from poisoning (pg 57).

Grade B, Level 1+

D Non-selective beta-blockers, like propranolol, should be avoided in stimulant toxicity as unopposed alpha agonism may worsen accompanying hypertension (pg 57).

Grade D, Level 3

D Physostigmine should be considered for treating tachycardia resulting from pure anticholinergic poisoning (pg 58).

Grade D, Level 3

GPP Lidocaine is the drug of choice for most ventricular arrhythmias due to drug toxicity (pg 58).

GPP

C Sodium bicarbonate should be used in impaired conduction defect caused by sodium channel blocking agents such as tricyclic antidepressants (pg 58).

Grade C, Level 2+

B Titrated doses of benzodiazepine can be used to treat hypertension associated with drug-induced hyperadrenergic states (pg 59).

Grade B, Level 1+

D High dose vasopressor therapy for hypotension caused by poisoning needs to be titrated to response and complications (pg 59).

Grade D, Level 3

D Calcium chloride or gluconate can be given for calcium-channel blocker overdose (pg 59).

Grade D, Level 3

D Glucagon can be given for beta-blocker and calcium-channel blocker overdose (pg 59).

Grade D, Level 3

D High dose insulin euglycaemia therapy (HIE) is efficacious for use during calcium-channel and beta-blocker overdose (pg 60).

Grade D, Level 3

D Life support with circulatory assist device, such as intra-aortic balloon pump and bypass circuits (example: extracorporeal life support system) should be considered in severe refractory hypotension that is unresponsive to maximal medical therapy. Deployment of these devices should be preplanned in advance (pg 60).

Grade D, Level 3

GPP For poisoned patients presenting with depressed conscious level due to unspecified drugs, the following treatment should be considered: naloxone, glucose, oxygen and thiamine (pg 60).

GPP

B Routine toxicology screen for poisoning agents in the blood and urine or other body fluids is not advised (pg 60).

Grade B, Level 1-

D Checking serum paracetamol level should be considered, especially in a situation of parasuicide where the history may not be forthcoming. Paracetamol is the most common drug involved in parasuicides locally and is readily amenable to treatment with antidotes (pg 61).

Grade D, Level 4

D Patients, who ingested drugs that are of sustained-release formulation; have a prolonged half-life; or active metabolites that have prolonged effects, should be observed for a longer period of time (pg 61).

Grade D, Level 4

Decontamination after poisoning

Single dose activated charcoal

C Single dose activated charcoal is indicated as a gastric decontaminant agent if a patient has ingested a potentially toxic amount of a poison up to 1 hour following ingestion (pg 62).

Grade C, Level 2+

GPP The recommended dose for activated charcoal is as follows (pg 63):

- Children up to 1 year of age: 10-25 g or 0.5 – 1 g/kg.
- Children from 1 to 12 years of age: 25 to 50 g or 0.5 to 1 g/kg.
- Adolescents and adults: 25 to 100 g.

GPP

C Activated charcoal can be used with additives like orange juice, chocolate syrup and cola to improve its palatability. However use of these additives may decrease activated charcoal's adsorptive properties (pg 64).

Grade C, Level 2-

C Use of activated charcoal with cathartics does not improve outcome of gastric decontamination compared to activated charcoal alone (pg 64).

Grade C, Level 2-

D Use of activated charcoal with other forms of gastric emptying (e.g. gastric lavage) may be indicated in specific types of poisoning where the poison is seriously life-threatening; the dose ingested is of a massive amount; the poison is in a sustained-release preparation; the poison slows gastrointestinal motility (pg 65).

Grade D, Level 3

C Use of activated charcoal should not be used at home as first aid because its benefit has not been proven (pg 65).

Grade C, Level 2+

Gastric lavage

C Gastric lavage should not be employed routinely, if ever, in the management of poisoned patients.

In certain cases where the procedure is of attractive theoretical benefit (e.g. recent ingestion of a very toxic substance), the substantial risks should be weighed carefully against the sparse evidence that the procedure is of any benefit (pg 65).

Grade C, Level 2+

Ipecac

C Ipecac has no proven acute role in gastrointestinal contamination management as there is insufficient data to support or exclude its administration soon after poisons ingestion (pg 68).

Grade C, Level 2+

B Use of ipecac as a first aid measure at home has not been proven to be beneficial (pg 69).

Grade B, Level 2++

Cathartics

C The administration of a cathartic alone has **no** role in the management of the poisoned patient and is **not** recommended as a method of gut decontamination (pg 69).

Grade C, Level 2+

C Based on available data, the routine use of a cathartic in combination with activated charcoal is not endorsed (pg 70).

Grade C, Level 2+

GPP If a cathartic is used, it should be limited to a single dose in order to minimize adverse effects of the cathartic (pg 70).

GPP

Whole bowel irrigation

C Whole bowel irrigation (WBI) should not be used routinely in the management of the poisoned patient (pg 71).

Grade C, Level 2+

C The concurrent administration of activated charcoal and WBI may decrease the effectiveness of the charcoal (pg 73).

Grade C, Level 2-

C WBI should be considered for potentially toxic ingestions of sustained-release or enteric-coated drugs particularly for those patients presenting greater than two hours after drug ingestion and there is a lack of other options for gastrointestinal decontamination (e.g. substantial amounts of iron/ingestion of illicit packets of drugs) (pg 73).

Grade C, Level 2+

C WBI is contraindicated in patients with bowel obstruction, perforation, ileus, and in patients with hemodynamic instability or compromised unprotected airways.

It should be used cautiously in debilitated patients or in patients with medical conditions that may be further compromised by its use (pg 74).

Grade C, Level 2+

Poisons management at home

C Ipecac should no longer be used routinely as a home treatment strategy (pg 74).

Grade C, Level 2+

C It is premature to recommend the administration of activated charcoal in the home (pg 74).

Grade C, Level 2-

GPP The first action for a caregiver of a child who may have ingested a toxic substance is to consult with a doctor (pg 74).

GPP

Enhancing the elimination of toxic substances from the body

Multiple-dose activated charcoal (MDAC)

D Based on experimental and clinical studies, multiple-dose activated charcoal should be considered only if a patient has ingested a life-threatening amount of carbamazepine, dapsone, phenobarbital, quinine or theophylline (pg 75).

Grade D, Level 3

D Volunteer studies have demonstrated that multiple-dose activated charcoal increases the elimination of amitriptyline, dextropropoxyphene, digoxin, disopyramide, nadolol, phenylbutazone, phenytoin, piroxicam, and sotalol. There is insufficient clinical data to support or exclude the use of this therapy. The use of multiple-dose charcoal in salicylate poisoning is controversial (pg 75).

Grade D, Level 4

D Co-Administration of a cathartic to MDAC is unproven. Cathartics should not be administered to young children because of the propensity of laxatives to cause fluid and electrolyte imbalance (pg 75).

Grade D, Level 4

D Multiple-dose activated charcoal is administered orally. If appropriate, it may be given via a nasogastric tube. An antiemetic may be given intravenously, if vomiting, to ensure compliance. Smaller, more frequent doses of charcoal may be tried to prevent regurgitation.

The optimum dose of charcoal is unknown but it is recommended that after an initial dose of 50–100 g to an adult, activated charcoal should be administered at a rate of not less than 12.5 g/h or equivalent.

Lower doses (10–25 g) of activated charcoal may be employed in children less than 5 years of age as usually, they have ingested smaller overdoses and their gut lumen capacity is smaller (pg 75).

Grade D, Level 4

D Multi-Dose Activated Charcoal should be discontinued if there is significant clinical improvement or serum drug concentrations have fallen to nontoxic levels (pg 76).

Grade D, Level 4

Urinary pH manipulation

D Urine alkalinisation increases the urine elimination of salicylate, chlorpropamide, 2,4-dichlorophenoxyacetic acid (herbicide), diflunisal, fluoride, mecoprop (herbicide), methotrexate and phenobarbital. High urine flow (approximately 600 mL/h) and urine alkalinisation should also be considered in patients with severe 2,4-dichlorophenoxyacetic acid and mecoprop poisoning (pg 76).

Grade D, Level 3

D Volume overload may complicate therapy in patients with pre-existing cardiac disease. Significant pre-existing heart disease is a relative contraindication.

Urinary pH manipulation is contraindicated in patients with established or incipient renal failure, pulmonary oedema and cerebral oedema (pg 77).

Grade D, Level 4

D Hypokalemia is the most common complication. Alkalotic tetany occurs occasionally, but hypocalcaemia is rare. There is no evidence to suggest that relatively short-duration alkalemia poses a risk to life in normal individuals or in those with coronary and cerebral arterial disease (pg 77).

Grade D, Level 4

D Urinary acidification (urine pH < 5.5) with ammonium chloride or ascorbic acid was historically used to treat intoxications with weak bases such as amphetamines, quinidine or phencyclidine. However, this practice has been abandoned, as efficacy has not been established and iatrogenic toxicity (severe acidosis) can occur (pg 77).

Grade D, Level 4

D Discontinue urine alkalisation when plasma salicylate concentrations fall below 350 mg/L in an adult or 250 mg/L in a child (pg 78).

Grade D, Level 4

Extracorporeal techniques

GPP Extracorporeal techniques are considered if the patient is critically ill and the blood level of a poison is in the known lethal range or associated with serious consequences (pg 79).

GPP

Antidotes

GPP Consider using specific antidotes in a timely manner when clinically indicated. Certain antidotes have been shown to improve survival and patient outcomes in poisonings and drug overdoses (pg 80).

GPP

GPP Indications for the use of antidotes in children are generally the same as for adults. Certain antidotes have been shown to improve survival and outcomes in paediatric poisonings and drug overdoses (pg 80).

GPP

GPP Do not withhold antidotes for pregnant women who had experienced poisonings and drug overdoses, especially if the symptoms are life-threatening or severe (pg 81).

GPP

GPP Institutions that manage acute poisoning and drug overdoses should adequately stock the appropriate antidotes (pg 83).

GPP

Analgesics

Non-steroidal anti-inflammatory drugs (NSAID) poisoning (excluding salicylates)

Definition:

D Symptomatic patients irrespective of reported dose ingested (pg 84).
Grade D, Level 4

C Ingestions of less than 100 mg/kg of most NSAIDs (except mefenamic acid and phenylbutazone) are unlikely to cause any significant toxicity. Massive ingestions with severe symptomology are seen with ingestions greater than 400 mg/kg (pg 85).

Grade C, Level 2++

D Refer to Emergency Department / Hospital for further evaluation and management if (pg 85):

- Patient is symptomatic (irrespective of dose).
- If toxic dose is consumed (see above).
- Suspected non-accidental ingestion (irrespective of dose).
- Poor home support (lives alone, inability of caregivers to monitor).

Grade D, Level 4

B Activated charcoal should be given within 1 hour of ingestion (pg 86).

Grade B, Level 1+

D Aspiration risk, including mental status and the ability to protect the airway, must be assessed in all patients before any attempts to administer activated charcoal (pg 86).

Grade D, Level 4

D Supportive treatment and a brief period of observation are usually all that is necessary in most cases of non-steroidal anti-inflammatory drug (NSAID) overdose, with the exception of mefenamic acid and phenylbutazone (pg 86).

Grade D, Level 4

D If more than 6 hours had passed since the suspected toxic ingestion and the patient is clinically well, the patient does not require further evaluation for toxicity (**except** for mefenamic acid and phenylbutazone).

In **mefenamic acid** and **phenylbutazone** poisoning, a 24-hour post ingestion observation is advised due to the increased risk in complications (pg 87).

Grade D, Level 3

C Seizures secondary to NSAIDs toxicity can be effectively treated with benzodiazepines (pg 87).

Grade C, Level 2++

B NSAID levels correlate poorly with symptoms and are not usually clinically useful (pg 87).

Grade B, Level 2+

D Routine measurement of renal function is not indicated in patients with minor, asymptomatic ingestions.

In symptomatic patients or those with significant toxic ingestion, measurement of baseline renal function and electrolytes should be done (pg 87).

Grade D, Level 4

Opioids

D Refer to Emergency Department / Hospital for the following groups of patients (pg 88):

- All patients with suicidal intent, intentional abuse, or in cases in which a malicious intent is suspected (e.g. child abuse or neglect).
- All symptomatic patients.
- Patients who are suspected of ingesting toxic amounts of opioid.
- Patients with poor home support (e.g. lives alone, inability for caregivers to monitor).

Grade D, Level 4

D (pg 90)

- Capillary glucose: to exclude hypoglycaemia.
- Electrocardiogram (ECG): should be obtained when the patient is suspected of methadone/propoxyphene overdose; or when co-ingestion with other substances which may cause cardiovascular complications, such as cocaine or antidepressants is suspected (e.g. if intended self-harm is suspected).
- Other investigations:
 - In the setting of suspected prolonged immobilization: serum creatine phosphokinase concentration should be obtained to exclude rhabdomyolysis.
 - Serum creatinine and electrolytes: depending on clinical circumstances
 - Targeted blood toxicology: In any overdose scenario in which the opioid is formulated with paracetamol or self-harm is suspected, serum paracetamol concentration should be obtained.
 - Urine toxicologic screens should not be routinely obtained. Opioids are detectable in the urine for only two to four days after use. A positive test may indicate recent use but not current intoxication, or may even represent a false positive. Conversely, many opioids,

especially the synthetic drugs, will produce false-negative results in many commonly available urine screens.

Grade D, Level 3

C (pg 91)

- Initial management should focus on support of the patient's airway and breathing.
- While pulse-oximetry is useful in monitoring oxygenation, its usefulness may be limited if supplemental oxygen is given.
- Capnography if available may be useful for monitoring the ventilatory effort of opioid-poisoned patients.

Grade C, Level 2++

C Patients with respiratory insufficiency should be supported with bag mask ventilation and 100% oxygen to correct respiratory acidosis before or while the opioid antagonist is administered (pg 92).

Grade C, Level 2++

B For suspected pulmonary oedema, oxygen and positive pressure ventilation may be required (pg 92).

Grade B, Level 1+

B Activated charcoal (1 g/kg, maximum of 50 g) can be given to patients who have ingested within 1 hour of overdose, if the airway is first assessed and protected, as needed, prior to the procedure (pg 92).

Grade B, Level 1+

D In Lomotil (diphenoxylate and atropine) poisoning, gastric lavage within 2 hours of overdose and multi-dose activated charcoal should be considered (pg 92).

Grade D, Level 3

D In body packing with leakage and overdose, whole body bowel irrigation can be considered if airway is protected (pg 92).

Grade D, Level 3

Salicylate poisoning

Refer to emergency department / hospital referral for further evaluation and management:

D All symptomatic patients should be referred to an emergency department regardless of dose ingested (e.g. haematemesis, tachypnoea, hyperpnoea, dyspnoea, tinnitus, deafness, lethargy, seizures, unexplained lethargy or confusion) (pg 100).

Grade D, Level 3

D All patients with known or suspected suicidal intent or non-accidental ingestion (e.g. child abuse) irrespective of amount ingested (pg 100).

Grade D, Level 4

D If asymptomatic and had suspected toxic ingestion (pg 100):

- Acute ingestion of aspirin or equivalent exceeding 150 mg/kg or 6.5 g, whichever is less.
- Ingestion of oil of wintergreen (98% methyl salicylate) if:
 - Under 6 years of age: greater than a lick or taste.
 - Patients 6 years of age or older: > 4 mL.

Grade D, Level 3

C If the accidental ingestion occurred >12 hours (24 hours for enteric-coated tablets) and the patient is asymptomatic, no further evaluation is required (pg 100).

Grade C, Level 2+

Mucocutaneous and ocular salicylate exposure

D For asymptomatic patients with dermal exposures to methyl salicylate or salicylic acid, the skin should be thoroughly washed with soap and water and the patient can be observed for symptoms (pg 101).

Grade D, Level 3

D For patients with an ocular exposure of methyl salicylate or salicylic acid, the eye(s) should be irrigated with room temperature tap water for 15 minutes. If after irrigation the patient is having pain, decreased visual acuity or persistent irritation, refer to an ophthalmologist (pg 101).

Grade D, Level 4

Management of salicylate poisoning

D Intubation of the salicylate-poisoned patient can be detrimental and should be avoided unless necessary (pg 101).

Grade D, Level 3

D If intubation and mechanical ventilation is necessary for severe obtundation, hypotension, hypoventilation or severe metabolic acidosis, ensure appropriately high minute ventilation and maintain alkalemia (via serial blood gas analysis) with serum pH 7.50-7.55 (pg 101).

Grade D, Level 4

D Consider haemodialysis for patients who require intubation (pg 102).

Grade D, Level 4

D Pulmonary oedema and acute lung injury may occur and should be treated with oxygen and if available, non-invasive ventilation. Intubation and mechanical ventilation with positive end-expiratory pressure (PEEP) may be necessary, but should be avoided if possible (pg 102).

Grade D, Level 3

D Intravenous fluids should be administered as necessary to replace insensible fluid losses from hyperpyrexia, vomiting, diaphoresis, and elevated metabolic rate (pg 102).

Grade D, Level 4

D There should be judicious administration of fluids in the presence of suspected pulmonary oedema or cerebral oedema (pg 102).

Grade D, Level 4

D All patients with salicylate poisoning with altered mental status should be given supplemental glucose, regardless of serum glucose levels (pg 102).

Grade D, Level 4

D Supplemental potassium should be given to maintain serum potassium 4-4.5 mmol/L, unless renal failure is present (pg 102).

Grade D, Level 4

D Gastrointestinal decontamination with activated charcoal can be considered in patients with significant acute salicylate overdose irrespective of the suspected time of ingestion (pg 103).

Grade D, Level 2+

D Multi-dose activated charcoal should be considered in massive salicylate ingestions every 4 hours for 24 hours in a dose of 1 g/kg (maximum 50 g) until symptoms have resolved and plasma salicylate concentration is < 30 mg/dL (pg 103).

Grade D, Level 2+

B Enhanced salicylate elimination via urine alkalinisation with sodium bicarbonate is an essential component in the management of the salicylate-poisoned patient (pg 103).

Grade B, Level 1+

D Alkalemia from respiratory alkalosis is not a contraindication to sodium bicarbonate therapy (pg 103).

Grade D, Level 3

C Haemodialysis is the definitive treatment to prevent and treat salicylate induced end-organ injury (pg 103).

Grade C, Level 2++

D Early consultation to the relevant specialists may be required in severe salicylate poisoning (pg 104).

Grade D, Level 4

C The indications for haemodialysis are primarily clinical and include (pg 104):

- Severe acidosis or hypotension refractory to optimal supportive care (regardless of absolute serum aspirin concentration).
- Evidence of end-organ injury (i.e. seizures, rhabdomyolysis, pulmonary oedema).
- Renal failure.
- Plasma salicylate concentration > 100 mg/dL (> 7.2 mmol/L) in the setting of acute ingestion; or plasma salicylate concentration > 60 mg/dL (> 4.3 mmol/L) in the setting of chronic salicylate use.
- Haemodialysis should be considered for patients who require mechanical ventilation, unless that indication for mechanical ventilation is respiratory depression secondary to a co-ingestant.

Grade C, Level 2++

D A salicylate level and blood gas should be drawn 2-3 hourly until both the plasma salicylate level is falling and the acid-base status is stable or improving for two consecutive readings (pg 104).

Grade D, Level 4

D Check urea and electrolytes every 3-4 hours. The serum potassium should be kept in the range 4 to 4.5 mmol/L (pg 104).

Grade D, Level 4

Paracetamol poisoning

Toxic ingestion

Definition:

D Symptomatic: e.g. repeated vomiting, abdominal tenderness in the right upper quadrant or mental status changes (pg 107).

Grade D, Level 4

D If **unknown** dose, assume toxic ingestion (pg 107).

Grade D, Level 4

C Acute single dose poisoning:

- 200 mg/kg or more; or 10 g (whichever is less) (pg 107).
 - Both paediatric and adults.

Grade C, Level 2++

D Repeated supratherapeutic ingestion (>24 hours staggered dose) (pg 107):

- In children (< 6 years) or high risk group: 4 g or more than 100 mg/kg/day (whichever is less).
- In children (> than 6 years old) or adults: 6 g or 150 mg/kg/day (whichever is less).

Grade D, Level 4

Sustained-release preparations

C In a single acute ingestion, if more than 200 mg/kg or 10 g (whichever is less) has been ingested, N-acetylcysteine treatment should be started immediately (pg 108).

Grade C, Level 2++

C In all cases, serum paracetamol levels should be taken at 4 hours or more post-ingestion (as with standard preparations) and repeated 4 hours later. If either level is above the normogram line, N-acetylcysteine should be commenced or continued. N-acetylcysteine may be discontinued if both levels fall below the normogram line (pg 108).

Grade C, Level 2++

Management of paracetamol poisoning

D Presence of hypoglycaemia may be secondary to hepatic failure and intensive care monitoring is required (pg 109).

Grade D, Level 4

• Prehospital

B Activated charcoal (1 g/kg, up to 50 g) can be considered if available, patient is alert and co-operative, a toxic dose of acetaminophen has been taken and fewer than 2 hours have elapsed since the ingestion (pg 110).

Grade B, Level 1+

D Gastrointestinal decontamination could be particularly important if N-acetylcysteine cannot be administered within 8 hours of ingestion (pg 110).

Grade D, Level 4

• ED/Hospital Management

B Activated charcoal (1 g/kg, up to 50 g) can be given if less than 2 hours (pg 110).

Grade B, Level 1+

D May have a role in sustained-release preparations even after 2 hours of ingestion (pg 110).

Grade D, Level 4

D Limited studies available but charcoal haemoperfusion may be considered in severe paracetamol poisoning in the intensive care setting, after consultation with the relevant specialists (pg 110).

Grade D, Level 3

A N-acetylcysteine is the antidote of choice for paracetamol poisoning and should be administered to all patients judged to be at risk of developing hepatotoxicity after paracetamol overdose (pg 110).

Grade A, Level 1+

C When risk assessment indicates that N-acetylcysteine is required, it is administered as a three-stage infusion, totalling 300 mg/kg over 20–21 hours (pg 111).

Grade C, Level 2++

C If hepatic injury is suspected after the three infusion stages, N-acetylcysteine is continued at the rate of the last infusion stage (100 mg/kg each 16 hours or 150 mg/kg/24 hours) until there is clinical and biochemical evidence of improvement (pg 111).

Grade C, Level 2++

B N-acetylcysteine reduces mortality if commenced late in patients with established paracetamol-induced fulminant hepatic failure. In this setting, N-acetylcysteine reduces inotrope requirements, decreases cerebral oedema and increases the rate of survival by about 30% (pg 111).

Grade B, Level 2++

D Anaphylactoid reactions manifested by rash, wheeze or mild hypotension occur in 5–30% of patients during the first two N-acetylcysteine infusions. Management is supportive, with temporary halting or slowing of the infusion, and administration of antihistamines (IV promethazine 0.2 mg/kg, up to 10 mg) (pg 112).

Grade D, Level 3

D The occurrence of an anaphylactoid reaction does not preclude the use of N-acetylcysteine on another occasion, if indicated (pg 112).

Grade D, Level 3

B Methionine can be considered as an alternative antidote for paracetamol poisoning, especially in the setting of known allergy to N-acetylcysteine (pg 112).

Grade B, Level 1+

Management of non-accidental toxic ingestions

D Admission is recommended, irrespective of levels for non-accidental ingestion. Serum levels must be tested. Multi-drug poisoning should be considered (pg 112).

Grade D, Level 4

ED/hospital management of accidental ingestions

Acute single dose toxic ingestion Asymptomatic patients

B If **< 2 hours**: Gastrointestinal decontamination via activated charcoal (1 g/kg, up to 50 g) for co-operative and alert patients (pg 113).

Grade B, Level 1+

C If **4-8 hours**: Measure paracetamol levels (at or after 4 hours post ingestion) (pg 113).

- Plot paracetamol level on normogram.
- Start IV N-acetylcysteine if over normogram at 150 mg/L (1000 μ mol/L) at 4 hours (line of possible hepatotoxicity).

Grade C, Level 2++

C If **> 8 hours**: Commence IV N-Acetylcysteine (do not wait for levels) (pg 113).

- Obtain paracetamol levels as soon as possible.
- Obtain ALT/AST stat and repeat at the end of N-acetylcysteine infusion or every 12 hours, whichever comes first.
- If the serum paracetamol level is subsequently found to be below the normogram line, N-acetylcysteine may be ceased; if above the line, it should be continued till paracetamol levels fall below the normogram line and ALT is static or normal.
- Obtain full blood count (platelet), INR or PT, urea and creatinine, electrolytes, glucose and arterial blood gas (if venous bicarbonate is low) and repeat as indicated.
- A baseline serum ALT level, international normalised ratio and platelet count provide useful baseline data for later risk assessments.

Grade C, Level 2++

Symptomatic patients (clinical or biochemical)

D Start IV N-Acetylcysteine without waiting for levels (even < 8 hours) (pg 113).

- Obtain paracetamol levels, ALT/AST, full blood count (platelet), INR or PT, urea and creatinine, electrolytes, glucose and arterial blood gas.
- If symptomatic and paracetamol levels are below the normogram, consider toxic co-ingestions.

Grade D, Level 3

Repeated Supratherapeutic Toxic Ingestion

D Commence IV N-Acetylcysteine (do not wait for levels) (pg 113).

- Obtain paracetamol and ALT/AST levels as soon as possible.
- If paracetamol < 10 mg/L and ALT/AST normal, stop infusion of NAC.
- Obtain INR or PT, urea and creatinine, electrolytes, glucose and arterial blood gas (if bicarbonate abnormal) at admission.
- Repeat ALT/AST and serum paracetamol levels at 8-12 hours.
- If ALT/AST normal or static and paracetamol < 10 mg/L, stop infusion of NAC.
- If abnormal, continue IV NAC and repeat ALT/AST 12 hourly and other investigations as indicated.

Grade D, Level 2+

Unknown time of ingestion

D Start IV N-acetylcysteine. Investigations and management are similar to supratherapeutic repeated dose ingestion (pg 114).

Grade D, Level 4

Severe paracetamol poisoning

C Metabolic (pg 115):

- Metabolic acidosis (pH < 7.3 or bicarbonate < 18) despite rehydration.
- Hypoglycaemia.
- Hypotension despite adequate fluid resuscitation.

CNS:

- Encephalopathy or signs of raised intracranial pressure.

Liver Function / Coagulopathy:

- INR > 2.0 at or before 48 hours or > 3.5 at or before 72 hours:
 - Consider measuring INR every 12 hourly.
 - Peak elevation occurs around 72 – 96 hours.
 - LFTs are not good markers of hepatocyte death.

Renal:

- Renal impairment (creatinine > 200 µmol/L):

- Monitor urine output.
- Daily urea, electrolytes and serum creatinine.
- Consider haemodialysis if $> 400 \mu\text{mol/L}$.

Resuscitation and intensive care monitoring required.

Grade C, Level 2++

D Consider referrals to liver transplant hepatologists and transferring to tertiary intensive care units with a liver transplant unit in Singapore (pg 115).

Grade D, Level 4

C Consider liver transplantation if (pg 115):

- Arterial pH < 7.3 or arterial lactate $> 3.0 \text{ mmol/L}$ after adequate fluid resuscitation.

OR

- If all three of the following occur in a 24-hour period:
 - Creatinine $> 300 \mu\text{mol/L}$.
 - PT > 100 (INR > 6.5).
 - Grade III / IV encephalopathy.

Strongly consider transplantation if:

- Arterial lactate $> 3.5 \text{ mmol/L}$ after early fluid resuscitation.

Grade C, Level 2++

Antihistamines / Anticholinergics

Referral for ED / hospital management

D All patients with suicidal intent, intentional abuse or in cases in which a malicious intent is suspected (e.g. child abuse or neglect) should be referred to an emergency department (pg 121).

Grade D, Level 4

D All symptomatic patients should be referred to an emergency department (pg 121).

Grade D, Level 4

D Poor home support (lives alone, inability of caregivers to monitor) (pg 121).

Grade D, Level 4

D Patients who are suspected of ingesting toxic amounts of anticholinergics should be referred to an emergency department or further management (pg 121).

Grade D, Level 4

Investigations

D Capillary glucose should be done in any patient presenting with altered conscious status (pg 121).

Grade D, Level 4

D Cardiac monitoring and ECG: it is crucial that patients suspected of having anticholinergic toxicity have an ECG to allow detection of QTc interval prolongation or frank arrhythmias. This can occur with overdose of tricyclic antidepressants, certain phenothiazines (e.g. mesoridazine and thioridazine), diphenhydramine and other agents with anticholinergic properties (pg 121).

Grade D, Level 3

D Urine analysis/microscopy and serum creatinine kinase: rhabdomyolysis in anti-cholinergic toxicity can occur secondary to prolonged seizures or may be atraumatic in doxylamine and diphenhydramine poisoning (pg 122).

Grade D, Level 3

D Serum drug levels of anticholinergic agents are not helpful or readily available in the clinical setting; the diagnosis of anticholinergic toxicity is based on clinical findings and less often the result of a diagnostic/therapeutic trial of physostigmine (pg 122).

Grade D, Level 2+

Management

D Patients should have intravenous access, supplemental oxygen, cardiac monitoring and continuous pulse oximetry (pg 122).

Grade D, Level 3

D Patients with severe anticholinergic toxicity and/or treated with physostigmine should be monitored in an intensive care unit for observation (pg 122).

Grade D, Level 3

(1) Gastric lavage:

D May be considered in patients with history of significant overdosing and potential for high morbidity as gastric emptying may be delayed (pg 123).

Grade D, Level 3

(2) Activated charcoal:

D If the patient's mental status is intact and ingestion of an anticholinergic agent is likely, activated charcoal (1 g/kg; maximum 50 g) should be given (pg 123).

Grade D, Level 2+

Physostigmine

D The main management for most patients with cholinergic toxicity is supportive care alone, but some literature report benefit in selected patients (pg 124).

Grade D, Level 3

C Physostigmine may be indicated when patients manifest isolated moderate to severe agitation/delirium secondary to anticholinergic toxicity (pg 124).

Grade C, Level 2+

D Physostigmine should not be given if a condition other than a purely anticholinergic poisoning is suspected (e.g. tricyclic antidepressant overdose) as it is associated with cardiac adverse events and deaths (pg 124).

Grade D, Level 3

D Before physostigmine is given, the patient should be placed on a cardiac monitor; and atropine and resuscitative equipment should be available (pg 124).

Grade D, Level 3

D Physostigmine may be superior to benzodiazepines in the management of agitation and delirium due to anticholinergic toxicity in selected patients (pg 124).

Grade D, Level 2+

D Diagnostic trial in patients presenting with agitation and delirium with suggestive history which may avoid the use of many invasive and radiological investigations (pg 124).

Grade D, Level 2+

Psychotropics

Benzodiazepines

D Qualitative screening of urine or blood is not recommended. Screening rarely influences treatment decisions because of long turnaround time, lack of available or reliable tests, poor correlation clinically and may not alter emergency treatment options. However urine and blood screening may support evidence of exposure (pg 129).

Grade D, Level 3

GPP Monitor arterial blood gas if there is respiratory depression. Obtain serum electrolytes, glucose, BUN levels. Useful tests to exclude other causes of respiratory depression and predict severity of respiratory depression (pg 129).

GPP

D Diagnosis is usually based on a history of ingestion. Specific serum levels may confirm diagnosis. Urine and blood screens are also available (pg 130).

Grade D, Level 3

A Although flumazenil may be effective to reverse coma from suspected drug poisoning in patients presenting to the emergency department, its routine use is not recommended.

Routine use of flumazenil is not recommended as benzodiazepine overdose is seldom fatal and flumazenil has side effects (pg 130).

Grade A, Level 1+

A Flumazenil is not recommended in patients with epilepsy, benzodiazepine dependence or suspected multi-agent overdoses.

Co-ingested substances, such as heterocyclic antidepressants, are known to produce seizures (pg 130).

Grade A, Level 1+

Selective serotonin reuptake inhibitor (SSRI)

D Asymptomatic patients or those with mild effects following isolated unintentional acute SSRI ingestions of up to five times an initial adult therapeutic dose can be observed at home with instructions to seek medical attention if symptoms develop.

The therapeutic index is wide and overdoses up to 5 times the therapeutic doses may be tolerated without serious toxicity (pg 133).

Grade D, Level 4

D For patients already on an SSRI, those with ingestion of up to five times their own single daily therapeutic dose can be observed at home with instructions to seek medical attention if symptoms develop (pg 133).

Grade D, Level 4

GPP (pg 134)

- Monitor arterial blood gas if there is respiratory depression.
- Monitor serum electrolytes, glucose, BUN.
- Useful tests to exclude other causes of respiratory depression and predict severity of respiratory depression.

GPP

GPP Cardiac monitoring is recommended in symptomatic cases.

Some drugs can prolong QT and in overdoses, arrhythmias need to be excluded (pg 134).

GPP

D Use intravenous benzodiazepines for seizures, and external cooling measures for hyperthermia (>104°F or >40°C) seen with SSRI-induced serotonin syndrome. Institute emergency and supportive measures as they occur (pg 134).

Grade D, Level 4

D Sodium bicarbonate may be used for QRS widening in patients with cardiac conduction abnormalities after SSRI poisoning. This reverses the sodium channel-dependent membrane depressant effects and may correct the cardiac conduction abnormalities (pg 134).

Grade D, Level 4

GPP Provide IV fluids and maintenance of the airway and ventilation if required. Institute emergency and supportive measures as required clinically (pg 135).

GPP

GPP Inotropic agents should be started for hypotension not responding to fluid resuscitation. Institute emergency and supportive measures as they occur (pg 135).

GPP

D Cyproheptadine may be considered for suspected serotonin syndrome refractory to standard treatment measures. Cyproheptadine is a histamine H1 blocker which antagonises serotonin receptors. Anecdotal case reports have shown improved clinical symptoms with its use (pg 135).

Grade D, Level 3

D Chlorpromazine may be considered for suspected serotonin syndrome refractory to standard treatment measures. Chlorpromazine is a serotonin receptor antagonist neuroleptic. Anecdotal case reports have shown improved clinical symptoms with its use (pg 135).

Grade D, Level 3

D Dantrolene may be considered for suspected serotonin syndrome refractory to standard treatment measures. Dantrolene relaxes skeletal muscles and prevents hyperthermia. Anecdotal case reports have shown improved clinical symptoms with its use (pg 135).

Grade D, Level 3

D In the absence of an established toxic dose, the presence of more than mild clinical effects (vomiting, somnolence, mydriasis, diaphoresis, including those consistent with serotonin syndrome) should be used as an indication for emergency department referral, regardless of the dose reportedly ingested.

Patients who have unintentional SSRI ingestions and are asymptomatic may stay at home with poison centre follow-up. A patient suspected of a significant overdose is at risk of serious toxicity and serotonin syndrome (pg 136).

Grade D, Level 3

Antipsychotics

B Clinical manifestations of atypical antipsychotic toxicity generally include varying degrees of central nervous system depression (drowsiness), agitation, anticholinergic effects, pupillary changes, seizures, hypotension or hypertension, and cardiac conduction abnormalities (prolongation of the QTc and QRS intervals). Clozapine has been shown to cause agranulocytosis in 1–2% of patients after 1 year of therapy. Morbidity usually results from cardiotoxicity (hypotension, ventricular arrhythmias or conduction delay); or neurotoxicity (respiratory depression, coma, seizures or delirium) (pg 138).

Grade B, Level 1-

D Patients with stated or suspected self-harm should be referred to an emergency department immediately. This is regardless of the dose reported (pg 139).

Grade D, Level 4

C Asymptomatic patients without evidence of attempted self-harm are unlikely to develop symptoms if the time since ingestion is greater than 6 hours. They do not need referral into hospital (pg 139).

Grade C, Level 3

D All patients (12 years of age or older) who are naïve to atypical antipsychotic medications, and are experiencing no more than mild drowsiness can be observed at home, unless they have ingested more than five times the initial adult dose of the antipsychotic medication (i.e. if they ingested more than aripiprazole 50 mg, clozapine 62.5 mg, olanzapine 25 mg, quetiapine 125 mg, risperidone 5 mg, ziprasidone 100 mg) (pg 139).

Grade D, Level 4

D If a patient on chronic atypical antipsychotic therapy ingested more than 5 times their current single dose (not daily dose), they should be referred to the emergency department (pg 139).

Grade D, Level 3

D Ipecac syrup should be avoided due to insufficient evidence of its effectiveness. (Olanzapine, ziprasidone) (pg 139).

Grade D, Level 3

D Decontaminate with activated charcoal. Consider attempting gastric lavage if ingestion was within a few hours since anticholinergic action slows GI transit. (Olanzapine, quetiapine) (pg 139).

Grade D, Level 3

D Hypotension should be treated with IV crystalloid infusions. If vasopressors are required, norepinephrine or phenylephrine is preferred. Agents with beta-agonist activity (dopamine, epinephrine) may worsen vasodilatory effects (hypotension) and should be avoided. Hypotension is due to atypical antipsychotic-induced alpha blockade (pg 140).

Grade D, Level 3

D For drug-induced dystonia in the adult, give IV benztropine 1-2 mg or diphenhydramine 50 mg IV/IM over 2 minutes. For that in the child, give diphenhydramine 1 mg/kg/dose IV over 2 minutes (maximum 5 mg/kg/day or 50 mg/m²/day) (pg 140).

Grade D, Level 3

D Perform continuous cardiac monitoring. Monitor antimuscarinic effects, and check creatine kinase (CK) levels in patients with prolonged agitation, excessive rigidity or coma. In patients with neurologic symptoms, monitor for respiratory depression (pulse oximetry and/or ABGs) (pg 140).

Grade D, Level 3

D Haemodialysis, haemoperfusion, forced diuresis and exchange transfusion are unlikely to be useful following overdose, because of the relatively large volume of distribution and high degree of protein binding. (Ziprasidone, clozapine) (pg 140).

Grade D, Level 3

D Treat seizures with IV benzodiazepines (pg 140).

Grade D, Level 3

C Neuroleptic Malignant Syndrome should be treated with oral or parenteral dantrolene (pg 141).

Grade C, Level 2+

C All patients less than 12 years of age who are naïve to atypical antipsychotics, and are experiencing no more than mild drowsiness (lightly sedated and can be aroused with speaking voice or light touch) can be observed at home. However, refer if they have ingested more than four times the initial adult dose; or a dose that is equal to or more than the lowest reported acute dose that resulted in moderate toxicity, whichever dose is smaller (i.e. aripiprazole 15 mg; clozapine 50 mg; olanzapine 10 mg; quetiapine 100 mg; risperidone

1 mg; or ziprasidone 80mg) (pg 141).

Grade C, Level 3

C Clinical manifestations of typical antipsychotics poisoning generally include neuroleptic malignant syndrome, rigidity, dystonia, fever and widened QRS interval (pg 141).

Grade C, Level 2+

D The primary treatment of cardiotoxicity is plasma alkalinisation with sodium bicarbonate and hyperventilation (pg 141).

Grade D, Level 4

GPP Patients with altered mental state or persistent tachycardia despite intravenous fluids should be closely monitored. Benzodiazepines or physostigmine could be administered to manage tachycardia (pg 142).

GPP

Tricyclic Antidepressants (TCAs)

C Consider referral to a hospital emergency department if ingested either of the following amounts (whichever is lower) (pg 146):

- An amount that exceeds the usual maximum single therapeutic dose;

OR

- An amount equal to or greater than the lowest reported toxic dose
 - For amitriptyline, clomipramine, doxepin and imipramine: 5 mg/kg.
 - For nortriptyline and trimipramine: 2.5 mg/kg.

This recommendation applies both to patients who are naïve to the specific drug and to patients currently taking TCAs. For patients currently on TCAs, the extra doses should be added to the daily dose taken for comparison to the threshold doses stated above.

Grade C, Level 2+

C For unintentional poisonings, asymptomatic patients do not need referral to an emergency department facility if more than 6 hours have elapsed since the ingestion of the TCA. These patients are unlikely to develop symptoms (pg 146).

Grade C, Level 2+

B ECG readings are recommended over serum TCA drug level to predict seizure and arrhythmia (pg 147).

Grade B, Level 1+

D Gastric lavage may be considered for massive ingestions, up to 2-4 hours post-ingestion in potentially toxic TCA overdoses.

Gastric emptying time may be delayed due to anticholinergic effects of the TCAs (pg 149).

Grade D, Level 3

D Activated charcoal may be used for gastric decontamination. However, the routine use of multiple-dose activated charcoal is not recommended.

Activated charcoal slurry 1 g/kg may be administered as soon as possible after a potentially toxic ingestion in a healthcare setting (due to the risk of aspiration), as TCAs are known to undergo enterohepatic recirculation. Administration of subsequent doses should be considered in patients with serious toxicity, because of the possibility of desorption of TCA from charcoal. It should also be considered in patients who ingest modified-release formulations (pg 149).

Grade D, Level 3

GPP Haemodialysis and haemoperfusion may be considered in patients with very severe TCA poisoning.

Due to the very large volume of distribution and high protein binding of TCAs, haemodialysis and haemoperfusion are not as effective in enhancing drug removal (pg 149).

GPP

C Sodium bicarbonate is the mainstay of therapy in TCA overdose.

Bolus doses of 1-2 mEq/kg should be given to achieve and maintain a QRS width of 100 milliseconds or less. In patients with dysrhythmia, serum pH should be maintained at 7.45 to 7.55. Other causes of widened QRS should be considered if the patient fails to respond to sufficient doses of sodium bicarbonate therapy (pg 149).

Grade C, Level 2-

GPP Use of physostigmine as an antiarrhythmic is not recommended.

In the setting of TCA overdose, it has been associated with the development of seizures and fatal dysrhythmias (pg 149).

GPP

GPP Avoid antiarrhythmic drugs from class Ia (quinidine, procainamide, disopyramide), class Ic (flecainide), class II, and class III (bretylum, amiodarone). These agents may prolong depolarisation, QTc interval and predispose to arrhythmias.

The correction of hypotension, hypoxia and acidosis will reduce the cardiotoxic effects of tricyclics. Ventricular arrhythmias refractory to sodium bicarbonate may require treatment with lidocaine, magnesium sulphate, or both (pg 150).

GPP

D Hypotension refractory to fluid resuscitation and sodium bicarbonate may require vasopressor support (norepinephrine, phenylephrine). Inotrope support (dopamine) may not be as effective (pg 150).

Grade D, Level 3

GPP For TCA-associated convulsions, benzodiazepines are recommended. The efficacy of phenytoin is not proven (pg 150).

GPP

GPP Flumazenil is not recommended in patients who have co-ingested TCA and benzodiazepines (pg 150).

GPP

D Symptoms of TCA toxicity generally present within 2 hours of ingestion. All patients with suspected significant cyclic antidepressant exposure should undergo cardiac monitoring for a minimum of 6-8 hours. Major complications (such as seizures and arrhythmias) typically occur in the first 6 hours after ingestion. Monitoring in symptomatic patients should continue until the ECG findings have been normal for 12-24 hours. Patients may be discharged then if there are no signs of toxicity and no significant ECG abnormalities (QRS < 100 milliseconds) (pg 150).

Grade D, Level 3

C While serum TCA levels may be used to confirm suspected poisoning, the levels do not correlate with toxic effects and are not predictive. ECG is recommended over serum TCA levels to predict seizure and arrhythmia risk (pg 151).

Grade C, Level 2+

Organophosphates (OP)

GPP The diagnosis of anticholinesterase poisoning is made by a combination of suspected exposure to a pesticide / insecticide and clinical signs and symptoms of a cholinergic crisis. Acetylcholinesterase levels, if available, should be used as supporting evidence of such poisonings (pg 153).

GPP

GPP The management of Intermediate Syndrome (IMS) involves prompt recognition of the condition and the institution of good supportive care, including ventilatory support as appropriate (pg 157).

GPP

GPP (pg 160)

- Resuscitation should proceed according to standard BCLS/ACLS protocols as indicated in all patients.
- The risk of secondary poisoning of health care workers from handling contaminated patients and property is of concern. However, the likelihood of severe poisoning is reportedly low. We recommend the use of simple protective measures: use of universal precautions, properly ventilated care areas and proper containment measures (including removal and containment of contaminated items & clothing) and prompt decontamination of patients as needed.

GPP

D (pg 161)

- Skin exposure would require irrigation of the skin with copious amounts of water and liberal use of soap. It is important for health care workers to wear appropriate protective gear before removing contaminated clothing and items from patients.
- Eye exposure should be irrigated with copious amount of normal saline. In all cases refer to ophthalmologist for further management. The routine use of atropine eye drops for relief of ocular symptoms is not recommended.
- General recommendations for gastric decontamination from oral exposure should be followed.

Grade D, Level 3

C Muscarinic antagonist: Atropine or glycopyrronium bromide (pg 162). Atropine use reverses the cholinergic effects. In particular, aim to dry bronchial secretions and reverse bronchospasm and to facilitate ventilation and oxygenation.

Glycopyrronium bromide can be an alternative for peripheral symptoms.

Grade C, Level 2+

A Pralidoxime should be used with caution for OP poisoning. It should be given in consultation with a clinical toxicologist or an expert in the care of poisoned patients (pg 166).

Grade A, Level 1+

C Benzodiazepines are recommended to control seizures and agitation in patients poisoned by organophosphorus compounds (pg 168).

Grade C, Level 2-

B The routine use of serum alkalinization using sodium bicarbonate is currently not recommended (pg 169).

Grade B, Level 1-

C Charcoal haemoperfusion or haemodialysis or haemofiltration are not recommended for managing poisonings with OP (pg 169).

Grade C, Level 2-

GPP (pg 169)

- There should be adequate fluid resuscitation and correction of acid-base and electrolyte disturbances as is deemed appropriate.
- Patients with OP poisoning tend to be fluid depleted due to the excessive sweating, gastrointestinal and urinary loss.
- There is no evidence that aggressive fluid resuscitation in patients with bronchorrhoea is dangerous provided atropine is also given simultaneously to dry the lung secretions.

GPP

GPP (pg 170)

- For accidental exposures in the workplace, it is important to remove the victim from further exposure and take measures to investigate and mitigate the source of exposure.
- It is mandatory to report occupational toxic exposure to Ministry of Manpower – *Refer to Annex D: Resources for industrial chemical exposure.*

GPP

Industrial chemicals (Hydrofluoric acid only)

GPP Dermal and ocular decontamination should be immediately performed using water or saline. The clothes should be removed and the exposed area washed by copious irrigation for at least 30 minutes (pg 175).

GPP

D Dialysis could be used for patients with severe systemic fluoride poisoning to lower F⁻ and potassium levels (pg 175).

Grade D, Level 3

D Apply calcium gluconate gel 2.5% liberally over the exposed dermal area and rub. Allow it to remain in place for a minimum of 30 minutes. Reapply gel every 4-6 hours (pg 176).

Grade D, Level 3

D Burns involving the fingers can be treated by placing the hands and gel in tight-fitting impervious gloves. Continue for at least 15 minutes after relief of pain (pg 176).

Grade D, Level 3

D Perform subcutaneous infiltration of calcium gluconate by injecting 0.3-0.5 mL/cm² of 5% calcium gluconate with a 27G to 30G needle when local gel application therapy fails, the site has sufficient tissue space and is not amenable for regional perfusion therapy (e.g. the thigh) (pg 176).

Grade D, Level 3

D Use the Bier block method for intravenous regional application of 2.5% calcium gluconate. A volume of 40 mL of 2.5% solution calcium gluconate is given via the regional intravenous anaesthesia route after the pressure cuff is inflated. The cuff is left inflated for about 20 minutes (pg 176).

Grade D, Level 3

D If intravenous regional perfusion therapy fails to relieve pain, intra-arterial application of 2.5% calcium gluconate should be tried. Usually the brachial or radial artery is cannulated depending on the site of injury and about 40 mL of 2-2.5% calcium gluconate is infused over 4 hours. May repeat cycle 4 hours later. About 1 – 3 cycles may be needed (pg 176).

Grade D, Level 3

D Administer bronchodilators for victims with bronchospasm together with parenteral corticosteroids as part of supportive treatment for respiratory irritation. Nebulisation using 1 mL of 10% calcium gluconate and 3 mL of normal saline (2.5% calcium gluconate) has been advocated. It has been shown that there are minimal side-effects when used at that concentration (pg 177).

Grade D, Level 3

D Do not use calcium gluconate gel for eyes and do not irrigate with calcium salts. If pain persists after irrigation, consider administration of 1% calcium gluconate eye drops every 2 – 3 hours for several days (pg 177).

Grade D, Level 3

A Treat hypocalcaemia using intravenous 10% calcium gluconate infusions with doses of 0.1 to 0.2 mL/kg up to 10 mL. Infusions can be repeated until serum calcium, ECG, or till symptoms improve. Calcium levels should be checked hourly (pg 178).

Grade A, Level 1+

Caustics and detergents

B Patients with suicidal ingestion or are persistently symptomatic after caustic ingestion should be referred for further investigations.

Suicidal ingestion, ingestion of concentrated acid or alkaline, or persistent symptoms predicts severe injury to the aerodigestive tract (pg 182).

Grade B, Level 2+

B Assessment of severity of corrosive injuries should not be based on degree of oropharyngeal burns.

The degree of oropharyngeal burns does not predict upper digestive tract injuries or stricture formation (pg 182).

Grade B, Level 2+

B Assess degree of injury in both adult and children with a flexible oesophageal-gastro-duodenoscopy (OGD).

The extent and depth of acute oesophageal and gastric injury are found to accurately predict stricture formation. OGD is the instrument of choice and it has been shown that it can be safely performed up to 48 hours after caustic ingestion (pg 182).

Grade B, Level 2+

GPP Perform contrast imaging studies with water-soluble contrast if OGD cannot be completed (pg 183).

GPP

GPP Skin exposure should be irrigated with a copious amount of water. Eye exposure should be irrigated with a copious amount of normal saline. In all cases of eye exposure, promptly refer to an ophthalmologist (pg 184).

GPP

GPP Gastric decontamination and activated charcoal are **not** recommended. Dilution with milk and water may be attempted in patients who are able to tolerate fluid. Neutralization of caustics is contraindicated (pg 185).

GPP

GPP To reduce stricture formation, the following treatments may be considered - bowel rest, proton pump inhibitor, intravenous antibiotics and intravenous steroids (pg 185).

GPP

Bites and stings

Snakebites

D Ensure that the snake is no longer a threat before instituting first aid. Keep calm. Do not attempt to incise the bite wound or suck the venom out. Transport to hospital as soon as possible (pg 187).

Grade D, Level 3

D Bind the crepe bandage firmly around the entire bitten limb, as tightly as for a sprained ankle. It should be loose enough to allow a finger to be easily slipped between its layers, and not occlude the peripheral pulse. Include a rigid splint or sling to avoid any muscular contraction of the bitten limb. Avoid tight tourniquets that may occlude circulation.

Movement or muscular contraction increases absorption of venom into the bloodstream and lymphatics (pg 187).

Grade D, Level 3

D In clinically significant envenoming, compression bandages should not be released until the patient is under medical care in hospital, resuscitation facilities are available and antivenom treatment has been started (pg 187).

Grade D, Level 3

D PIB is not recommended in cases of viper bites.

PIB may increase the danger of local necrotic effects of viper venom (pg 187).

Grade D, Level 3

D The pressure immobilisation may be removed if the clinical examination is normal and clinically insignificant envenoming is suspected.

Re-evaluate 1-2 hours later with laboratory tests. If laboratory tests are normal, repeat at least twice (pg 188).

Grade D, Level 4

D Observe all cases of probable venomous snake bite for at least 12 hours, after the bite or after removal of PIB. Monitor vital signs, limb circulation, wound infection, including urine for output and myoglobinuria. Monitor for an increase in girth and leading edge of oedema (pg 189).

Grade D, Level 4

D Secure airway and assist ventilation if required. Treat shock, renal failure, myoglobinuria or haemoglobinuria. Correct coagulopathy (pg 189).

Grade D, Level 4

D In systemic envenoming, an appropriate antivenom is indicated.

Antivenom therapy should be repeated after 1-2 hours, if there is persistent or recurrent coagulopathy or bleeding or deteriorating neurotoxic or cardiovascular signs along with full supportive treatment. Antivenom may

reverse systemic envenoming even when this had been present for several days. Antivenom is effective in reversing signs of local envenoming only if it is given within the first few hours after the bite (pg 189).

Grade D, Level 4

D Signs of local envenoming that indicate antivenom therapy include rapid extension of swelling (within a few hours of bites), local swelling involving more than half of the bitten limb, swelling after bites on the digits, enlarged tender lymph node draining the bitten limb (pg 189).

Grade D, Level 4

D Administer antivenom intravenously. Local or intramuscular administration of antivenom is not recommended. The initial dose of antivenom is usually empirical. Children are given exactly the same dose of antivenom as adults (pg 190).

Grade D, Level 4

B Pre-treatment with subcutaneous epinephrine [0.25 mL (1:1000)], reduces acute adverse reactions to antivenom. Patients with high-risk of developing allergic reaction may be pre-treated **empirically** with subcutaneous epinephrine, intravenous antihistamines (both anti-H1 and anti-H2) and corticosteroid (pg 190).

Grade B, Level 1+

D In asthmatic patients, prophylactic use of an inhaled adrenergic β_2 agonist may reduce the risk of bronchospasms (pg 190).

Grade D, Level 4

D Skin Tests for antivenom hypersensitivity are not recommended as skin tests are not predictive and may delay treatment and can themselves be sensitizing (pg 190).

Grade D, Level 4

D Rarely, compartmental syndrome could develop despite aggressive antivenom therapy, and if so, an orthopaedic referral is needed. The compartment pressure should be measured before resorting to fasciotomy (pg 190).

Grade D, Level 4

D Fluorescent staining and slit lamp examination should be performed to diagnose corneal ulceration. Topical antimicrobials (tetracycline or chloramphenicol) should be applied to prevent endophthalmitis or blinding corneal opacities. Use a dressing pad to close the eye (pg 191).

Grade D, Level 4

D Stingers should be removed by forceps or scraping with care to avoid breaking the venomous sac as soon as possible (pg 194).

Grade D, Level 3

Bees and wasps stings

GPP Treatment is symptomatic. Oral or injectable antihistamines may be used to reduce itching and swelling. Cool compress (ice should not be placed directly on the skin), elevations to limit oedema and local wound care have been recommended. Patients with severe symptoms, including airway, cardiovascular, or pulmonary compromise, or persistent symptoms should receive a short course of corticosteroids (pg 194).

GPP

D In cases of anaphylactic reaction, epinephrine should be given and repeated after 5 minutes in the absence of clinical improvement (pg 195).

Grade D, Level 4

D Patients with multiple stings may warrant extended observation at least 24 hours after envenomation, with close monitoring of serum chemistries, haemoglobin, myoglobin and creatinine phosphokinase (pg 195). (Healthy adults with > 50 stings, the elderly and in those with underlying medical problems and > 1 sting per kg in children)

Grade D, Level 3

D When there is severe systemic reaction of massive envenomation, careful monitoring for: rhabdomyolysis, thrombocytopenia, cardiac arrhythmias, renal failure and possible dialysis should be instituted (pg 195).

Grade D, Level 3

D In cases of corneal bee stings, pain relief should be provided. An urgent referral to the ophthalmologist should be done to rule out infection, uveitis and inflammatory glaucoma. Broad-spectrum topical antibiotics could be given to prevent secondary infection. Surgical removal of the embedded stinger is controversial (pg 195).

Grade D, Level 3

GPP Individuals who are aware they are allergic to stings should be advised to carry epinephrine auto injector (pg 195).

GPP

GPP Immunotherapy is indicated in adults and children who had life threatening reactions to bee or wasp stings including cardiovascular and respiratory symptoms, provided that either skin test or serum IgE is positive (pg 195).

GPP

Marine Envenomation

D Resuscitate and manage cardiorespiratory arrest (from stonefish, stingray, jellyfish, blue-ringed octopus envenomation) (pg 198).

- Treat anaphylaxis, if present.
- Tetrodotoxin envenoming or neurotoxicity from jelly fish stings will require intubation and ventilation, if respiratory paralysis occurs.
- Treat any major haemorrhage.

Grade D, Level 4

D Administer analgesics, including local anaesthetics where indicated (pg 198).

- Update the tetanus immunisation status.
- Relevant radiological investigations, surgical removal of foreign material and surgical debridement may be required to address the local lesion.

Grade D, Level 4

D Secondary infection, chronic ulcer and osteomyelitis can occur. Prophylactic antibiotic should be given in contaminated wounds (pg 198).

Grade D, Level 4

B First aid for stingray and stonefish stings is hot, non-scalding (not higher than 45°C) water immersion as the venom is heat labile (pg 198).

Grade B, Level 2++

A Hot water immersion may be useful for pain relief following jellyfish stings after the tentacles have been removed (pg 198).

Grade A, Level 1-

1 Poison management systems

Introduction

“What is it that is not a poison? All things are poison and nothing is without poison. Solely, the dose determines that a thing is not a poison.” Paracelsus (1493–1541), the Renaissance Father of Toxicology, in his Third Defense”.¹

A recent study detailing the demographic of poisoned patients in Singapore has been recently published.² The scale of the problem is not unlike most developed countries and accounts for approximately 1% of restructured public hospital Emergency Department (ED) workload, giving a poison exposure rate of 1.7 per thousand population. The estimated case fatality rate was 0.8 per thousand ED attendances for poisoning. It is of note that most accidental poisonings involves young patients (mean age 31.8 years) in their economically active years with a sizeable number occurring as a result of work related toxic exposures (8.1%). Also noteworthy is that the proportion of children (< 13 years of age) suffering a toxic exposure accounted for 7.4 % of victims but the large majority were the result of accidental exposures (91%), suggesting a need for poison prevention activities in this high risk group. A single toxin was involved most of the time (88.5%) but up to a maximum of 6 agents per incident has been reported to occur. The oral route of toxic exposure was usually the case and a large majority of incidents occurred in the home environment (39.2%). The common poisons included alcohol (27.8%); analgesics (13.2%) including paracetamol, NSAIDs, sedatives (8.4%); bites and stings (14.7%); and industrial chemicals (10.4%). Approximately a third of patients with toxic exposure were admitted with 4.7% of cases requiring close monitoring in a high dependency or intensive care setting. Of those admitted, a third required a short stay lasting less than 24 hours suggesting a possible cost benefit approach of a short stay ward for these cases with initial intensive management and monitoring.

The mortality from toxic exposures is low with good supportive care. Hence, the main challenge for clinician is to identify promptly those patients who might develop serious complications and those who might potentially benefit from specific interventions.

The range of toxins is wide and includes the following:

- Prescription medications.
- Over-the-counter (OTC) medications and health supplements.
- Traditional medicines including herbals.
- Drugs of abuse.
- Household and industrial chemicals.
- Natural toxins - poisonous plants and animals.

The reasons for toxic exposures are as wide and varied from recreational use to abuse of medications to accidental home or occupational exposures, deliberate self harm and environmental pollution. **The clinical spectrum of poisoning hence include acute, acute on chronic and chronic intoxications. These clinical guidelines are limited to acute poisonings of common toxins in the local context to maintain focus on the principles of emergency management of poisoning.**

Overview of management of poisoning

- Concerns about poisoning
- Management of poisoning
- Poison prevention
- Poisons resources

1.1 Concerns about poisoning

When managing patients with toxic exposures there are several concerns that the physician is faced with including the following:

- *Is the substance toxic? How toxic is it?*
- *Was there a toxic exposure?*
- *How can I manage the patient?*
 - Home with advice.
 - Observe and Discharge.
 - Admit.

1.1.1 Is the substance toxic? How toxic is it?

It is noted that all chemicals are potentially toxic to humans. However, the factors for determining individual toxicity are multifactorial. In

order to predict health effects from chemical exposures the following should be taken into account:

- Inherent toxicity of agent (e.g. water and oxygen has low inherent toxicity which require significant exposure doses before toxicity results compared to ricin which has high inherent toxicity resulting in toxicity with low dose exposure).
- Physico-chemical properties of the toxins.
- Exposure dose.
- Route of exposure.
- Physiological and genetic factors of the individual.
- In some cases environmental factors especially for exposure via the inhalational route (e.g. prolonged confined space exposure to inhaled toxins).

1.1.2 Was there a toxic exposure?

- *Admission of poisoning*
- *Witness account*
- *Circumstantial evidence*
- *High index of suspicion of poisoning*

The question of whether a toxic exposure had contributed to the patients' clinical presentation is rather challenging and dependent on the treating clinicians' training and experience as well as index of suspicion.

In some situations there may be admission of exposure to a toxic substance by the patient but occasionally in patients with altered mental states or deliberate self harm this history may be lacking and even misleading. In such cases, collateral history should be obtained from witnesses or paramedical staff with corroborating evidence from the site (such as unusual smells or even empty pill bottles or tablet packages etc) and should alert one to a possible toxic exposure and which may also give a clue to the possible agents involved. With linked electronic medical records and prescriptions amongst the restructured hospitals in Singapore, a search could also be mounted on medications available to the patient giving a clue as to the possible toxins involved. Careful clinical examination looking for toxidromes will add further weight to the possible toxicants from their anticipated health effects.

1.1.3 How can I manage the patient?

Finally, the clinician will be faced with decisions on management and disposition for which the above considerations are crucial to determine if the patient can be safely sent home with advice, monitored in a short stay unit before discharge or admitted for monitoring of target organ damage and specific / supportive care.

In this regard, the physician has to assess and appreciate that there are different severities of poisoning; from mild, moderate to severe. This depends on the specific poison concerned, the length of time that the person is exposed to the poison, the route of exposure (on the skin or by the mouth), and the age and weight of the patient. These factors determine the toxicity and the extent of medical treatment needed. For example, diabetes medicine prescribed by a doctor is beneficial to an elderly grandfather. However, the same dose taken by his 1 year-old grandchild could result in serious toxicity.

The specific outcomes in each case are also influenced by the resources available to the primary physicians managing the patient. In particular, consultation with a clinical toxicologist, if available, would be ideal in most toxic exposure scenarios so that the necessary assessment and relevant investigations are performed early to help determine the need for further interventions. The availability of a comprehensive toxicology laboratory services capable of quantitative and qualitative measurements of specific toxins with short turnaround times are crucial to critical decision making and hence also influence the final outcome. The availability of psychological support services in the form of counsellors, social workers and psychiatrist and half way houses, may also contribute to disposition decisions for patients with mild toxic exposures secondary to deliberate self harm, who can be potentially discharged back to the community.

In communities with poisons call centres, members of the public with toxic exposures can contact them directly in order to obtain first aid advice and need for seeking further medical attention. This has been noted to be a cost effective and safe strategy in many studies.³⁻⁹ These centres are also a useful resource to healthcare providers for the purpose of guiding them on management decisions for their patients who may have been exposed to a variety of toxic agents.¹⁰⁻¹⁵ These benefits of a poison centre have been demonstrated locally in a pilot project run as a drug & poison information centre (DPIC) from 2004

to 2008.¹⁶ In the local context, patients may contact his doctors' office for advice on toxic exposures.

1.2 Management of poisonings

The holistic management of toxic exposures should include the following considerations based on a risk assessment approach¹⁷ :

- Resuscitation and Stabilization (Chapter 2)
- Toxic Diagnosis
- Therapeutic interventions
 - Decontamination (Chapter 3)
 - Enhanced elimination of absorbed toxins (Chapter 4)
 - Antidotes (Chapter 5)
- Supportive care
- Psychosocial interventions (Annex C)

A brief account follows which is further elaborated on in the relevant Chapters in the practice guidelines.

1.2.1 Resuscitation and stabilization

- Treat life threatening problems:
 - ABC's.
 - Considerations for management of the severely poisoned patient: Standard ACLS versus Toxic-ACLS.
- Do not become a casualty yourself:
 - Personal protection is to be considered at all times (gloves, mask, protective suits).
 - Need for decontamination to be considered early.

The management of the poisoned patients follows the same approach as the management of any other life threatening conditions with three additional considerations.

(1) Firstly, the risk of potential secondary chemical exposure to rescuers and healthcare staff managing poisoned patients warrant strict attention to the use of universal precautions and the need for decontamination of casualties in order to not compromise the safety of the staff. In addition, decontamination of the victim reduces continued exposure of the victim to the toxin hence playing an important role in toxic management. Last but not least, the use of decontamination in hazardous materials incidents limits the spread of toxic chemicals, which potentially could lead to closure of critical facilities such as the emergency department due to secondary contamination. The impact of this is disastrous

especially when it occurs at a time when there is a surge in demand. Lessons learnt from the Sarin incident in Tokyo¹⁸ should be a constant reminder to pay attention to this uniquely poison management-related consideration.

- (2) Secondly, resuscitation of the severely poisoned patient must take into account the potential drugs involved and should not automatically follow standard ACLS¹⁹⁻²⁰ as the mechanism of toxicity of particular agents generating cardiac arrhythmias or haemodynamic instability do not occur via the same mechanism as that of primary cardiac diseases for which the standard ACLS protocols are geared to deal with. Indeed some knowledge of the specific mechanism of toxicity have been exploited in the clinical setting providing effective antidotes as first line alternatives to standard ACLS recommendations (e.g. use of glucagon in patients with symptomatic bradycardias from beta-blocker overdose).
- (3) Thirdly, it should be remembered that the patient with toxic exposure is in a dynamic state as continuous absorption of drug may cause abrupt changes in the level of consciousness and circulatory changes, which may predispose the patient to respiratory difficulties including the risk of aspiration and haemodynamic instabilities. Hence, the caring physician should be mindful of the need for repeated frequent clinical assessment, aided judiciously by the use of continuous vital signs monitoring devices (heart rate, respiratory rate, blood pressure, oxygen saturation and telemetry) in selected patients with toxins that are notorious for causing precipitous changes in the clinical condition. The risk benefits of the need for invasive procedures, such as prophylactic pre-emptive intubations to secure airway to prevent potential deterioration and to facilitate therapeutic interventions, should be carefully weighed in the context of rapid deterioration in the patient's clinical condition. Unfortunately, considerations on these issues are closely tied to the availability and utilization practices of limited resources such as monitored beds and intensive care beds which are constantly in demand.

1.2.2 Toxicological diagnosis

Several considerations are needed in making a toxicological diagnosis and in some instances this may be challenging with the lack of information from the patient either due to deliberate concealment and genuine lack of appreciation or awareness of the situation (e.g. drug-drug interactions between traditional and western medications) or secondary to altered mental states of the victim. In order not to

miss toxic conditions, it is always prudent for clinicians to give consideration of a possible toxic cause in particular when the clinical presentation does not allude to a specific diagnosis. It is also important to consider toxicological conditions in the context of multiple victims arriving from a common site with a similar spectrum of clinical symptoms and signs, as this suggests exposure to a toxin likely from the environment.

- **Identify the toxic agent / class**
 - **History**
 - **Medications and products brought in from scene**
 - **Electronic medical records (EMR) and E-prescription records**
 - **Contacting patient's primary physician**
 - **Physical examination**
 - **Toxidrome recognition**

Establishing the specific toxin or toxins responsible for the poisoning is crucial to the management of final outcome. Although some patients may be able to provide the specifics of these toxins, in many cases this is lacking. Hence, it is necessary for the astute physician to find resourceful ways in identifying these agents (some of which are mentioned above).

Very often it is impossible to establish the specific toxin or toxins contributing to the patient's clinical condition. If attempts to obtain the specific agent are in vain the physician could perform a careful examination to look for a toxidromes which are a constellation of signs and symptoms that point towards establishing a particular class of toxins that is likely contributing to the patients' presentation. This useful clue allows generic toxic interventions directed towards the particular class of toxins to proceed without specific knowledge of the particular toxin and hence reduces delay in toxic management. Some examples of toxidromes are given below.

Sympathomimetic Toxicidrome

Signs & Symptoms	Possible toxins
<ul style="list-style-type: none">- Anxiety / Delirium- Hypertension- Tachycardia- Hyperpyrexia- Mydriasis- Diaphoresis	<ul style="list-style-type: none">- Cocaine, Amphetamines, phencyclidine (PCP), Lysergic acid (LSD)- Withdrawal from narcotics, benzodiazepine, alcohol, long term beta-blocker therapy

Cholinergic Toxicidrome

Signs & Symptoms	Possible toxins
<ul style="list-style-type: none">- Salivation- Lacrimation- Urinary incontinence- Defaecation- Gastric cramping, hypermotility- Emesis	<ul style="list-style-type: none">- Organophosphate compounds- Carbamate insecticides

Once poisoning is suspected or confirmed, a thorough evaluation of the patient is in line comprising a detailed history, physical examination and targeted investigations.

1.2.2.1 Clinical evaluation of the poisoned patient

The clinical evaluation of the poisoned patient has the primary objective of triaging poisoned patients into mild, moderate and severe categories of poisoning by obtaining a targeted history, performing a careful physical examination and specific laboratory evaluation. This will not only help prognosticate but also determine the extent of therapeutic interventions and type of in-patient resources that need to be committed in each case.

1.2.2.2 History

- **Fact finding mission** – From patient, paramedics, family, friends, GP, circumstantial evidence such as empty packets, vomitus with pill fragments.
- **Who was exposed?** Demographic information including age, sex, weight.

- **What was ingested?** Name of agent and type of formulation e.g. tablets or liquid, extended release, ingredients on combination tablets, concentration of active compounds etc.
- **What else was ingested?** Any other co-ingestant especially medications from other physicians, alcohol, traditional medications and health supplements.
- **How much exposure?** To be estimated in mg / kg body weight. For cutaneous exposure: body surface area exposed.
- **When did poisoning occur?** Exact timing of ingestion or timings of ingestion episodes.
- **What were the symptoms post exposure?**
- **How was patient exposed to toxin?** Pertaining to route of exposure either oral, inhalation, cutaneous, or injection. For cutaneous and inhalational exposure: duration of exposure before decontamination or removal from toxic environment respectively.
- **Why exposed?** The reason for toxic exposure accidental versus intentional. Occupational exposures require notification to the Ministry of Manpower for occupational safety measures to be looked into while deliberate self harm requires referral for pastoral care and counselling.
- **AMPLE history?** As for any patient with trauma an AMPLE history comprising history of allergies, medications patient is regularly on, past medical problems, last meal and drink, and events that led to the poisoning as outlined above should be obtained.

1.2.2.3 Examination

- **Use all your senses to search for the clues:**
 - **LOOK**
 - Track marks in cubital fossa and groin suggestive of intravenous drug abuse.
 - Residue deposits around mouth nose, body surface.
 - Unusual colour of vomitus, urine.
 - **FEEL**
 - Temperature, sweating.
 - **SMELL**
 - Alcohol and other unique odours.

- **Assess ABCDE:**
 - **Airway & Breathing**
 - Ability to protect airway.
 - Respiratory rate & depth.
 - Oxygen saturation.
 - **Circulation**
 - Pulse rate and regularity.
 - Blood pressure.
 - **Disability**
 - Glasgow Coma Scale (GCS).
 - Pupil size and equality.
 - Do random glucose to exclude hypoglycaemia.
 - **Exposure**
 - To look out for external evidence of trauma such as head injury that may provide an alternative explanation for patient's condition.

1.2.2.4 Toxicological investigations

Targeted investigations are to be done in toxic exposures that supplement clinical evaluation with the objective of:

- (1) Assisting in confirming the diagnosis.
- (2) Helping predict severity of poisoning and prognostication.
- (3) To help determine the need for more intensive treatment.
- (4) To allow correction of baseline fluid, electrolyte and acid-base status.

The relevant investigations vary according to the specific poison involved and in some situations need to be done serially to assist in the continuing care of the poisoned patient. The following is a list of some of the useful investigations but the reader is advised to refer to the relevant Chapters for investigations related to specific poisoning agents.

- Random bedside glucose.
- ECG (electrocardiogram).
- Serum electrolytes and renal function.
- Liver function test.
- Creatine kinase.
- Full Blood Count.
- Clotting screen: PT/PTT/INR.
- Arterial blood gas.
- Specific toxin level e.g. serum paracetamol, salicylate, phenobarbital, theophylline, digoxin, iron, and lithium.

- Serum osmolality and osmolality gap.
- Abdominal X-ray may be useful in diagnosing certain radiopaque toxins which include chloral hydrate, heavy metals e.g. iron, iodides, phenothiazines, sustained-release preparations, solvents (chloroform, carbon tetrachloride), button batteries and play doh. However, the absence of radiopaque density on X-ray cannot exclude poisoning.
- Others e.g. CXR, CT.

The physician intending to use the laboratory to measure specific serum toxin levels should be knowledgeable about the capabilities and range of tests that are available in their local laboratory. They should know which tests to order, be aware as to the appropriate specimen that needs to be collected, the turnaround times for results and limitations of the assay techniques employed. It should be emphasized that serum toxic levels should be used as an adjunct to help guide the management of the poisoned patient. In this regards, it is important to note that serum toxin levels do not necessarily correlate with severity of toxicity. Hence, serum toxic levels should be interpreted in the context of the relevant clinical setting.

1.2.2.5 Comprehensive toxicology screening tests

In spite of providing direct evidence of intoxication, screening tests have many limitations and alter management in a small number of cases.²¹⁻²⁴ Hence, routine toxicology screen on blood, urine and stomach washout contents is not recommended as they do not influence specific management for the toxic exposure in most situations. In addition, these tests are not widely available and turnaround times may be prolonged making little impact to the clinical management. Therefore, the decision to order screening tests is left to the managing physician. However, some of these tests are important from the medico-legal perspective in certain situations e.g. blood alcohol level in drink driving cases.

1.2.3 Therapeutic interventions for poisoning

Therapeutic interventions for poisoning include decontamination, techniques to enhanced elimination of absorbed toxins and use of specific antidotes. Before the use of these modalities it is important to consider the following:

- (1) Is the toxic exposure potentially life threatening?

- (2) Does the procedure improve the final clinical outcome?
- (3) Does the benefit of the procedure outweigh its risks?

If the answer to these questions is yes, then it is worthwhile considering the therapeutic modality concerned. This risk assessment approach to poisoning allows early management decisions to be made with respect to these critical time sensitive interventions that may be important to the final clinical outcome for the patient. However, it must be noted that poisoning is a dynamic process with ongoing exposure and continual absorption of toxins occurring. This may result in rapid changes in the patient's condition and hence frequent sequential assessment should be carried out and the necessary adjustments to the treatment plan should be done accordingly.

1.2.3.1 Decontamination

- Decontamination involves removal of toxins from portals of entry before absorption into the blood stream. The entry of toxins into the body occurs via the oral, inhalational and dermal routes. The foetus gets exposure through the trans-placental route and hence toxic exposures in pregnant patients need to take into account the unborn child when considering therapeutic options and their indications.
- The method used for decontamination depends on route of poisoning:
 - Inhalational exposure: evacuation from toxic environment and provision of supplemental oxygen.
 - Dermal exposure: removal of contaminated clothing and shower or irrigation of affected site (dust before shower for dry chemical).
 - For eye exposure: removal of chemicals by copious irrigation of the affected eye by up to 1 litre of saline or symptomatic improvement occurs.
 - Oral exposure: inducing emesis, performing gastric lavage, activated charcoal, whole bowel irrigation, cathartics. Emesis is not recommended in the local context due to the risk involved and minimal clinical benefit especially with easy access to advanced care in Singapore.

NB: Knowledge of route of exposure to a toxin allows rescuers and health care providers to determine the appropriate protective gear needed to reduce secondary exposure to the particular toxin e.g. face mask with appropriate filter should be worn to reduce the entry of toxins via the inhalation route.

1.2.3.2 Enhanced elimination of absorbed toxins

Enhanced elimination of absorbed toxins entails the use of interventions that attempt removal of toxins that have been absorbed and circulating in the blood stream or distributed to the tissues. General characteristics of toxins that are amenable to removal by this means include toxins that have a low volume of distribution, low protein binding, prolonged elimination half-life, and low pKa, which maximizes transport across mucosal membranes into the GI tract or urinary tract. As most of these interventions involve invasive measures the benefits and risks of these interventions should be carefully considered in each case. The techniques (refer to Chapter 4 on Enhancing the elimination of toxic substances from the body for details) utilized in this context include the following:

- Multiple dose activated charcoal (MDAC)
- Alkaline diuresis
- Haemodialysis and Charcoal Haemoperfusion
- Plasma exchange

1.2.3.3 Antidotes

Despite the vast number of poisons in existence, there are only a small number with a specific antidote to counter and reverse its actions. Even in this small group with a specific antidote available, the use of it should take into account the risk and benefits of using these antidotes. In some situations, the use of these antidotes may actually worsen the condition, e.g. patients with combined poisoning with tricyclic antidepressants (TCA) and benzodiazepine agents face increased risk from use of flumazenil (benzodiazepine antagonist) due to unmasking of central nervous system stimulant effects of antidepressants resulting in seizures. As most antidotes are costly, a national stockpile should be established with an inventory list made available to physicians who will then be knowledgeable in how to obtain them in an emergency situation.

1.2.4 Supportive care

As for management of all emergency conditions, supportive treatment and nursing care are of paramount importance in sustaining life. Supportive care and observation may be necessary in poisonings to help evaluate delayed effects of certain poisonings; to manage an underlying disease that has been exacerbated because of the overdose;

and to evaluate and treat complications. Hence, in the context of toxic exposures, the following need to be taken into account:

(1) Vital signs.

Appropriate measures are to be taken to maintain vital signs to support organ function.

(2) Fluid / Electrolyte / Acid-Base status.

Correction of fluid deficits, electrolytes abnormalities and acid-base states.

(3) Delayed effects of poisoning.

Monitoring for delayed effects of poisoning.

(4) Monitor and treat secondary complications from poisoning.

This includes complications such as aspiration pneumonia secondary to vomiting with the airway unprotected; intracranial haemorrhage secondary to falls; or trauma secondary to altered mental states, etc.

(5) Follow up for end organ damage.

Last but not least to review for resolution of end organ damage with appropriate follow up tests.

The siting for further care following the emergent management of the poisoned patient is critical in preventing morbidity and mortality in this group of patients. With limited intensive care and high dependency resources in hospitals, this crucial decision lies with the emergency physician in consultation with the intensivist and toxicologist, if available. To assist deciding on the setting of care for the poisoned patient, there is a need to take into consideration the severity of intoxication, anticipation of potential serious toxic effects and the need for invasive therapeutic and supportive measures.

1.2.5 Psychosocial and workplace safety interventions

Depending on the reason for poisoning, referral to the appropriate specialist or agency to help resolve issues for the patient and prevent further occurrence of similar situations in the community is critical. In many cases, poisonings incidents are accidental and involve young children. Most of such exposures can be managed at home under the advice and supervision of trained personnel, thus saving caregivers undue stress and an unnecessary trip to the emergency department. In intentional exposure, psychological support and counselling are important in prevention of poisoning at the community level.

The following psychosocial considerations should form part of the management plan and disposition of all patients with toxic exposures:

- Referral to medical social worker (MSW) for counselling.
- Psychiatric referral and follow up.
- Workplace accident reporting to Ministry of Manpower (MOM).

1.3 Poison prevention

A wide variety of poisons exist in the environment that we work, live and play. Besides the intentional use of chemicals for poisoning, a large majority of poisonings occur secondary to accidental exposures. Hence, it is important to educate people on poison safety issues and hence prevent accidental poisonings. Accidental poisonings are known to be fairly common in the home and workplace with the extremes of ages more affected in the former. Children less than 5 years are inquisitive by nature and love to explore their surroundings. They are attracted to the colourful appearance of many household products and medicine, thinking that they are candy or a beverage. As their mobility and physical capacity increases, they are able to reach for medications and household items easily, especially if it is not stored properly. Typically, they would play with and taste anything they can get their hands on. In some cases they mimic adults and copy their actions, resulting in accidental overdose when they consume medications lying within their reach.

Most of the chemicals found in household items result in toxicity if not used appropriately. However, the effects depend on the concentration, pH and the potency of the chemicals, apart from the amount that the victim is exposed to.

Some examples of common household chemicals and their effects include the following:

- Cleaning agents may contain corrosive alkalis e.g. ammonium hydroxide, caustic soda, caustic lime.
- Detergents and antiseptic agents.
- Bleaching agents.

Likewise accidental poisonings can occur in the workplace. When such a sentinel event occurs, it is important for the physician managing the patient, to notify the relevant authority (Ministry of Manpower) in order to investigate and mitigate issues that led to such an incident at the workplace, hence improving workplace safety.

Fortunately, most accidental poisonings are mild, and most are not known to produce long-term adverse effects, and hence can be safely managed in the home or primary care setting with appropriate advice. This can potentially save the patient undue stress and an unnecessary trip to the Emergency Department.

Some useful tips for dealing with poisons exposure in the community follows:

(1) What should be done when poisoning is suspected in the community?

Call the ambulance (995) if:

- The patient has collapsed with no breathing or pulse, and start CPR.
- The patient is unconscious.
- The patient starts to have fits/seizures.

(2) First aid for suspected poisoning

First Aid for Suspected Poisoning

- If the victim has swallowed a poison, do not make him vomit. This could harm him further. However, if the victim starts to vomit spontaneously, turn him to lie on his left side to prevent the vomit from getting into the air passage. Do not give him any food or drink unless advised.
- If the victim has inhaled a poison, move him to fresh air immediately and open all the doors and windows to improve ventilation. Rescuers should take care not to breathe in the fumes themselves, and should leave the area as soon as possible.
- If the victim has poison on his skin, remove all contaminated clothing and rinse the skin under running water for at least 15 minutes.
- If the poison enters the eyes, remove contact lenses, if any, and rinse the affected eye gently under running water for at least 15 minutes. The victim should be encouraged to blink the eye while rinsing it but caution should be taken to prevent run-off water from entering the unaffected eye. Advise the victim not to rub the eye.

In seeking medical advice, always bring the chemical bottle with the label as overexposure to certain chemicals cause characteristic symptoms and the doctor needs to know what the chemical is before prescribing further treatment.

(3) Information needed for assessing toxic exposure include:

- The age and weight of the patient.
- The substance(s) and amount taken.
- Reason for toxic exposure.
- The time when the exposure occurred.
- Any symptoms that the patient might be experiencing.
- Any treatment you have done before calling.
- Past medical and medication history.

(4) Safety tips to prevent household poisoning:

- Follow the directions and warnings on the label before using it. Do not mix chemicals (e.g. bleach and toilet-bowl cleaner) unless specifically instructed.
- Keep products in their original containers with clearly labelled contents.
- Work with chemicals in well-ventilated areas. Turn on fans and open windows when using household chemical products. Avoid breathing chemical fumes.
- Before applying pesticides, ensure your children and their toys are not in the vicinity.
- Do not store cleaning products and food in the same cabinet.
- Keep household chemicals away from children's reach and sight. Use child resistant containers when available.
- Store toxic household and garden products in cabinets fitted with safety latches and/or locks.
- Never leave household chemicals unattended while in use and ensure that an adult is present. Put away the product immediately after use.
- Never equate medicines with candy when administering drugs to children.
- Educate children about the dangers of poisons in the home.
- Throw away old and/or expired household or chemical products.

(5) Poison control measures at the work place

In order to reduce the incidence of accidental poisonings in the workplace the following measures should be considered. The hierarchy of control measures in place

1. Elimination of toxic chemicals where possible, e.g. Industry is gradually moving away from production of lead based products.
2. Substitution of toxic chemicals with agents that are less toxic but equally effective.
3. Engineering controls measures to reduce exposure of the worker to toxic chemicals. Examples include:
 - Automation of industrial processes.
 - Installation of ventilation systems such as local exhaust ventilation to prevent build up of toxic chemicals at the work environment.
4. Administrative measures:
 - Adopting safe work practices (codes of practice) including updating of staff on chemical hazards in the workplace, frequent reminders for following safe work procedures and need for appropriate medical surveillance where needed.
5. Provision of Personal Protective Equipment (PPE) if workplace exposure is unavoidable. This should be done in conjunction with proper selection and fitting of such equipment as well as providing training and competency checks to ensure proper use of this equipment.
6. Legislation:
 - Mandatory medical surveillance of exposed workers by means of biological monitoring e.g. blood lead and haemoglobin levels on all exposed workers to be done biannually.
 - Environmental monitoring of toxins in the air e.g. monitoring lead levels in air to ensure that it does not exceed the Permissible Exposure Limit (PEL).
 - Mandatory notification of workplace accidents to Ministry of Manpower (MOM).

1.4 Poisons Resources

Many countries have Poison Control Centres which provide health care providers and the community access to basic poisons information. These centres provide poisons information for toxic exposures, including advice on first aid and detailed management interventions

relevant to the enquirer in a time sensitive manner. As a result, these centres are noted to have been useful in improving patient care and outcomes from toxic exposures while rationalizing the use of limited hospital resources; in particular by providing telephone triage for toxic exposures resulting in avoidance of unnecessary visits to emergency departments.

A wide variety of other sources of poison information are available including propriety online poisons databases, textbooks on toxicology and clinical toxicologists. However, in order to expedite the management of poisonings, it is important for the physician to be aware of the poisons resources available in his local set up. Poisons management resources available in Singapore are listed in the toxipedia website (<http://toxipedia.org/display/wlt/Singapore>).

2 Principles of management of acute poisoning – resuscitating the poisoned patient

The critically poisoned patient should be managed according to standard advanced cardiac life support (ACLS) measures. However, there are special exceptions during critical poisoning because of altered pharmacokinetic and pharmacodynamic conditions. It is not the intent of this chapter to describe the standard ACLS measures.

Due to the infrequent occurrence of severe poisoning, evidence to support these recommendations are mainly based on case reports, case series and animal studies.

Frequently, resuscitation efforts are stopped after 30 minutes of resuscitation if there are no signs of life. However, in drug-induced cardiac arrest, vigorous attempts at supporting circulation, including the use of cardiopulmonary bypass or extracorporeal membrane oxygenation, have been associated with recovery of good neurologic function. Examples include poisoning due to cardiac medications such as propranolol and verapamil and antidepressive agents such as imipramine.²⁵⁻²⁸

GPP In a critically poisoned patient, measures beyond standard resuscitative protocol like those listed above need to be implemented and a specialist experienced in poisoning management should be consulted.

GPP

D Prolonged resuscitation should be attempted in drug-induced cardiac arrest.

Grade D, Level 3

2.1 Airway and breathing

The principles involved in assessing adequate airway protection and need for endotracheal intubations are similar to non-poisoned patients. However, in the resuscitation of a poisoned patient, intubation and mechanical ventilation should be considered especially early for specific circumstances, such as corrosive injury to the airway or ingestion of highly toxic poisons like tricyclic antidepressants.

2.1.1 Opioid poisoning

Opioids, such as heroin, commonly cause respiratory depression followed by respiratory failure. Naloxone is an antagonist that can quickly reverse opioid-induced respiratory depression. It can be administered via the intravenous, intramuscular or subcutaneous route. Hence, careful and repeated administration of naloxone, together with bag-valve-mask ventilation, may obviate the need for endotracheal intubation and its attendant complications in patients with a palpable pulse.²⁹⁻³⁰

C Titrated doses of naloxone, together with bag-valve-mask ventilation, should be administered for suspected opioid-induced coma, prior to intubation for respiratory insufficiency.

Grade C, Level 2+

2.2 Circulation

Many poisoning agents affect the cardiovascular system and cause significant hemodynamic changes.

2.2.1 Bradycardia

Common toxicology agents that cause bradycardia include beta-blockers, calcium-channel blockers (CCBs), digoxin and acetylcholine receptor antagonists such as organophosphates and carbamates. Interference with cellular physiology and receptor blockade may result in symptomatic bradycardia refractory to standard ACLS protocols. Further management in these situations may require the use of antidotes.

For example, the administration of atropine for organophosphate poisoning may be lifesaving (refer to Chapter 9 on Organophosphates). Another example would be poisoning due to beta-blockers and CCBs. The resultant bradycardia and hypotension is commonly refractory to usual vasopressor therapy and intravenous calcium, glucagon and high-dose insulin euglycaemia therapy may be warranted.³¹⁻³⁴ Please refer to Annex A for further information on these specific antidotes.

D In bradycardia due to calcium channel or beta-blocker toxicity that is refractory to conventional vasopressor therapy, intravenous calcium, glucagon or insulin should be used.

Grade D, Level 3

B Patients with actual or potential life threatening cardiac arrhythmia, hyperkalaemia or rapidly progressive toxicity from digoxin poisoning should be treated with digoxin-specific antibodies.³⁵⁻³⁶

Grade B, Level 2++

2.2.2 Tachycardia

Many poisoning agents cause tachycardia from excessive catecholamine release, anticholinergic effect and other drug-specific mechanisms. Common examples of such agents include the sympathomimetics, theophylline, tricyclic antidepressants and the anticholinergic medications. The tachycardia due to poisoning may be refractory to standard ACLS protocols.

Benzodiazepines, such as lorazepam or diazepam, are safe and effective in attenuating the excessive catecholamine release and controlling tachycardia.³⁷⁻⁴⁰ However, the patients should be monitored carefully to avoid respiratory depression. Beta-blockers need to be used with caution. Non-selective beta-blockers, such as propranolol, can potentially cause paradoxical hypertension due to unopposed alpha effects and are contraindicated in poisoning due to sympathomimetic agents.⁴¹⁻⁴² A short-acting selective β -1 blocker, such as esmolol, may be used if the tachycardia remains uncontrolled with benzodiazepines. Theophylline has an anti-adenosine effect and consequently, SVT due to theophylline toxicity may not respond to adenosine. In pure anticholinergic poisoning, one small study suggests that physostigmine may be superior to benzodiazepines alone.

B Titrated doses of benzodiazepine should be given in hyperadrenergic-induced tachycardia states resulting from poisoning.

Grade B, Level 1+

D Non-selective beta-blockers, like propranolol, should be avoided in stimulant toxicity as unopposed alpha agonism may worsen accompanying hypertension.

Grade D, Level 3

D Physostigmine should be considered for treating tachycardia resulting from pure anticholinergic poisoning.

Grade D, Level 3

2.2.3 Ventricular arrhythmia

Drug induced VT / VF should be treated with standard ACLS protocol. Lidocaine is considered the drug of choice for ventricular arrhythmias due to poisoning. Class 1A, 1C antiarrhythmics and sotalol are contraindicated for TCA poisoning as they can cause synergistic toxicity.

GPP Lidocaine is the drug of choice for most ventricular arrhythmias due to drug toxicity.

GPP

2.2.4 Impaired conduction

Impaired conduction caused by sodium channel blocking agents such as tricyclic antidepressants, type 1a and 1c drugs, diphenhydramine and cocaine cause prolonged QRS, prolonged QT, hypotension and ventricular arrhythmias. Administration of sodium bicarbonate provides both the sodium load necessary to overcome the sodium blockade as well as the additional benefit of systemic alkalization.⁴³⁻⁴⁴ While no studies address the optimal target pH, it is reasonable to aim for a pH of 7.45 to 7.55.

C Sodium bicarbonate should be used in impaired conduction defect caused by sodium channel blocking agents such as tricyclic antidepressants.

Grade C, Level 2+

2.2.5 Hypertension

Significant drug-induced hypertension should generally not be treated with long-acting agents as there may be rebound hypotension when the drug effect wears off. Short-acting antihypertensive agents include nitroprusside, nitroglycerin and short-acting beta-blockers like esmolol. Non-selective beta-blockers such as propranolol should be avoided (see section on tachycardia). Direct vasodilators, such

asphenolamine, may be required to treat overdose by drugs with direct adrenergic activity, such as amphetamines.

Hyperadrenergic states as in sympathomimetic drug overdose or drug withdrawal syndromes frequently result in agitation, tachycardia and hypertension. Benzodiazepine is a useful and safe first line drug in drug-induced hypertension in these situations.^{37-40, 45}

B Titrated doses of benzodiazepine can be used to treat hypertension associated with drug-induced hyperadrenergic states.

Grade B, Level 1+

2.2.6 Hypotension

Drug-induced hypotension is generally due to hypovolemia with decreased contractility and decreased systemic vascular resistance (SVR). Some drugs however, cause increased SVR instead. The first line of treatment is fluid loading but be careful of precipitating pulmonary congestion. This is followed by standard doses of vasopressors, such as dopamine and norepinephrine.

D High dose vasopressor therapy for hypotension caused by poisoning needs to be titrated to response and complications.⁴⁶⁻⁴⁷

Grade D, Level 3

Serious complications can result from high dose vasopressor use and these include arrhythmia, end organ ischemia and infarction.

Specific inotropic agents should be considered for specific class of poisoning when there is decreased contractility not responding to standard therapies. These include calcium, glucagon and high dose insulin euglycaemia therapy.

D Calcium chloride or gluconate can be given for calcium-channel blocker overdose.^{31-32,48}

Grade D, Level 3

D Glucagon can be given for beta- blocker and calcium-channel blocker overdose.⁴⁹⁻⁵⁰

Grade D, Level 3

D High dose insulin euglycaemia therapy (HIE) is efficacious for use during calcium-channel and beta-blocker overdose.^{33, 51-53}

Grade D, Level 3

D Life support with circulatory assist device, such as intra-aortic balloon pump and bypass circuits (example: extracorporeal life support system) should be considered in severe refractory hypotension that is unresponsive to maximal medical therapy.^{27-28, 54} Deployment of these devices should be preplanned in advance.

Grade D, Level 3

These devices are expensive, manpower intensive and available only in certain institutions.

2.3 Deficits

GPP For poisoned patients presenting with depressed conscious level due to unspecified drugs, the following treatment should be considered: naloxone, glucose, oxygen and thiamine.

GPP

Although flumazenil may be effective in the reversal of coma in patients presenting to the emergency department with coma from suspected drug poisoning, routine use of flumazenil is not recommended as benzodiazepine overdose is seldom fatal.

2.4 Investigations and disposal

In patients with deliberate self-harm, some screening test should be done even if the patient is asymptomatic. The screening tests could include a renal panel with bicarbonate level, an electrocardiogram and serum paracetamol level.⁵⁵⁻⁵⁶ Paracetamol poisoning is the most common poisoning in Singapore, has delayed hepatotoxicity presentation and there is an effective antidote, N-acetylcysteine. A routine toxicological screen is generally not recommended for all patients with poisoning.⁵⁷⁻⁵⁸ This however, could be considered in cases with severe poisoning with an unknown agent, in a comatose patient or for medico-legal purposes, such as industrial incidents. In such cases, the decision to order screening tests is left to the managing physician.

B Routine toxicology screen for poisoning agents in the blood and urine or other body fluids is not advised.

Grade B, Level 1-

D Checking serum paracetamol level should be considered, especially in a situation of parasuicide where the history may not be forthcoming. Paracetamol is the most common drug involved in parasuicides locally and is readily amenable to treatment with antidotes.

Grade D, Level 4

Most poisoned patients can be managed in the general ward, if admitted. Intensive care management would depend on the type and quantity of drugs ingested as well as the patients' clinical condition.

D Patients, who ingested drugs that are of sustained-release formulation; have a prolonged half-life; or active metabolites that have prolonged effects, should be observed for a longer period of time.⁵⁹

Grade D, Level 4

3 Decontamination after poisoning

This section refers to decontamination of poisons ingested orally.

3.1 Single dose activated charcoal

C Single dose activated charcoal is indicated as a gastric decontaminant agent if a patient has ingested a potentially toxic amount of a poison up to 1 hour following ingestion (*).

Grade C, Level 2+

*please see indications and contraindications below.

3.1.1 Indications

If a patient has ingested a potentially toxic amount of a poison up to 1 hour following ingestion, activated charcoal (AC) has been found to be a useful means of gastrointestinal decontamination.⁶⁰⁻⁶¹

3.1.2 Contraindications⁶⁰⁻⁷¹

- Patients with an unprotected airway (depressed state of consciousness without endotracheal intubation).
- Patients at risk of aspiration (e.g. hydrocarbon with high aspiration potential).
- Patients at risk of haemorrhage or GI perforation due to pathology, recent surgery or medical conditions.
- Where AC in the GIT may obscure endoscopic visualisation, though corrosives by themselves are not a contraindication and AC can be used if there are co-ingestants that are systemic toxins.
- Struggling child and uncooperative adults.

3.1.3 Complications⁶⁰⁻⁷¹

Inappropriate use of AC can lead to more serious morbidities:

- Aspiration leading to pulmonary problems.
- Emesis – especially when AC is administered with sorbitol.
- Theoretical risk GI obstruction, constipation, or haemorrhagic rectal ulceration (none reported with single dose AC).
- Corneal abrasions on direct ocular contact.

3.1.4 Substances where Activated Charcoal (AC) is of no proven use / contraindicated / poorly adsorbed^{60-61,70-71}

- Alkali
- Ethanol & other alcohols
- Ethylene glycol
- Fluoride
- Inorganic salts
- Iron
- Lithium
- Mineral acids
- Potassium
- Hydrocarbons
- Caustics

3.1.5 Dosage recommendation⁶⁰⁻⁶¹

The dose is roughly based on 10:1 ratio of AC to the drug for adsorption.

- Children up to 1 year of age: 10-25 g or 0.5 – 1 g/kg.
- Children up to 1 to 12 years of age: 25 to 50 g or 0.5 to 1 g/kg.
- Adolescents and adults: 25 to 100 g.

Although dosing via body weight is recommended for children, there are no data or scientific rationale to support this recommendation.

GPP The recommended dose for activated charcoal is as follows:

- Children up to 1 year of age: 10-25 g or 0.5 – 1 g/kg.
- Children from 1 to 12 years of age: 25 to 50 g or 0.5 to 1 g/kg.
- Adolescents and adults: 25 to 100 g.

GPP

3.1.6 Palatability of AC

The palatability of AC affects its eventual acceptance by patients, especially in children. Use of various substances to mask its taste and improve its palatability has been studied.⁷²⁻⁸²

Ultimately it may be a balance between improving palatability of AC and the effect of the substance used with AC affecting AC's adsorptive properties.

<i>Substance</i>	<i>Effect on Adsorptive Properties</i>	<i>Improvement in Palatability</i>
Ice cream / Sherbet	Reduced efficacy	Nil / Minimal
Chocolate syrup	Conflicting results	Improved
Cola	No data	Improved
Orange juice	No data	Nil / Minimal

C Activated charcoal can be used with additives like orange juice, chocolate syrup and cola to improve its palatability. However use of these additives may decrease AC's adsorptive properties.

Grade C, Level 2-

3.1.7 Use of ACs with cathartics⁶²⁻⁶³

There is no difference in transit time between Magnesium citrate/Sodium sulfate with AC or use of AC alone.
(See References under "Cathartics" below)

C Use of activated charcoal with cathartics does not improve outcome of gastric decontamination compared to AC alone.

Grade C, Level 2-

3.1.8 Use of ACs with other forms of gastric emptying⁶²⁻⁶³

AC may be used with other forms of gastric emptying in the following clinical situations:

- Symptomatic patients presenting in the first hour after ingestion of substances that may result in life-threatening and/or severe, difficult to treat cardiovascular consequences:
 - calcium-channel blockers, beta-blockers, tricyclic antidepressants.
- Symptomatic patients who have ingested agents that slow gastrointestinal motility.
- Patients taking sustained-release medications.

- Patients taking massive or life-threatening amounts of medication (especially paracetamol, theophylline, aspirin, ibuprofen) – where the grams ingested will likely supersede the AC: Drug ratio of 10:1.

D Use of activated charcoal with other forms of gastric emptying (e.g. gastric lavage) may be indicated in specific types of poisoning where the poison is seriously life-threatening; the dose ingested is of a massive amount; the poison is in a sustained-release preparation; the poison slows gastrointestinal motility.

Grade D, Level 3

C Use of activated charcoal should not be used at home as first aid because its benefit has not been proven.

Grade C, Level 2+

3.2 Gastric lavage

C Gastric lavage should not be employed routinely, if ever, in the management of poisoned patients.

In certain cases where the procedure is of attractive theoretical benefit (e.g. recent ingestion of a very toxic substance), the substantial risks should be weighed carefully against the sparse evidence that the procedure is of any benefit.

Grade C, Level 2+

3.2.1 Indications^{83,84}

Gastric lavage should not be employed routinely, if ever, in the management of poisoned patients. Gastric lavage does not appear to push contents/ingestants antegrade-wise.⁸⁵⁻⁸⁸

3.2.2 Contraindications^{83,89-94}

- Loss of airway protective reflexes, (depressed state of consciousness)
 - unless intubated tracheally.
- Ingestion of a corrosive substance, such as a strong acid or alkali.
- Ingestion of a hydrocarbon with high aspiration potential.
- Patients who are at risk of haemorrhage or GI perforation due to pathology, recent surgery, or other medical condition such as a coagulopathy.

3.2.3 Complications^{83,89-103}

- Aspiration pneumonia – due to unprotected airway.
- Perforation of the oesophagus has been reported with charcoal in the peritoneum, presumably from GI perforation.
- Laryngospasm/hypoxia/tension pneumothorax/charcoal empyema.
- Tachycardia and cardiac dysrhythmias (atrial and ectopic beats; transient ST elevations).
- Fluid and electrolyte imbalance (particularly in children lavaged with water instead of saline) – hypernatremia; water intoxication.
- Small conjunctival haemorrhage.

3.2.4 Technique of gastric lavage⁸³⁻⁸⁴

Gastric lavage is not recommended outside of a health care facility. The procedure should be explained to the patient, if conscious and not confused, and verbal consent obtained.

A patient without previous experience of the procedure should be told that a tube will be passed into their stomach so that the poison can be ‘washed out’.

In case of emesis, and before undertaking lavage, it is essential to ensure that a reliable suction apparatus is available and functioning. Endotracheal or nasotracheal intubation should precede gastric lavage in the comatose patient without a gag reflex. An oral airway should be placed between the teeth to prevent biting of the endotracheal tube if the patient recovers consciousness or has a convulsion during the procedure.

The patient should be placed in the left lateral/head down position (20° tilt on the table).

The length of tube to be inserted is measured and marked before insertion.

A large bore 36–40 French or 30 English gauge tube (external diameter approximately 12–13.3 mm) should be used in adults; and 24–28 French gauge (diameter 7.8–9.3 mm) tube in children.

The orogastric tube should be for single-use only. The lavage tube should have a rounded end and be sufficiently firm to be passed into the stomach via the mouth, yet flexible enough not to cause any mucosal damage.

The tube should be lubricated with a hydroxyethylcellulose jelly before being passed. A nasogastric tube is of insufficient bore to produce a satisfactory lavage as particulate matter, including medicines, will not pass; moreover, damage to the nasal mucosa may produce severe epistaxis.

Force should not be used to pass the tube, particularly if the patient is struggling. Once passed, the position of the tube should be checked either by air insufflation, while listening over the stomach, and/or by aspiration with pH testing of the aspirate.

Traditionally, an aliquot of this sample has been retained for toxicological analysis though, except in the case of forensic examinations, the majority of laboratories now prefer blood and urine for analysis.

Lavage is carried out using small aliquots of liquid. In an adult, 200–300 mL (preferably warm 38°C) fluid, such as normal saline (0.9%) or water, should be used. In a child, warm normal saline (0.9%) 10 mL/kg body weight should be given.

The volume of lavage fluid returned should approximate the amount of fluid administered. Water should be avoided in young children because of the risk of inducing hyponatremia and water intoxication.

Small volumes are used to minimize the risk of gastric contents entering the duodenum during lavage, since the amount of fluid affects the rate of gastric emptying. Warm fluids avoid the risk of hypothermia in the very young and very old and those receiving large volumes of lavage fluid. Lavage should be continued until the recovered lavage solution is clear of particulate matter. It should be noted that a negative or poor lavage return does not rule out a significant ingestion

3.3 Ipecac

3.3.1 Introduction¹⁰⁴⁻¹⁰⁵

Ipecac is an emetic agent and the chief active ingredients are two alkaloids: emetine and cephaeline (up to 90% of the alkaloids in ipecac) and present in a ratio that does not exceed 2.5:1.

3.3.2 Indications¹⁰⁴⁻¹¹¹

There is insufficient data to support or exclude ipecac administration soon after poison ingestion. Ipecac should be considered only in an alert conscious patient who has ingested a potentially toxic amount of a poison. As the effect of ipecac diminishes with time and as clinical studies have demonstrated no benefit from its use, it should be considered only if it can be administered within 60 minutes of the ingestion. Even then, clinical benefit has not been confirmed.

C Ipecac has no proven acute role in gastrointestinal contamination management as there is insufficient data to support or exclude its administration soon after poisons ingestion.

Grade C, Level 2+

3.3.3 Contraindications^{104-105,106-107}

- Compromised airway protective reflexes (including coma and convulsions).
- Ingestion of a substance that might compromise airway protective reflexes or anticipate the need for advanced life support within 60 minutes.
- Ingestion of hydrocarbons with high aspiration potential.
- Ingestion of a corrosive substance, such as an alkali or strong acid.
- Debilitated, elderly patients or medical conditions that may be further compromised by the induction of emesis.

3.3.4 Complications¹¹²⁻¹²⁶

- Diarrhoea / vomiting / prolonged vomiting (> 1 hour).
- Lethargy / drowsiness.
- Aspiration / Mallory-Weiss / pneumomediastinum.

- Irritability / hyperactivity.
- Fever / diaphoresis.
- Fatalities: traumatic diaphragmatic hernia / intracranial haemorrhage / gastric rupture.

B Use of ipecac as a first aid measure at home has not been proven to be beneficial.

Grade B, Level 2++

3.4 Cathartics

3.4.1 Types and action of osmotic cathartics¹²⁷

- Saccharide cathartics (e.g. sorbitol).
- Saline cathartics (e.g. magnesium citrate, magnesium sulphate, sodium sulphate).

Cathartics accelerate the expulsion of poison from the GIT as most drug absorption occurs rapidly in the upper GI tract. The use of cathartics is most likely to benefit patients who have ingested materials that are absorbed slowly. Slow-release products are a potential example, but there are little clinical data on the efficacy of cathartics.

3.4.2 Indications¹²⁷⁻¹³⁷

The administration of an osmotic cathartic alone has **no** role in the management of the poisoned patient and is **not** recommended as a method of gut decontamination. Based on available data, the routine use of a cathartic in combination with AC is not endorsed. If a cathartic is used, it should be limited to a single dose in order to minimize adverse effects of the cathartic.

C The administration of a cathartic alone has **no** role in the management of the poisoned patient and is **not** recommended as a method of gut decontamination.

Grade C, Level 2+

3.4.3 Dosage regimens (single doses)¹²⁷

a) Sorbitol

The dose of sorbitol is approximately 1–2 g/kg body weight.

The recommended dose of 70% sorbitol is 1–2 mL/kg in adults and 35% sorbitol 4.3 mL/kg in children.

b) Magnesium Citrate

A commonly recommended dose is magnesium citrate 10% solution 250 mL in an adult and 4 mL/kg body weight in a child.

C Based on available data, the routine use of a cathartic in combination with AC is not endorsed.

Grade C, Level 2+

GPP If a cathartic is used, it should be limited to a single dose in order to minimize adverse effects of the cathartic.

GPP

3.4.4 Contraindications¹²⁷⁻¹³⁷

- Absent bowel sounds, recent abdominal trauma, recent bowel surgery, intestinal obstruction or intestinal perforation.
- Ingestion of a corrosive substance.
- Volume depletion, hypotension or significant electrolyte imbalance.
- Magnesium cathartics should not be given to patients with renal failure, renal insufficiency or heart block.
- Cathartics should be administered cautiously to the very young (<1 year of age) and to the very old.

3.4.5 Complications - single dose¹²⁷⁻¹³⁷

- Nausea, abdominal cramps, vomiting.
- Transient hypotension.
- Diaphoresis.

3.4.6 Complications - multiple or excessive doses¹²⁷⁻¹³⁷

- Dehydration.
- Hyponatremia in patients receiving sodium-containing cathartics.

- Hypermagnesemia in patients receiving magnesium-containing cathartics.

3.5 Whole bowel irrigation (WBI)

3.5.1 Introduction¹³⁸⁻¹³⁹

WBI cleanses the bowel by the enteral administration of large amounts of an osmotically balanced polyethylene glycol electrolyte solution (PEG-ES) which induces a liquid stool.

WBI has the potential to reduce drug absorption by decontaminating the entire gastrointestinal tract by physically expelling intraluminal contents. The concentration of polyethylene glycol and electrolytes in PEG-ES causes no net absorption or secretion of ions, so no significant changes in water or electrolyte balance occur.

WBI should not be used routinely in the management of the poisoned patient. No controlled clinical trials have been performed and there is no conclusive evidence that WBI improves the outcome of the poisoned patient.

C Whole bowel irrigation (WBI) should not be used routinely in the management of the poisoned patient.

Grade C, Level 2+

3.5.2 Dosage regimens¹³⁸⁻¹³⁹

- WBI fluid is best administered through a nasogastric tube.
- There are no dose-response studies upon which to base dosing. However, a recommended dosing schedule for WBI is:
 - Children 9 months to 6 years: 500 mL/h.
 - Children 6–12 years: 1000 mL/h.
 - Adolescents and adults: 1500–2000 mL/h.

3.5.3 Technique of whole bowel irrigation¹³⁸

The following equipment is needed for whole bowel irrigation:

- A small bore (12 F) nasogastric tube.
- A feeding bag used for NG tube feedings.

- An intravenous pole.
- A supply of polyethylene glycol electrolyte solution.
- A commode.

Before commencing, it is preferable to confirm radiologically that the tip of the NG tube is in the midportion of the stomach as this position increases the likelihood of anterograde propulsion of the ingestant.

The patient should be seated or the head of the bed elevated to at least 45 degrees. Placing the patient in an upright position promotes the settling of the ingestant into the distal portion of the stomach, decreases the likelihood of vomiting, and establishes a dependent relationship of the intestines to the stomach.

WBI should be continued at least until the rectal effluent is clear although the duration of treatment may be extended based on corroborative evidence (e.g. radiographs or ongoing elimination of toxins) of continued presence of toxins in the gastrointestinal tract. (E.g. 4 hours for delayed release-aspirin).

After completion of WBI, additional liquid bowel movements will occur.

3.5.4 Emesis during WBI¹³⁸⁻¹³⁹

This is usually due to the ingestant or prior use of ipecac. Parenteral antiemetic which does not impair consciousness – e.g. metoclopramide (and has both antiemetic and gastric emptying properties) may be used to minimise emesis. The likelihood of emesis is also decreased by keeping the patient’s upper half of the body upright. If emesis still occurs despite the above measures, decrease the infusion rate by 50% for 30–60 minutes and then return to the original rate.

3.5.5 WBI and AC¹⁴⁰⁻¹⁴⁴

Studies support that there is competition between polyethylene glycol and ingested drugs for charcoal binding sites. It is difficult to determine the relevance of these in vitro data to clinical practice. If AC and WBI use is clinically indicated, there is the potential for decreased effectiveness of charcoal.

C The concurrent administration of activated charcoal and WBI may decrease the effectiveness of the charcoal.

Grade C, Level 2-

3.5.6 Indications¹⁴⁵⁻¹⁵⁴

- WBI should be considered for potentially toxic ingestions of sustained-release or enteric-coated drugs.
- WBI should be considered in the management of patients who have ingested substantial amounts of iron because of the high morbidity and mortality of this poisoning and a lack of other options for gastrointestinal decontamination.
- WBI should be considered for the removal of ingested packets of illicit drugs.
- WBI should **not** be used routinely, but could have potential value in a limited number of toxic ingestions, based on experimental studies and anecdotal reports.

C WBI should be considered for potentially toxic ingestions of sustained-release or enteric-coated drugs particularly for those patients presenting greater than two hours after drug ingestion and there is a lack of other options for gastrointestinal decontamination (e.g. substantial amounts of iron/ingestion of illicit packets of drugs).

Grade C, Level 2+

3.5.7 Contraindications¹⁴⁵⁻¹⁵⁴

- Bowel perforation.
- Bowel obstruction.
- Clinically significant gastrointestinal haemorrhage ileus.
- Unprotected or compromised airway.
- Hemodynamic instability.
- Uncontrollable intractable vomiting.

C WBI is contraindicated in patients with bowel obstruction, perforation, ileus, and in patients with hemodynamic instability or compromised unprotected airways.

It should be used cautiously in debilitated patients or in patients with medical conditions that may be further compromised by its use.

Grade C, Level 2+

3.5.8 Complications¹⁴⁵⁻¹⁵⁴

- Nausea, vomiting, abdominal cramps, and bloating (described when WBI was used in preparation for colonoscopy).
- Vomiting is more likely to occur if the patient has been treated recently with ipecac / ingested an agent that produces vomiting.
- Patients with compromised and unprotected airways are at risk for pulmonary aspiration during WBI.

3.6 Poisons management at home¹⁵⁵⁻¹⁵⁷

C Ipecac should no longer be used routinely as a home treatment strategy.

Grade C, Level 2+

C It is premature to recommend the administration of activated charcoal in the home.

Grade C, Level 2-

GPP The first action for a caregiver of a child who may have ingested a toxic substance is to consult with a doctor.

GPP

4 Enhancing the elimination of toxic substances from the body

Enhanced elimination techniques are seldom used. It may be indicated in a known poison whose elimination can be enhanced; failure of a patient to respond to maximal supportive care; or the clinical course is predicted to be complicated. The expected benefits must be weighed against the risk of complications associated with the technique.

4.1 Multiple-dose activated charcoal (MDAC)

MDAC is the repeated administration (more than 2 doses) of oral AC with the intent of enhancing drug elimination.

4.1.1 Indications

D Based on experimental and clinical studies, multiple-dose activated charcoal should be considered only if a patient has ingested a life-threatening amount of carbamazepine, dapsone, phenobarbital, quinine or theophylline.¹⁵⁸

Grade D, Level 3

D Volunteer studies have demonstrated that multiple-dose activated charcoal increases the elimination of amitriptyline, dextropropoxyphene, digoxin, disopyramide, nadolol, phenylbutazone, phenytoin, piroxicam, and sotalol. There is insufficient clinical data to support or exclude the use of this therapy. The use of multiple-dose charcoal in salicylate poisoning is controversial.

Grade D, Level 4

D Co-Administration of a cathartic to MDAC is unproven. Cathartics should not be administered to young children because of the propensity of laxatives to cause fluid and electrolyte imbalance.

Grade D, Level 4

4.1.2 Dosage regimen

D Multiple-dose activated charcoal is administered orally. If appropriate, it may be given via a nasogastric tube. An antiemetic may be given intravenously, if vomiting, to ensure compliance. Smaller,

more frequent doses of charcoal may be tried to prevent regurgitation. The optimum dose of charcoal is unknown but it is recommended that after an initial dose of 50–100 g to an adult, activated charcoal should be administered at a rate of not less than 12.5 g/h or equivalent. Lower doses (10–25 g) of activated charcoal may be employed in children less than 5 years of age as usually, they have ingested smaller overdoses and their gut lumen capacity is smaller.

Grade D, Level 4

D Multi-Dose Activated Charcoal should be discontinued if there is significant clinical improvement or serum drug concentrations have fallen to nontoxic levels.

Grade D, Level 4

4.1.3 Contraindications and complications

Refer to sections 3.1.2 and 3.1.3 for contraindications and complications of activated charcoal under Chapter 3: Gastrointestinal decontamination.

4.2 Urinary pH manipulation

4.2.1 Urinary alkalinisation

Urinary alkalinisation is the administration of intravenous sodium bicarbonate to produce urine with a pH ≥ 7.5 . The emphasis of urine alkalinisation is the manipulation of urine pH rather than diuresis, except in severe 2,4-dichlorophenoxyacetic acid and mecoprop poisoning where high urine flow is also required. The terms forced alkaline diuresis and alkaline diuresis has been discontinued.

4.2.1.1 Indication

D Urine alkalinisation increases the urine elimination of salicylate, chlorpropamide, 2,4-dichlorophenoxyacetic acid (herbicide), diflunisal, fluoride, mecoprop (herbicide), methotrexate and phenobarbital. High urine flow (approximately 600 mL/h) and urine alkalinisation should also be considered in patients with severe 2,4-dichlorophenoxyacetic acid and mecoprop poisoning.¹⁵⁹

Grade D, Level 3

4.2.1.2 Contraindications

D Volume overload may complicate therapy in patients with pre-existing cardiac disease. Significant pre-existing heart disease is a relative contraindication.

Urinary pH manipulation is contraindicated in patients with established or incipient renal failure, pulmonary oedema and cerebral oedema.¹⁵⁹

Grade D, Level 4

4.2.1.3 Complications

D Hypokalemia is the most common complication. Alkalotic tetany occurs occasionally, but hypocalcaemia is rare. There is no evidence to suggest that relatively short-duration alkalemia poses a risk to life in normal individuals or in those with coronary and cerebral arterial disease.¹⁵⁹

Grade D, Level 4

D Urinary acidification (urine pH < 5.5) with ammonium chloride or ascorbic acid was historically used to treat intoxications with weak bases such as amphetamines, quinidine or phencyclidine. However, this practice has been abandoned, as efficacy has not been established and iatrogenic toxicity (severe acidosis) can occur.¹⁵⁹

Grade D, Level 4

4.2.2 Procedure for performing urine alkalinisation in salicylate poisoning[†]

4.2.2.1 Baseline

- (1) Measure plasma creatinine and electrolytes.
- (2) Measure plasma glucose.
- (3) Measure arterial acid-base status.

[†] The guidelines are as above but the requirements on the use of sodium bicarbonate may vary according to the patient.

4.2.2.2 Clinical preliminaries

- (1) Establish an intravenous line.
- (2) Insert a central venous line, if appropriate.
- (3) Insert a bladder catheter.
- (4) Correct any fluid deficit.
- (5) Correct hypokalemia, if indicated.
- (6) Measure urine pH using narrow-range indicator paper (use fresh urine as pH will change as carbon dioxide blows off on standing) or pH meter.

4.2.2.3 Achieving alkalinisation

The following is a suggested regime for achieving urinary alkalinisation in salicylate poisoning:

- (1) Give sodium bicarbonate starting from 1-2 mmol/kg of an 8.4 % solution intravenously over 1 hour and titrate until urine is alkalinized.
- (2) The period of administration of the loading dose of sodium bicarbonate may be shortened and/or the dose increased if there is pre-existing acidemia.

4.2.2.4 Maintaining urine alkalinisation

- (1) Give additional boluses of intravenous sodium bicarbonate to maintain urine pH in the range 7.5–8.5.

4.2.2.5 Monitor

- (1) Urine pH every 15–30 minutes until urine pH is in the range 7.5–8.5, then hourly.
- (2) Plasma potassium levels hourly, and correct if necessary.
- (3) Central venous pressure hourly.
- (4) Acid-base status hourly. (Note: Arterial pH should not exceed 7.5).
- (5) Plasma salicylate concentrations hourly.
- (6) Urine output should not exceed 100–200 mL/h.

D Discontinue urine alkalinisation when plasma salicylate concentrations fall below 350 mg/L in an adult or 250 mg/L in a child.

Grade D, Level 4

* The guidelines are as above but the requirements on the use of sodium bicarbonate may vary according to the patient.

4.3 Extracorporeal techniques

There are no clinical trials that have been done.

GPP Extracorporeal techniques are considered if the patient is critically ill and the blood level of a poison is in the known lethal range or associated with serious consequences.

GPP

The compound should have chemical and pharmacokinetic characteristics amenable to removal and potentially affords significant increases in the drug clearance by extracorporeal techniques.

Renal failure and the need to correct fluid and electrolyte abnormalities and if the usual route of elimination is impaired should also be taken into consideration.

4.4 Exchange transfusion

Exchange transfusion refers to the removal of a quantity of blood from a poisoned patient and its replacement with an identical quantity of whole blood; the process is usually repeated two to three times. Exchange transfusions are rarely indicated but may be useful in the treatment of massive haemolysis (e.g. due to arsine or sodium chlorate poisoning), methemoglobinemia, sulfhemoglobinemia (e.g. secondary to hydrogen sulphide exposure). Complications of the technique include transfusion reactions, hypocalcaemia and hypothermia.

5 Antidotes

An antidote is a drug used to neutralize or counteract the effects of poisoning. There are many drugs and chemicals that can cause toxicity, but only about 40 specific antidotes available for use in acute and chronic poisoning. The use of antidotes should be guided by assessment of the risk-benefit ratio. Most poisoning cases respond to good supportive management (that includes airway management, circulatory support and appropriate monitoring); antidotes may be required for the more serious poisonings.¹⁶⁰⁻¹⁶²

GPP Consider using specific antidotes in a timely manner when clinically indicated. Certain antidotes have been shown to improve survival and patient outcomes in poisonings and drug overdoses.

GPP

Most of the antidotes have not been systematically studied and the bulk of evidence for their use is derived from limited data from animal and human studies, case reports, pharmacokinetics and pathophysiologic information. Note that studies in animal models and human volunteers generally do not replicate clinical situations encountered in patients. Human studies are scarce as serious poisonings that warrant the use of antidotes are rare; however, it is unethical to withhold treatment from a critically ill patient. The use of antidotes will change with time as new evidence become available.

For some poisons, an antidote must be used during the early stages of poisoning to prevent irreversible injury.¹⁶³ For example, delay in administration of the cyanide kit to a patient may allow hypoxic brain injury to occur.

GPP Indications for the use of antidotes in children are generally the same as for adults. Certain antidotes have been shown to improve survival and outcomes in paediatric poisonings and drug overdoses.

GPP

Most studies on the use of antidotes have excluded paediatric patients and the use of these antidotes is by extrapolation of their effects in an adult population.¹⁶⁴

Paediatric patients are not mini-adults and generally would require dose adjustments when administering the antidote. However, the doses of some antidotes (e.g. snake antivenom and digoxin Fab) are dependent on the amount of poison sustained, and paediatric doses are similar to adult doses, irrespective of patient's body weight.¹⁶⁵

GPP Do not withhold antidotes for pregnant women who had experienced poisonings and drug overdoses, especially if the symptoms are life-threatening or severe.

GPP

In pregnancy, consider the benefit-risk profile of using an antidote. Both mother and foetus may be harmed by the poisoning, or by the adverse effects of the antidote. In severe poisonings, the inherent toxicity of the poisoning substance may far exceed the risks associated with the use of the antidote. Conversely, teratogenicity, especially with the use of antidotes during the first trimester, has not been well researched, and most studies on the use of antidotes have excluded pregnant patients.¹⁶⁶

The majority of antidotes are classified as US FDA pregnancy risk category C (see table 1 for definitions of categories)¹⁶⁷, where the benefit–risk ratio is not clearly defined. There are very few antidotes listed as category D, where there are significant risks of teratogenicity. However, these categorizations are based on chronic or repeated use, and may not be relevant in single or brief antidotal use (e.g. benzodiazepine). In the case of penicillamine, safer alternatives are available and should be used instead.

Table 1. US FDA Categories for Drug Use in Pregnancy

Category	Description	Examples for Cat D/X
A	Adequate, well-controlled studies in pregnant women have not shown an increased risk of foetal abnormalities.	-
B	Animal studies have revealed no evidence of harm to the foetus; however, there are no adequate and well-controlled studies in pregnant women. Or Animal studies have shown an adverse effect, but adequate and well-controlled studies in pregnant women have failed to demonstrate a risk to the foetus.	-
C	Animal studies have shown an adverse effect and there are no adequate and well-controlled studies in pregnant women. Or No animal studies have been conducted and there are no adequate and well-controlled studies in pregnant women.	-
D	Studies, adequate well-controlled or observational, in pregnant women have demonstrated a risk to the foetus. However, the benefits of therapy may outweigh the potential risk.	Iodide Benzodiazepines Penicillamine Ethanol
X	Studies, adequate well-controlled or observational, in animals or pregnant women have demonstrated positive evidence of foetal abnormalities. The use of the product is contraindicated in women who are or may become pregnant	None

** FDA categorization of pregnancy risk is generally based on anticipated chronic use or repeated use, and may not be relevant to single or brief antidotal therapy.*

If antidote use is clearly indicated (i.e. when it will be used in a non-pregnant woman), then it should be used for the pregnant woman. There have been fatalities documented where antidotes were withheld because of fear of teratogenicity.¹⁶⁸ In certain poisonings, antidote use should be considered even if there is no imminent risk to the mother,

because the poison may affect the foetus to a greater extent (e.g. carbon monoxide and paracetamol poisoning).

GPP Institutions that manage acute poisoning and drug overdoses should adequately stock the appropriate antidotes.

GPP

Antidote stocking is dependent on the possible poisoned patient profiles.¹⁶⁹

It needs to take into account:

- (1) The efficacy of the antidote.
- (2) The urgency of use – is it needed immediately or within an hour of patient presentation to prevent major morbidity or death?
- (3) The frequency of its use – how often is it utilized, how many patients should the institution prepare for?
- (4) Cost and inventory management.

An example is to have sufficient antidote to treat a 70-100 kg patient for at least the initial 8 hours post-presentation, or until additional stocks of antidote can be obtained. Studies have shown that there is inadequate stocking of antidotes in institutions that accept emergency admissions but the exact stocking level has not been well-defined.

Another consideration for antidote stocking is their use in mass casualty hazardous material incidents from deliberate or accidental release of toxic chemicals.

6 Analgesics

6.1 Non-steroidal anti-inflammatory drugs (NSAID) poisoning (excluding salicylates)

6.1.1 Epidemiology²

Non-Steroidal Anti-inflammatory Drugs toxic ingestion is a fairly common cause of pharmaceutical poisoning in Singapore. Most are due to accidental ingestions especially in the paediatric age group and suicide attempts. NSAID overdose is not generally associated with significant morbidity.

6.1.2 Pharmacokinetics¹⁷⁰

Oral absorption of Non-Steroidal Anti-inflammatory Drugs approaches 100% and peak serum levels usually occur within 1-2 hours. Large toxic ingestions or concomitant food consumption can delay peak levels to up to 3-4 hours. NSAIDs are weak acids that are extensively (up to 99 percent) protein bound, with a small volume of distribution (0.1 to 0.2 L/kg). Low-protein disease states or large ingestions can decrease plasma protein binding, increasing the volume of distribution and allowing greater penetration into body tissues and the central nervous system. Most NSAIDs are metabolised by hepatic biotransformation with urinary excretion.

The elimination half-life is usually less than 8 hours but ranges depending on the specific class and initial dose:

- **Short half-life (< 8 hours):** ibuprofen, indomethacin, ketorolac, diclofenac.
- **Long half-life (> 8 hours):** naproxen (9 to 20 hours), oxaprozin (25 to 50 hours), piroxicam (30 to 86 hours), phenylbutazone (50 to 100 hours).

6.1.3 Toxic ingestion¹⁷¹

Definition:

D Symptomatic patients irrespective of reported dose ingested.

Grade D, Level 4

C Ingestions of less than 100 mg/kg of most NSAIDs (except mefenamic acid and phenylbutazone) are unlikely to cause any significant toxicity.

Massive ingestions with severe symptomology are seen with ingestions greater than 400 mg/kg.

Grade C, Level 2++

D Refer to Emergency Department / Hospital for further evaluation and management if:

- Patient is symptomatic (irrespective of dose).
- If toxic dose is consumed (see above).
- Suspected non-accidental ingestion (irrespective of dose).
- Poor home support (lives alone, inability of caregivers to monitor).

Grade D, Level 4

6.1.4 Clinical presentation

The most common signs and symptoms are nausea, vomiting, drowsiness, blurred vision, and dizziness which usually only require symptomatic management.

- **Central nervous system toxicity:**

- Altered mental status.¹⁷²
- Seizures¹⁷³⁻¹⁷⁹

(1) Seizures have been reported with ingestions of propionic acids (ibuprofen), pyrazolones (phenylbutazone), acetic acids (diclofenac and indomethacin), and anthranilic acids (mefenamic acid and meclofenamate).

(2) Seizures are effectively treated with benzodiazepines.

- **Renal toxicity:**

- Acute forms of renal insufficiency or failure and renal papillary necrosis are rare in NSAID overdose.
- Most commonly, these pathologic processes occur in patients with decreased effective arterial volume (congestive heart failure, cirrhosis, protracted dehydration), age-related underlying renal dysfunction or massive overdose.

- **Acid-base abnormalities:**
 - Metabolic Acidosis: an increased anion gap metabolic acidosis may be seen after large ingestions of NSAIDs, particularly ibuprofen, naproxen and phenylbutazone.
 - Respiratory Acidosis: may be seen in patients with altered mental status and may require assisted ventilation.
- **Allergic reactions:**
 - Symptoms can range in severity from urticaria, angio-oedema to full anaphylaxis.
 - Management of allergic reactions due to NSAID ingestion is the same as that from any other cause.
- **Haematological:**
 - Aplastic anaemia and agranulocytosis have been associated with the use of phenylbutazone and indomethacin.
 - Patients may present with bleeding tendencies due to platelet insufficiency.
 - Discontinuation of the drug has been shown to reverse the hematologic disturbances.
 - Treatment is supportive.

6.1.5 Management¹⁸⁰⁻¹⁸³

Resuscitation

- Secure airway, breathing and circulation as necessary.
- No specific recommendations.

GI decontamination

B Activated charcoal should be given within 1 hour of ingestion.

Grade B, Level 1+

D Aspiration risk, including mental status and the ability to protect the airway, must be assessed in all patients before any attempts to administer activated charcoal.

Grade D, Level 4

Symptomatic treatment

D Supportive treatment and a brief period of observation are usually all that is necessary in most cases of non-steroidal anti-inflammatory drug (NSAID) overdose, with the exception of mefenamic acid and phenylbutazone.

Grade D, Level 4

D If more than 6 hours had passed since the suspected toxic ingestion and the patient is clinically well, the patient does not require further evaluation for toxicity (**except** for mefenamic acid and phenylbutazone).

In **mefenamic acid** and **phenylbutazone** poisoning, a 24-hour post ingestion observation is advised due to the increased risk in complications.

Grade D, Level 3

C Seizures secondary to NSAIDs toxicity can be effectively treated with benzodiazepines.

Grade C, Level 2++

6.1.6 Monitoring¹⁸⁴⁻¹⁹⁰

Serum NSAID levels

B NSAID levels correlate poorly with symptoms and are not usually clinically useful.

Grade B, Level 2+

Renal function¹⁸⁵

D Routine measurement of renal function is not indicated in patients with minor, asymptomatic ingestions.

In symptomatic patients or those with significant toxic ingestion, measurement of baseline renal function and electrolytes should be done.

Grade D, Level 4

Blood gas analysis¹⁹¹

- **Metabolic acidosis:** An increased anion gap metabolic acidosis may be seen after large ingestions of NSAIDs, particularly ibuprofen, naproxen, and phenylbutazone.
- **Respiratory acidosis:** Patients with altered mental status may require analysis to ascertain respiratory insufficient and need for assisted ventilation.

Full Blood Count¹⁹¹

Baseline haemoglobin and platelet level may be done, especially if there are clinical signs of bleeding.

6.2 Opioid poisoning

6.2.1 Epidemiology²

Opioid toxic ingestion, as part of analgesics overdose, is a fairly common cause of pharmaceutical poisoning in Singapore. Most are due to non-accidental ingestions.

6.2.2 Pharmacokinetics¹⁹²⁻¹⁹³

Clinical effects of most opioids persist for 3-4 hours. Notable exceptions are fentanyl, which may persist for 1 hour and methadone for 24-48 hours. The oral absorption of Lomotil (diphenoxylate and atropine) is usually delayed due to the atropine anticholinergic effects. Most opioids are metabolised by liver with its metabolites excreted primarily by the kidneys. Consequently, urinary metabolites can be detected on urine drug screen up to four days after the last use (occasionally longer in chronic users). Renal dysfunction can lead to toxicity caused by accumulation of active metabolites.

- **Drug interactions**

Opioids interact with various drugs. Increased opioid toxicity is seen in co-ingestion of:

- Phenothiazines.
- Cyclic antidepressants.
- Enzyme inhibitors e.g. cimetidine, erythromycin, etc.
- Other sedative drugs (e.g. alcohol, benzodiazepines).

6.2.3 Clinical manifestations of opioid toxicity

D Refer to Emergency Department / Hospital for the following groups of patients:

- All patients with suicidal intent, intentional abuse, or in cases in which a malicious intent is suspected (e.g. child abuse or neglect).
- All symptomatic patients.
- Patients who are suspected of ingesting toxic amounts of opioid.
- Patients with poor home support (e.g. lives alone, inability for caregivers to monitor).

Grade D, Level 4

The classic findings of opioid toxicity are CNS depression, respiratory depression and miosis.

- **Central nervous system:**¹⁹⁴
 - CNS depression is the major clinical manifestation.
 - Increasing doses lead to increasing degrees of sedation. Initially, there is analgesia and sedation, followed by loss of response to verbal stimuli, loss of response to tactile stimuli, loss of control over normal respiration and failure of temperature and blood pressure regulation.
 - Seizures can occur after intravenous fentanyl and sufentanil administration, as well as after the prolonged use of meperidine and large ingestions of propoxyphene, tramadol or pentazocine.
 - A Parkinsonian-like syndrome has been associated with some opioid-based designer drugs.
- **Pulmonary:**
 - Most opioid-related deaths are caused by respiratory depression which may be subtle, especially in paediatric and elderly patients.
 - Serial clinical assessment, pulse oximetry, blood gas analysis or nasal end-tidal carbon dioxide monitoring (if available) may be required.
 - Noncardiogenic pulmonary oedema may complicate opioid overdose. Clinical findings of pulmonary oedema in the presence of respiratory depression and miotic pupils should prompt the diagnosis.
 - Resolution of pulmonary oedema is usually rapid once assisted ventilation is instituted.
 - Bronchospasm via histamine release can occur and is relieved by bronchodilator therapy.
 - Aspiration pneumonia can occur due to an unprotected airway secondary to CNS obtundation.
- **Cardiac:**¹⁹⁵
 - Opiates may cause bradycardia and hypotension.
 - The drug-induced bradycardia and increased automaticity can cause arrhythmia, including potentially lethal ventricular tachyarrhythmias.
 - ECG changes seen in propoxyphene and its metabolite norpropoxyphene. Manifestations are similar to those seen in tricyclic antidepressant poisoning, with QRS and QT

prolongation, varying degrees of heart block and tachyarrhythmias.

- **Ophthalmologic manifestations:**¹⁹⁶⁻¹⁹⁸
 - Miosis (pupillary constriction) usually occurs in opioid poisoning.
 - However mydriasis or normal pupils may be seen with overdose of meperidine, morphine (rarely), propoxyphene, dextromethorphan, pentazocine, early Lomotil (diphenoxylate and atropine) poisoning. Occasionally, mydriasis may be seen if hypoxic brain injury had occurred following prolonged respiratory depression.
- **Gastrointestinal symptoms:**
 - Constipation results from decreased motility and increased sphincter tone in the rectum.
- **Musculoskeletal manifestations:**¹⁹⁹
 - All opioid agonists can produce skeletal muscle rigidity, even at low doses. Acute rhabdomyolysis and renal failure may occur with the use of heroin, methadone and propoxyphene.
- **Others:**
 - Pethidine and pentazocine have serotonergic effects and may cause the serotonin syndrome (usually in combination with other drugs).

6.2.3.1 Laboratory evaluation and ancillary studies

- Acute opioid poisoning is a clinical diagnosis; the management of a patient with an opioid toxidrome is unchanged by the results of a toxicological screen.
- Most patients with mild or moderate poisoning can be managed successfully without any further laboratory investigation.

6.2.3.2 Investigations to be considered

D

- Capillary glucose: to exclude hypoglycaemia.
- Electrocardiogram (ECG): should be obtained when the patient is suspected of methadone/propoxyphene overdose; or when co-

ingestion with other substances which may cause cardiovascular complications, such as cocaine or antidepressants is suspected (e.g. if intended self-harm is suspected).

- **Other investigations:**
 - In the setting of suspected prolonged immobilization: serum creatine phosphokinase concentration should be obtained to exclude rhabdomyolysis.
 - Serum creatinine and electrolytes: depending on clinical circumstances
 - Targeted blood toxicology: In any overdose scenario in which the opioid is formulated with paracetamol or self-harm is suspected, serum paracetamol concentration should be obtained.
 - Urine toxicologic screens should not be routinely obtained. Opioids are detectable in the urine for only two to four days after use. A positive test may indicate recent use but not current intoxication, or may even represent a false positive. Conversely, many opioids, especially the synthetic drugs, will produce false-negative results in many commonly available urine screens.

Grade D, Level 3

6.2.3.3 Management of acute toxicity

- Most of the direct morbidity and mortality related to opiate use occur after acute ingestion. They are caused by complications such as anaphylaxis, pulmonary oedema, acute respiratory acidosis, and aspiration pneumonitis.
- Immediate management involves airway management and administration of an opioid antagonist.

6.2.3.4 Specific respiratory issues



- Initial management should focus on support of the patient's airway and breathing.
- While pulse-oximetry is useful in monitoring oxygenation, its usefulness may be limited if supplemental oxygen is given.
- Capnography if available may be useful for monitoring the ventilatory effort of opioid-poisoned patients.

Grade C, Level 2++

C

- Patients with respiratory insufficiency should be supported with bag mask ventilation and 100% oxygen to correct respiratory acidosis before or while the opioid antagonist is administered.

Grade C, Level 2++

B

- For suspected pulmonary oedema, oxygen and positive pressure ventilation may be required.

Grade B, Level 1+

6.2.3.5 Other considerations²⁰⁰⁻²⁰¹

- Cardiovascular compromise, hypoglycaemia, seizure, cardiac arrhythmias and hypothermia should be managed with standard therapies.
- During the secondary survey, look for signs of trauma, particularly to the head.

6.2.4 Gastrointestinal decontamination

6.2.4.1 Activated charcoal

B Activated charcoal (1 g/kg, maximum of 50 g) can be given to patients who have ingested within 1 hour of overdose, if the airway is first assessed and protected, as needed, prior to the procedure.

Grade B, Level 1+

D In Lomotil (diphenoxylate and atropine) poisoning, gastric lavage within 2 hours of overdose and multi-dose activated charcoal should be considered.

Grade D, Level 3

6.2.4.2 Whole bowel irrigation

D In body packing with leakage and overdose, whole body bowel irrigation can be considered if airway is protected.

Grade D, Level 3

6.2.5 Antidote^{200,202-208}

Opioid antagonists – Naloxone

Naloxone is the antagonist of choice for opioid toxicity with greater affinity for the receptors than do opioid agonists. It is optimally administered intravenously but can be also administered intramuscularly, subcutaneously or endotracheally. It has a shorter duration of action (1 to 2 hours) and may need to be administered repeatedly or continuously as required. Clinical effects of naloxone typically last 45 to 70 minutes. Its use should be restricted to patients with altered mental status and diminished respirations, miotic pupils, or circumstantial evidence of opiate abuse. The goal of naloxone administration is not a normal level of consciousness, but adequate ventilation.

(1) In patients with spontaneous respiratory but has hypoventilation:

- Paediatric Dosing (< 20 kg): 0.01 mg/kg IV (maximum 2 mg per dose). Titrated upwards till hypoventilation resolves.
- Adults and children (more than 20 kg): Initial dose of 0.5 mg and titrated upward every few minutes until the respiratory rate is 12 or greater.

(2) Apnoeic patients:

- Newborn with apnoea secondary to suspected maternal opioid abuse: 0.01 mg/kg IV/IM (maximum 0.4 mg per dose).
 - Note withdrawal reactions may be potentially life-threatening in the neonatal period and thus only low dose should be given as necessary.
- Paediatric Dosing (< 20 kg): 0.1 mg/kg IV (maximum 2 mg per dose).
 - Repeated doses or continuous infusions as required.
- Adults and children (more than 20 kg): higher initial doses of naloxone (0.2 to 1 mg) and titrated to clinical response.

(3) For life-threatening opioid toxicity:

- Paediatric Dosing (< 20 kg): 0.1 mg/kg IV (maximum 2 mg per dose).
 - Repeated doses or continuous infusions as required.
- Adults and children (more than 20 kg): 2 mg IV.
 - The dose should be repeated every 3 minutes until improvement in respiratory depression is noted.
 - If maximal cumulative dose of 10 mg is reached and the respiratory insufficiency has not improved, consider co-ingestions or other pathologies.

- For patients with suspected chronic opioid usage with symptomatic overdose, lower incremental doses of naloxone (0.2 mg or 0.4 mg per dose) with repeat doses every 3 to 5 minutes titrated to patient response to prevent acute withdrawal manifestations.
- Patients who had an initial response to naloxone must be carefully monitored every 10-15 minutes for level of consciousness, respirations, pulse, blood pressure, and vomiting as they could relapse.
- After ventilation is restored with naloxone, repeated doses may be required, depending on the quantity and duration of action of the opioid.
- As an alternative to repeat dosing, a naloxone infusion may be prepared by determining the total initial dose required to re-instate breathing, and delivering two-thirds of that dose every hour.
- If the patient develops withdrawal signs or symptoms during the infusion, stop the infusion.
- If intoxication recurs, restart the infusion at half the initial rate.
- If the patient develops respiratory depression during the infusion, re-administer half the initial bolus every few minutes until symptoms improve, then increase the infusion by half the initial rate.
- Symptoms of withdrawal should be managed expectantly only, not with opioids.

Appendix

Specific Agents	Specific Toxicity
Buprenorphine	Partial opioid agonist; may induce withdrawal in opioid-dependent patients.
Dextromethorphan	Serotonin syndrome, at high doses exhibits some μ effects of opioids (miosis, respiratory and CNS depression) but is not a pure opioid agonist.
Hydrocodone / Oxycodone	Often combined with paracetamol.
Methadone	Very long-acting; high dose can be associated with QTc prolongation (torsades de pointes).
Propoxyphene	Has Type IA antidysrhythmic properties which may result in QTc prolongation, torsades de pointes (management is similar to TCA poisoning); seizure.
Tramadol	Seizure.

6.3 Salicylate poisoning

6.3.1 Epidemiology^{2,209-210}

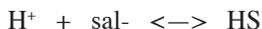
Salicylate poisoning is relatively uncommon in Singapore. Poisoning can follow the unintentional ingestion of a single large dose or it can follow repeated supratherapeutic doses, particularly in the elderly. Salicylates are also used as a means to attempt suicide. Some salicylates, such as methyl salicylate (oil of wintergreen), are not intended to be ingested but are ingested intentionally or swallowed mistakenly. Chronic dermal application of some salicylate-containing products can produce systemic toxicity.

6.3.2 Pharmacokinetics²⁰⁹⁻²¹¹

The type of formulation (e.g. liquid, effervescent, extended-release, enteric-coated) affects the degree of absorption. With therapeutic dosing of regular aspirin tablets, peak plasma concentrations are usually achieved 15-60 minutes after ingestion. Peak concentrations following ingestion of extended-release or enteric-coated preparations typically occur between 4-14 hours after ingestion. Peak concentrations in overdose may be delayed as a result of pylorospasm or bezoar formation.

In overdose, increased free fraction and consequent organ toxicity occurs because of saturation of protein binding. Salicylates are metabolised in the liver via glucuronidation, oxidation, and glycine conjugation. For children on chronic salicylate therapy, even a slight change in dose may result in a great increase in plasma concentration.

Salicylic acid (HS) is a weak acid that exists in a charged (deprotonated) and uncharged (protonated) form:



Treatment of salicylate intoxication is directed toward increasing systemic and urine pH and driving the above reaction to the left, “trapping” the salicylate anions in the blood and urine.

6.3.3 Determination of severity

In the initial assessment of the severity of toxicity, the following four factors should be considered:

- Dose ingested.
- Salicylate concentration.
- Clinical grading of toxicity.
- Acid-base grading of severity.

6.3.3.1 Toxic ingestion

The assessment of **acute** salicylate intoxication is based on dose.

Assessment of ACUTE salicylate intoxication based on dose ingestion	
Ingested Dose (mg/kg)	Estimated Severity
< 150	No toxic reaction expected
150-300	Mild to moderate toxic reaction
300-500	Serious toxic reaction
>500	Potentially lethal

Chronic toxicity can develop from doses of 100 mg/kg/day. Patients with cirrhosis, low protein states or renal impairment develop toxicity with lower doses.

6.3.4 Clinical presentation

The triad of salicylate poisoning consists of hyperventilation, tinnitus, and gastrointestinal irritation (classic salicylism).

Paediatric patients may not manifest respiratory alkalosis. In children, hyperventilation, dehydration and neurological dysfunction are greater in chronic overdoses compared with single acute ingestions. Mild pyrexia is common and is due to increased metabolic activity.

- **Gastrointestinal effects:** Nausea and vomiting are common. Less common are epigastric pain and haematemesis. Vomiting contributes significantly to electrolyte imbalance and dehydration. Aspirin, especially enteric-coated formulations, are

known to develop concretions and bezoars in the stomach and act as a direct GI irritant leading to nausea, vomiting, and abdominal pain.

- **Central nervous system effects:** CNS symptoms can occur with declining salicylate concentrations because of CNS trapping of ionised salicylate.

CNS Effects in salicylate poisoning	Clinical manifestations
Mild	Nausea, vomiting, tinnitus.
Moderate	Confusion, hyperventilation.
Severe	Hallucinations, seizures, coma, cerebral oedema.

- **Others:** Non-cardiogenic pulmonary oedema and renal failure occur occasionally and always in association with other signs of significant poisoning.

Clinical grading of salicylate toxicity	
Severity	Clinical features
Mild	Nausea, vomiting, tinnitus.
Moderate	Confusion, hyperventilation.
Severe	CNS: hallucinations, seizures, coma, cerebral. Respiratory: pulmonary oedema.

6.3.5 Biochemical presentation

In children with salicylate poisoning, plasma concentrations 6 hours after an **acute** overdose approximately correlate with toxicity as follows:

Severity of Acute Toxicity	Serum Concentration (Post 6 hours)
Mild Toxicity	30–50 mg/dL
Moderate Toxicity	50–70 mg/dL
Severe Toxicity	>75 mg/dL

Salicylate Concentration Conversion factor:

$$\text{mg/dL} \times 0.0072 = \text{mmol/dL}$$

$$\text{mmol/dL} \div 0.0072 = \text{mg/dL}$$

The use of Done Normogram formulated may have limited applicability in aspirin poisoned patients.

- **Metabolic acidosis:** Major feature of salicylate poisoning as a result of “uncoupling of oxidative phosphorylation” leading to:
 - Increase in metabolic rate.
 - Increased oxygen consumption.
 - Increased CO₂ formation.
 - Increased heat production.
 - Increased glucose utilisation.

This may be exacerbated by:

- Accumulation of organic acid metabolites.
- Starvation and dehydration induced ketosis.
- Lactic acidosis.

- **Glucose metabolism:**
 - Hypoglycaemia: Intracellular > extracellular.
 - May occur due to:
 - Increased peripheral glucose demand.
 - Increased rate of tissue glycolysis.
 - Impaired rate of glucose synthesis.
 - Note that tissue may be lower than plasma glucose.
 - Hyperglycaemia: may occur due to increased glycogenolysis.
- **Hypokalaemic** patients or patients with total body potassium depletion are unable to produce alkaline urine.
- **Coagulation effects:** Salicylates competitively inhibit vitamin K dependent synthesis of factors II, VII, IX and X. A prolonged prothrombin time, usually >2 times normal, occurs predictably in significant overdoses. Vitamin K will correct the prothrombin time rapidly. As in therapeutic use, aspirin, but not other salicylates, impairs platelet aggregation.

- **Hepatic effects:** Rises in transaminases may occur, are usually not clinically significant, and will resolve over several days.

Biochemical Investigations	Timing	Comments
FBC	Baseline	-
Coagulation profile	Baseline	Any coagulopathy should be corrected with IV Vitamin K.
Urea, calcium, creatinine, glucose	Baseline and repeat as necessary in moderate to severe salicylate poisoning.	Keep K ⁺ in the optimal range of 4 - 4.5 mmol/L.
Arterial blood gas	Baseline and repeat as necessary in moderate to severe salicylate poisoning.	-
Urinalysis and urine pH	Baseline and repeat as necessary in moderate to severe salicylate poisoning.	Keep urine pH between 7.5 - 8.5. Titrate bicarbonate infusion as necessary.
Plasma salicylate concentration	4-6 hours post ingestion.	Repeat salicylate level every 2 hours until levels declining; then as necessary.

Acid-base grading of severity of salicylate toxicity			
Stage	Blood pH	Urine pH	Comment
I	>7.4	>6	Respiratory alkalosis. Increased urinary excretion of NaHCO ₃ , K ⁺ and Ca ²⁺ .
II	>7.4	<6	Metabolic acidosis with compensating respiratory alkalosis. Intracellular K ⁺ depletion, urine H ⁺ excretion.
III	<7.4	<6	Severe hypokalaemia and metabolic acidosis.

6.3.5.1 Differential Diagnosis

- Diabetic ketoacidosis. (Glucose usually high in DKA whereas usually low in salicylate poisoning.)
- Severe dehydration/gastroenteritis with metabolic acidosis.
- Sepsis syndrome.
- Other forms of poisoning such as ethylene glycol or ethanol intoxication.
- Inborn error of metabolism. (Paediatrics.)

6.3.6 Refer to emergency department / hospital referral for further evaluation and management if²⁰⁹:

D All symptomatic patients should be referred to an emergency department regardless of dose ingested (e.g. haematemesis, tachypnoea, hyperpnoea, dyspnoea, tinnitus, deafness, lethargy, seizures, unexplained lethargy or confusion).

Grade D, Level 3

D All patients with known or suspected suicidal intent or non-accidental ingestion (e.g. child abuse) irrespective of amount ingested.

Grade D, Level 4

D If asymptomatic and had suspected toxic ingestion:

- Acute ingestion of aspirin or equivalent exceeding 150 mg/kg or 6.5 g, whichever is less.
- Ingestion of oil of wintergreen (98% methyl salicylate) if:
 - Under 6 years of age: greater than a lick or taste.
 - Patients 6 years of age or older: > 4 mL.

Grade D, Level 3

C If the accidental ingestion occurred >12 hours (24 hours for enteric-coated tablets) and the patient is asymptomatic, no further evaluation is required.

Grade C, Level 2+

6.3.7 Mucocutaneous and ocular salicylate exposure²⁰⁹

Skin and eye decontamination should be instituted as soon as possible.

D For asymptomatic patients with dermal exposures to methyl salicylate or salicylic acid, the skin should be thoroughly washed with soap and water and the patient can be observed for symptoms.

Grade D, Level 3

D For patients with an ocular exposure of methyl salicylate or salicylic acid, the eye(s) should be irrigated with room temperature tap water for 15 minutes. If after irrigation the patient is having pain, decreased visual acuity or persistent irritation, refer to an ophthalmologist.

Grade D, Level 4

6.3.8 Management of salicylate poisoning²⁰⁹⁻²¹¹

The goals of treatment of salicylate intoxication are to correct fluid and electrolyte imbalance and to enhance excretion.

Treatment of salicylate intoxication is directed toward increasing systemic and urine pH by the administration of sodium bicarbonate.

Salicylate excretion depends on the following factors:

- Dose of salicylates.
- Blood and urine pH: An alkaline urine (pH > 7.5) dramatically increases salicylate clearance by ion trapping.
- Potassium concentration: In the presence of hypokalaemia, urine alkalinisation is impossible.
- Hypokalaemia may be noted only when the serum pH is corrected as the acidosis may mask severe potassium depletion (particular common in chronic poisoning).
- Pre-existing liver or renal failure.

6.3.8.1 Resuscitation

(1) Airway²¹⁰⁻²¹²

D Intubation of the salicylate-poisoned patient can be detrimental and should be avoided unless necessary.

Grade D, Level 3

D If intubation and mechanical ventilation is necessary for severe obtundation, hypotension, hypoventilation or severe metabolic acidosis, ensure appropriately high minute ventilation and maintain alkalemia (via serial blood gas analysis) with serum pH 7.50-7.55.

Grade D, Level 4

D Consider haemodialysis for patients who require intubation.

Grade D, Level 4

(2) Breathing

Supplemental oxygen should be administered as needed.

D Pulmonary oedema and acute lung injury may occur and should be treated with oxygen and if available, non-invasive ventilation. Intubation and mechanical ventilation with positive end-expiratory pressure (PEEP) may be necessary, but should be avoided if possible.

Grade D, Level 3

(3) Circulation

D Intravenous fluids should be administered as necessary to replace insensible fluid losses from hyperpyrexia, vomiting, diaphoresis, and elevated metabolic rate.

Grade D, Level 4

D There should be judicious administration of fluids in the presence of suspected pulmonary oedema or cerebral oedema.

Grade D, Level 4

(4) Supportive treatment²⁰⁹⁻²¹¹

- Supplemental glucose:
 - Salicylate intoxication may decrease CNS glucose levels despite a normal peripheral glucose level.

D All patients with salicylate poisoning with altered mental status should be given supplemental glucose, regardless of serum glucose levels.

Grade D, Level 4

- Potassium repletion:
 - Hypokalemia, if present, must be treated aggressively as it results in ineffective urinary alkalisation.

D Supplemental potassium should be given to maintain serum potassium 4-4.5 mmol/L, unless renal failure is present.

Grade D, Level 4

6.3.8.2 *Gastrointestinal decontamination*²⁰⁹⁻²¹¹

D Gastrointestinal decontamination with activated charcoal can be considered in patients with significant acute salicylate overdose irrespective of the suspected time of ingestion.

Grade D, Level 2+

D Multi-dose activated charcoal should be considered in massive salicylate ingestions every 4 hours for 24 hours in a dose of 1 g/kg (maximum 50 g) until symptoms have resolved and plasma salicylate concentration is < 30 mg/dL.

Grade D, Level 2+

However, note that gastric irritation, nausea and altered mental status all combine to put the salicylate-poisoned patient at substantial risk for aspiration.

6.3.8.3 *Enhanced elimination*

(1) **Urinary and serum alkalinisation**²¹⁰⁻²¹¹

B Enhanced salicylate elimination via urine alkalinisation with sodium bicarbonate is an essential component in the management of the salicylate-poisoned patient.

Grade B, Level 1+

D Alkalemia from respiratory alkalosis is not a contraindication to sodium bicarbonate therapy.

Grade D, Level 3

For information on the regime for urinary alkalinisation, refer to section 4.2.2.3 under Chapter 4:Enhancing the elimination of toxic substances from the body.

(2) **Haemodialysis**²¹⁰⁻²¹¹

C Haemodialysis is the definitive treatment to prevent and treat salicylate induced end-organ injury.

Grade C, Level 2++

D Early consultation to the relevant specialists may be required in severe salicylate poisoning.

Grade D, Level 4

C The indications for haemodialysis are primarily clinical and include:

- Severe acidosis or hypotension refractory to optimal supportive care (regardless of absolute serum aspirin concentration).
- Evidence of end-organ injury (i.e. seizures, rhabdomyolysis, pulmonary oedema).
- Renal failure.
- Plasma salicylate concentration > 100 mg/dL (> 7.2 mmol/L) in the setting of acute ingestion; or plasma salicylate concentration > 60 mg/dL (> 4.3 mmol/L) in the setting of chronic salicylate use.
- Haemodialysis should be considered for patients who require mechanical ventilation, unless that indication for mechanical ventilation is respiratory depression secondary to a co-ingestant.

Grade C, Level 2++

6.3.8.4 Post stabilisation monitoring²¹⁰⁻²¹¹

Salicylate-poisoned patients require frequent laboratory monitoring to assess both clinical status and response to therapy.

D A salicylate level and blood gas should be drawn 2-3 hourly until both the plasma salicylate level is falling and the acid-base status is stable or improving for two consecutive readings.

Grade D, Level 4

D Check urea and electrolytes every 3-4 hours. The serum potassium should be kept in the range 4 to 4.5 mmol/L.

Grade D, Level 4

Ionic calcium should be also checked and managed as it may be low due to bicarbonate therapy/respiratory alkalosis.

Appendix²⁰⁹

Salicylate	Conversion factor	Type of use
Aspirin	1.00	Oral, suppositories
Bismuth subsalicylate*	0.50	Oral
Choline magnesium trisalicylate	1.30	Oral
Choline salicylate	0.75	Oral
Magnesium salicylate	1.21	Oral
Methyl salicylate	1.18	Dermal, flavoring agent
Oil of wintergreen†	1.40	Dermal, flavoring agent
Salicylic acid‡	1.30	Dermal
Salsalate	1.40	Oral
Sodium salicylate	1.13	Oral
Trolamine salicylate	0.63	Dermal

Multiply the dose of the non-aspirin salicylate by the conversion factor to get the equivalent dose of aspirin. The conversion factor is calculated by dividing the molecular weight of aspirin by that of the non-aspirin salicylate except for those that dissociate into more than 1 molecule of salicylate. Magnesium salicylate and salsalate yield two molecules of salicylate; choline magnesium trisalicylate yields three molecules of salicylate. Salsalate may not fully convert to salicylate.

*Pepto-Bismol, Maalox Total Stomach Relief, and Kaopectate (manufactured in 2004 and thereafter) contain 262 (regular strength) or 525 mg (extra strength) of bismuth subsalicylate per 15 mL, which yield 8.7 or 17.5 mg of an aspirin equivalent dose per mL, respectively.

†Oil of wintergreen is a liquid that contains methyl salicylate 98% w/w; 1 mL is equivalent to aspirin 1.4 g. The conversion factor allows for the specific gravity of 1.18 for w/w % expressions.

‡Salicylic acid in concentrations greater than 6% may be destructive to tissues upon contact; ingestion can produce chemical burns.

Reproduced from Chyka PA, Erdman AR, Christianson G et al. Salicylate poisoning: an evidence-based consensus guideline for out-of-hospital management. *Clin Toxicol (Phila)* 2007;45(2):95-131.

6.4 Paracetamol poisoning

6.4.1 Epidemiology

Paracetamol is the most widely used over-the-counter analgesic agent in the world. It is involved in a large proportion of accidental paediatric exposures and deliberate self-poisoning cases. In a retrospective review of toxic exposures in Singapore Emergency Departments, paracetamol (acetaminophen) was the most common pharmaceutical agent (13%).²

Most deaths from paracetamol poisoning occur in adults with acute overdose. In contrast, nearly all deaths attributed to acetaminophen reported in the medical literature regarding children under the age of 6 years have involved repeated supratherapeutic dosing.²¹³ Published data suggest that the mortality rate for patients with repeated ingestion is higher than that of single acute ingestion of acetaminophen.²¹⁴⁻²¹⁶

6.4.2 Pharmacokinetics

Paracetamol is rapidly absorbed from the small intestine. Peak serum concentrations occur within 1–2 hours for standard tablet or capsule formulations and within 30 minutes for liquid preparations. Peak serum concentrations after therapeutic doses do not usually exceed 20 mg/L.

Twenty percent of the ingested dose undergoes first-pass metabolism in the gut wall (sulphation). Distribution is usually within 4 hours of ingestion for standard preparations and 2 hours for liquid preparations. Volume of distribution is 0.9 L/kg.²¹³ Further elimination occurs by hepatic biotransformation. After therapeutic doses, the elimination half-life is 1.5–3 hours. About 90% is metabolised to inactive sulphate and glucuronide conjugates that are excreted in the urine.

Metabolism of the remaining drug is via cytochrome P450 (chiefly 2E1 and 3A4) and results in the highly reactive intermediary compound N-acetyl-p-benzoquinone imine (NAPQI). In normal conditions, NAPQI is immediately bound by intracellular glutathione and eliminated in the urine as mercapturic adducts.²¹⁷ With increased paracetamol doses, greater production of NAPQI may deplete glutathione stores. When glutathione depletion reaches a critical level (thought to be about 30% of normal stores), NAPQI binds to other

proteins, causing damage to the hepatocyte. Glutathione depletion secondary to prolonged fasting, malnourishment and chronic illnesses may also exacerbate the toxic effects.²¹⁸

6.4.3 Toxic ingestion²¹³

Definition:

D Symptomatic: e.g. repeated vomiting, abdominal tenderness in the right upper quadrant or mental status changes.

Grade D, Level 4

D If **unknown** dose, assume toxic ingestion.

Grade D, Level 4

C Acute single dose poisoning:

- 200 mg/kg or more; or 10 g (whichever is less).
 - Both paediatric and adults.

Grade C, Level 2++

D Repeated suprathapeutic ingestion (>24 hours staggered dose):

- In children (< 6 years) or high risk group: 4 g or more than 100 mg/kg/day (whichever is less).
- In children (> than 6 years old) or adults: 6 g or 150 mg/kg/day (whichever is less).

Grade D, Level 4

6.4.4 Factors in paracetamol poisoning and management^{213,217-219}

6.4.4.1 Time of Ingestion

- Acute, single ingestion.
- Repeated Suprathapeutic Ingestion of Paracetamol (RSTI).
- Unknown time of ingestion.

6.4.4.2 Risk stratification

Important considerations in Repeated Suprathapeutic Ingestion of Paracetamol (RSTI):

- High risk groups:
 - Regular ethanol consumption > 21 units/week in males; 14 units/week in females.
 - Conditions causing glutathione depletion: malnutrition, HIV, eating disorders, cystic fibrosis.
 - Regular use of enzyme-inducing drugs:
 - Anti-epileptics: carbamazepine, phenytoin, phenobarbitone.
 - Anti-TB drugs: isoniazid, rifampicin.
 - St John's Wort.
 - Age: less than 6 years.

6.4.5 Sustained-release preparations^{213,219-220}

Pharmacokinetic studies of small overdoses of slow-release paracetamol formulations in healthy volunteers showed that peak plasma concentrations usually still occur within 4 hours, and the apparent half-life is the same as or only slightly longer than that of conventional paracetamol preparations.

The bioavailability was not increased. However, there is a potential for slow absorption and thus a delayed peak serum paracetamol concentration above the normogram line.

C In a single acute ingestion, if more than 200 mg/kg or 10 g (whichever is less) has been ingested, N-acetylcysteine treatment should be started immediately.

Grade C, Level 2++

C In all cases, serum paracetamol levels should be taken at 4 hours or more post-ingestion (as with standard preparations) and repeated 4 hours later. If either level is above the normogram line, N-acetylcysteine should be commenced or continued. N-acetylcysteine may be discontinued if both levels fall below the normogram line.

Grade C, Level 2++

6.4.6 Referral for ED management²¹³

- Patient is symptomatic (irrespective of dose).
- If toxic dose is consumed (see above).
- Unknown dose taken.
- Suspected non-accidental ingestion (irrespective of dose).

- If the patient presents more than 36 hours after the suspected toxic ingestion and the patient is well, the patient does not require further evaluation for acetaminophen toxicity.
- Poor home support (lives alone, inability of caregivers to monitor).

6.4.7 Clinical symptoms and signs of paracetamol poisoning

- **Post acute ingestion (< 24 hours):** asymptomatic to non-specific gastrointestinal effects (anorexia, nausea, vomiting and right upper quadrant or hepatic tenderness).
- **24 to 48 hours:** tender hepatomegaly with jaundice.
- **Day 4 to 5 post poisoning:** acute liver and renal failure.
- **Other features:** erythema, urticaria, haemolytic anaemia, pancreatitis, haemorrhage.

6.4.8 Management of paracetamol poisoning

6.4.8.1 Resuscitation^{213,221}

- Immediate threats to the airway, breathing and circulation are extremely rare in isolated paracetamol overdose.
- In exceptional cases, massive ingestion causing extremely high serum paracetamol levels (i.e. > 800 mg/L) may be associated with an early decrease in level of consciousness and with lactic acidosis.
- Supportive management is appropriate in such cases, with N-acetylcysteine administered in routine doses, although prolonged infusions may be required.
- Recovery is usual with supportive care.
- Any alteration of conscious state should prompt bedside testing of the patient's serum glucose level and correction of hypoglycaemia.

D Presence of hypoglycaemia may be secondary to hepatic failure and intensive care monitoring is required.

Grade D, Level 4

6.4.8.2 Decontamination

(1) Activated charcoal

- **Prehospital**

B Activated charcoal (1 g/kg, up to 50 g) can be considered if available, patient is alert and co-operative, a toxic dose of acetaminophen has been taken and fewer than 2 hours have elapsed since the ingestion.

Grade B, Level 1+

While generally gastrointestinal decontamination with activated charcoal for oral poisoning is useful only within 1 hour of ingestion, there is evidence suggesting significant efficacy if given within 2 hours of ingestion specifically for paracetamol ingestion.

D Gastrointestinal decontamination could be particularly important if N-acetylcysteine cannot be administered within 8 hours of ingestion.

Grade D, Level 4

- **ED/Hospital Management**

B Activated charcoal (1 g/kg, up to 50 g) can be given if less than 2 hours.

Grade B, Level 1+

D May have a role in sustained-release preparations even after 2 hours of ingestion.

Grade D, Level 4

(2) Haemoperfusion^{213,220,221}

D Limited studies available but charcoal haemoperfusion may be considered in severe paracetamol poisoning in the intensive care setting, after consultation with the relevant specialists.

Grade D, Level 3

6.4.8.3 Antidote^{213,220-221}

(1) N- Acetylcysteine

A N-acetylcysteine is the antidote of choice for paracetamol poisoning and should be administered to all patients judged to be at risk of developing hepatotoxicity after paracetamol overdose.

Grade A, Level 1+

Intravenous N-acetylcysteine had been associated with fewer gastrointestinal adverse events compared to oral N-acetylcysteine.

C When risk assessment indicates that N-acetylcysteine is required, it is administered as a three-stage infusion, totalling 300 mg/kg over 20–21 hours.

Grade C, Level 2++

Administration of Intravenous N-acetylcysteine Infusion is a 3-stage infusion:

I) Adults

- (1) Initially 150 mg/kg in 200 mL glucose 5% given over 15 – 60 minutes; then
- (2) 50 mg/kg in 500 mL glucose 5% given over 4 hours; then
- (3) 100 mg/kg in 1000 mL glucose 5% given over 16 hours.

II) Paediatric

(A) If weight is less than 20 kg:

- (1) Initially 150 mg/kg in 3 mL/kg glucose 5% given over 15 – 60 minutes; then
- (2) 50 mg/kg in 7 mL/kg glucose 5% given over 4 hours; then
- (3) 100 mg/kg in 14 mL/kg glucose 5% given over 16 hours.

(B) If weight is more than 20 kg:

- (1) Initially 150 mg/kg in 100 mL glucose 5% given over 15 – 60 minutes; then
- (2) 50 mg/kg in 250 mL glucose 5% given over 4 hours; then
- (3) 100 mg/kg in 500 mL glucose 5% given over 16 hours.

C If hepatic injury is suspected after the three infusion stages, N-acetylcysteine is continued at the rate of the last infusion stage (100 mg/kg each 16 hours or 150 mg/kg/24 hours) until there is clinical and biochemical evidence of improvement.

Grade C, Level 2++

B N-acetylcysteine reduces mortality if commenced late in patients with established paracetamol-induced fulminant hepatic failure. In this setting, N-acetylcysteine reduces inotrope requirements,

decreases cerebral oedema and increases the rate of survival by about 30%.

Grade B, Level 2++

D Anaphylactoid reactions manifested by rash, wheeze or mild hypotension occur in 5–30% of patients during the first two N-acetylcysteine infusions. Management is supportive, with temporary halting or slowing of the infusion, and administration of antihistamines (IV promethazine 0.2 mg/kg, up to 10 mg).

Grade D, Level 3

D The occurrence of an anaphylactoid reaction does not preclude the use of N-acetylcysteine on another occasion, if indicated.

Grade D, Level 3

Severe life-threatening reactions are rare, but may occur in predisposed individuals, such as patients with asthma and in those who had ingested smaller amounts of paracetamol.

(2) Methionine

B Methionine can be considered as an alternative antidote for paracetamol poisoning, especially in the setting of severe reaction to N-acetylcysteine.

Grade B, Level 1+

- It is given orally 50 mg/kg/dose (maximum 2.5 g) every 4 hourly for 4 doses.
- It is associated with more adverse reactions than N-acetylcysteine.

6.4.9 Management of non-accidental toxic ingestions²¹³

D Admission is recommended, irrespective of levels for non-accidental ingestion. Serum levels must be tested. Multi-drug poisoning should be considered.

Grade D, Level 4

6.4.10 ED/hospital management of accidental ingestions

6.4.10.1 Acute single dose toxic ingestion

(1) Asymptomatic patients^{213,219-220}

B If < 2 hours: Gastrointestinal decontamination via activated charcoal (1 g/kg, up to 50 g) for co-operative and alert patients.

Grade B, Level 1+

C If 4-8 hours: Measure paracetamol levels (at or after 4 hours post ingestion).

- Plot paracetamol level on normogram.
- Start IV N-acetylcysteine if over normogram at 150 mg/L (1000 µmol/L) at 4 hours (line of possible hepatotoxicity).

Grade C, Level 2++

C If > 8 hours: Commence IV N-Acetylcysteine (do not wait for levels).

- Obtain paracetamol levels as soon as possible.
- Obtain ALT/AST stat and repeat at the end of N-acetylcysteine infusion or every 12 hours, whichever comes first.
- If the serum paracetamol level is subsequently found to be below the normogram line, N-acetylcysteine may be ceased; if above the line, it should be continued till paracetamol levels fall below the normogram line and ALT is static or normal.
- Obtain full blood count (platelet), INR or PT, urea and creatinine, electrolytes, glucose and arterial blood gas (if venous bicarbonate is low) and repeat as indicated.
- A baseline serum ALT level, international normalised ratio and platelet count provide useful baseline data for later risk assessments.

Grade C, Level 2++

(2) Symptomatic patients (clinical or biochemical)^{213,219,222}

D Start IV N-Acetylcysteine without waiting for levels (even < 8 hours).

- Obtain paracetamol levels, ALT/AST, full blood count (platelet), INR or PT, urea and creatinine, electrolytes, glucose and arterial blood gas.
- If symptomatic and paracetamol levels are below the normogram, consider toxic co-ingestions.

Grade D, Level 3

6.4.10.2 Repeated Supratherapeutic Toxic Ingestion^{213,216,219}

D Commence IV N-Acetylcysteine (do not wait for levels).

- Obtain paracetamol and ALT/AST levels as soon as possible.
- If paracetamol < 10 mg/L and ALT/AST normal, stop infusion of NAC.
- Obtain INR or PT, urea and creatinine, electrolytes, glucose and arterial blood gas (if bicarbonate abnormal) at admission.
- Repeat ALT/AST and serum paracetamol levels at 8-12 hours.
- If ALT/AST normal or static and paracetamol < 10 mg/L, stop infusion of NAC.
- If abnormal, continue IV NAC and repeat ALT/AST 12 hourly and other investigations as indicated.

Grade D, Level 2+

6.4.10.3 Unknown time of ingestion^{213,216,219}

D Start IV N-acetylcysteine. Investigations and management are similar to suprathreshold repeated dose ingestion.

Grade D, Level 4

6.4.10.4 Severe paracetamol poisoning

Hepatocellular necrosis is the major toxic effect of paracetamol poisoning.

Biochemical evidence of maximal damage may not be attained until 72-96 hours after ingestion of the overdose. Severe liver damage in the context of paracetamol poisoning has been defined as a peak plasma alanine aminotransferase (ALT) activity exceeding 1000 IU/L. For those institutions that do not have ready access to ALTs, aspartate transaminase (AST) may be used instead. An AST exceeding 1000 IU/L indicates severe liver damage.

A more accurate test for assessing prognosis is the prothrombin time (INR).

Acute renal tubular damage and necrosis may occur, usually in association with hepatocellular necrosis, but rarely in the absence of major liver damage.

6.4.10.5 Indicators of severe paracetamol poisoning

C Metabolic:

- Metabolic acidosis (pH < 7.3 or bicarbonate < 18) despite rehydration.
- Hypoglycaemia.
- Hypotension despite adequate fluid resuscitation.

CNS:

- Encephalopathy or signs of raised intracranial pressure.

Liver Function / Coagulopathy:

- INR > 2.0 at or before 48 hours or > 3.5 at or before 72 hours:
 - Consider measuring INR every 12 hourly.
 - Peak elevation occurs around 72 – 96 hours.
 - LFTs are not good markers of hepatocyte death.

Renal:

- Renal impairment (creatinine > 200 µmol/L):
 - Monitor urine output.
 - Daily urea, electrolytes and serum creatinine.
 - Consider haemodialysis if > 400 µmol/L.

Resuscitation and intensive care monitoring required.

Grade C, Level 2++

D Consider referrals to liver transplant hepatologists and transferring to tertiary intensive care units with a liver transplant unit in Singapore.

Grade D, Level 4

King's College Hospital Criteria for liver transplantation in paracetamol-induced acute liver failure^{219,221,223-224}

C Consider liver transplantation if:

- Arterial pH < 7.3 or arterial lactate > 3.0 mmol/L after adequate fluid resuscitation.

OR

- If all three of the following occur in a 24-hour period:
 - Creatinine > 300 µmol/L.
 - PT > 100 (INR > 6.5).
 - Grade III / IV encephalopathy.

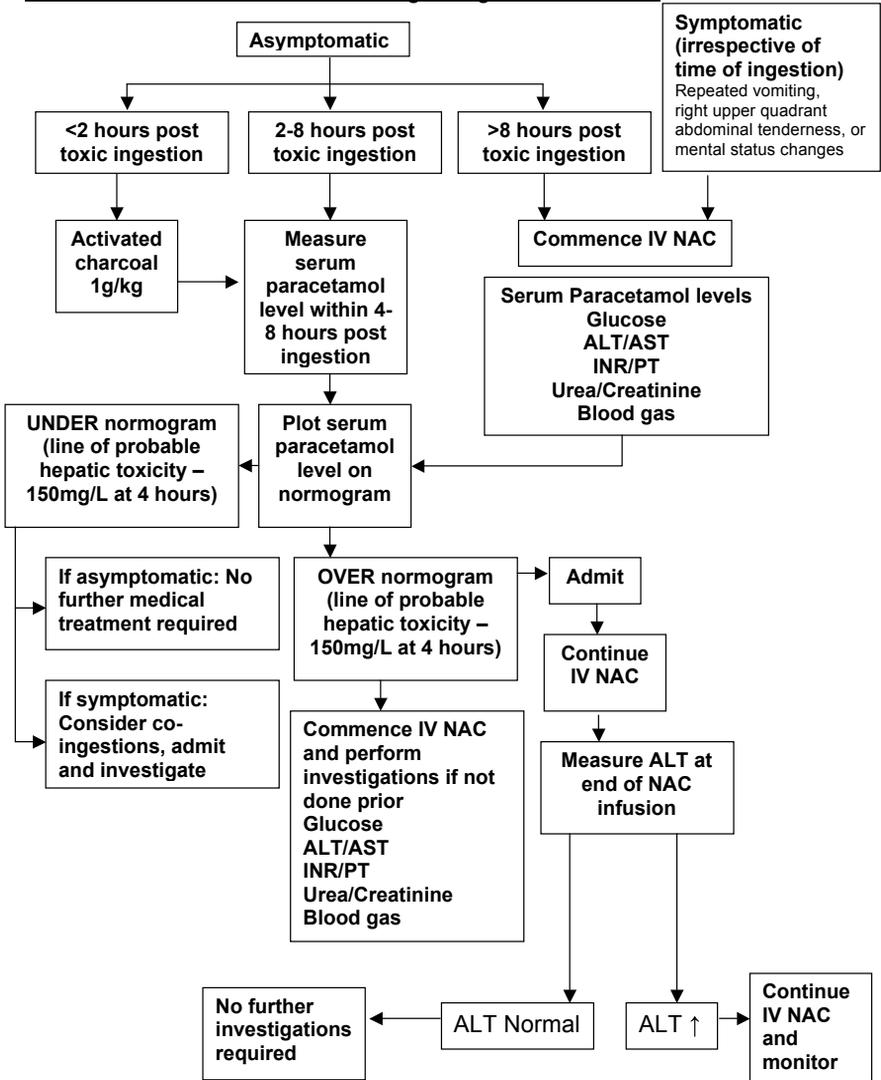
Strongly consider transplantation if:

- Arterial lactate > 3.5 mmol/L after early fluid resuscitation.

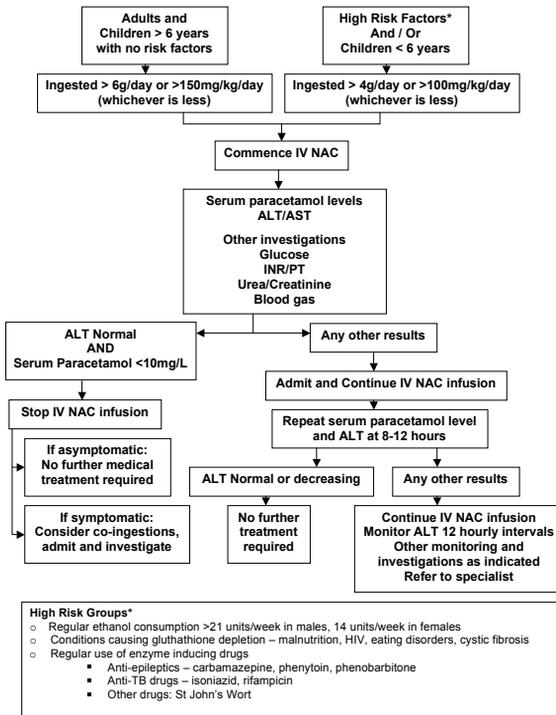
Grade C, Level 2++

Appendix

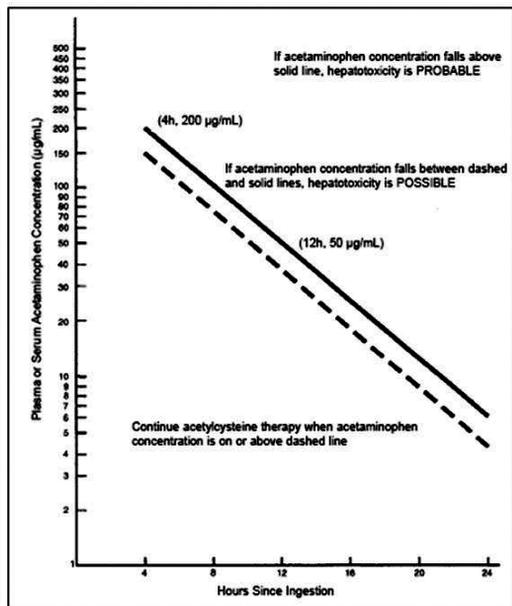
Acute Accidental Paracetamol Poisoning Management Flow Chart



Repeated Supratherapeutic Ingestion Management Flow Chart



Normogram relating plasma or serum acetaminophen concentration and probability of hepatotoxicity at varying intervals following ingestion of a single toxic dose of acetaminophen.



7 Antihistamines / Anticholinergics

7.1 Introduction

Many prescription drugs, over-the-counter medications and plants have anticholinergic properties.

Examples of substances possessing anticholinergic properties:

Class	Examples
Antihistamines	Chlorpheniramine, Cyproheptadine, Doxylamine, Hydroxyzine, Diphenhydramine, Meclizine, Promethazine, Loratadine, Cetirizine
Neuroleptics	Chlorpromazine, Clozapine, Mesoridazine, Olanzapine, Quetiapine, Thioridazine
Tricyclic Antidepressants	Amitriptyline, Amoxapine, Clomipramine, Desipramine, Doxepin, Imipramine, Nortriptyline
Antiparkinsonian Drugs	Trihexyphenidyl, Benztropine
Ophthalmic Drugs	Atropine, Cyclopentolate
Antispasmodics	Atropine (part of Lomotil), Clidinium, Dicyclomine, Hyoscine, Oxybutynin, Propantheline
Plants	Jimson Weed (<i>Datura stramonium</i>), Deadly Nightshade (<i>Atropa belladonna</i>), Henbane (<i>Hyoscyamus niger</i>)

In a retrospective review of toxic exposures in Singapore Emergency Departments, toxicity from pharmaceutical agents, such as cough and cold preparations (of which most have antihistamines) and antidepressants/antipsychotics (some of which have anticholinergic properties), was common.²

7.2 Pharmacokinetics

The onset of anticholinergic toxicity varies depending on the particular drug, but usually occurs within 1-2 hours of oral ingestion. Atropine is rapidly absorbed from the gastrointestinal tract, and achieves peak plasma concentrations within 2 hours. Diphenoxylate and atropine (e.g. Lomotil) is an antidiarrhoeal agent that may present with acute

toxicity up to 12 hours after ingestion with late effects seen up to 24 hours post ingestion. Toxicity from scopolamine may persist for 24-48 hours.²²⁵

7.3 Clinical features of anticholinergic overdose

The classic description of anticholinergic intoxication is well known:

(1) Skin/Mucous membrane:

- “Red as a beet”: Cutaneous vasodilation occurs as a means to dissipate heat by shunting blood to the skin, in order to compensate for the loss of sweat production.
- “Dry as a bone” (anhidrosis): Sweat glands are innervated by muscarinic receptors, so anticholinergic medications produce dry skin.
- “Hot as a hare” (anhydrotic hyperthermia): Interference with normal heat dissipation mechanisms (i.e. sweating) frequently leads to hyperthermia.

(2) Ophthalmic:

- “Blind as a bat” (nonreactive mydriasis): Muscarinic input contributes to both pupillary constriction and effective accommodation. Anticholinergic medications generally produce pupillary dilation and ineffective accommodation that frequently manifests as blurry vision.

(3) Central Nervous System:²²⁶

- “Mad as a hatter” (delirium; hallucinations): Blockade of muscarinic receptors in the central nervous system (CNS) accounts for these findings. Manifestations may include: anxiety, agitation, dysarthria, confusion, disorientation, visual hallucinations, bizarre behaviour, delirium, psychosis (usually paranoia), coma and seizures.
- Hallucinations are often described as “Alice in Wonderland-like” or “Lilliputian type,” where people appear to become larger and smaller. Patients with altered mental status often present with agitation and may appear to grab invisible objects from the air.
 - Seizures have been reported with most of these drugs; however the incidence is low except for pheniramine (approximately 30%).
 - Although central and peripheral anticholinergic effects are commonly seen together, in some cases, central effects may persist after resolution of peripheral symptoms.

(4) Genitourinary:

- “Full as a flask”: The detrusor muscle of the bladder and the urethral sphincter are both under muscarinic control; anticholinergic substances reduce detrusor contraction (thereby reducing or eliminating the desire to urinate) and prevent normal opening of the urethral sphincter (contributing to urinary retention).

(5) Other clinical features not included in the above mnemonic include:

- Cardiovascular:
 - Tachycardia, which is the earliest and most reliable sign of anticholinergic toxicity.
- Gastrointestinal:
 - Gut hypomotility with decreased bowel sounds or frank ileus.
 - These effects are not seen significantly with non-sedating antihistamines.
- Musculoskeletal:
 - Atraumatic rhabdomyolysis (about 7%) has been reported in doxylamine and diphenhydramine toxicity.
- Substances with anticholinergic properties may have other serious side effects:
 - Tricyclic antidepressants (TCA): quinidine-like sodium channel blockade (resulting in a prolonged QRS interval and arrhythmias) and alpha-blockade (resulting in hypotension) are usually more prominent.
Please refer to section 8.4 on TCA poisoning under Chapter 8: Psychotropics.
 - Phenothiazines: more sedating and alpha-blocking properties may result in hypotension.

7.3.1 Differences in toxicity

Orphenadrine is an extremely toxic drug with a high mortality. Death may occur within a few hours from seizures, myocardial depression, and arrhythmias.

In contrast, the other anticholinergic drugs usually cause delirium, sedation, excitation and peripheral anticholinergic effects but no life-threatening toxicity.

7.3.2 Differential diagnosis²²⁷⁻²²⁸

Sympathomimetic overdose and serotonin syndrome may cause agitation, tachycardia and hyperthermia, but can usually be differentiated from anticholinergic toxicity. Sympathomimetic overdose and serotonin syndrome generally cause diaphoresis, in contradistinction to anticholinergic overdose.

Sepsis and/or meningitis may present similarly.

7.4 Referral for ED / hospital management

D All patients with suicidal intent, intentional abuse or in cases in which a malicious intent is suspected (e.g. child abuse or neglect) should be referred to an emergency department.

Grade D, Level 4

D All symptomatic patients should be referred to an emergency department.

Grade D, Level 4

D Poor home support (lives alone, inability of caregivers to monitor).

Grade D, Level 4

D Patients who are suspected of ingesting toxic amounts of anticholinergics should be referred to an emergency department or further management.

Grade D, Level 4

- Diphenhydramine or Dimenhydrinate: 7.5 mg/kg or 300 mg (whichever is less).²²⁹
- All paediatric ingestion of Lomotil meant for adult consumption should be referred for further management and observed for at least 24 hours.

7.5 Investigations

D Capillary glucose should be done in any patient presenting with altered conscious status.

Grade D, Level 4

D Cardiac monitoring and ECG: it is crucial that patients suspected of having anticholinergic toxicity have an ECG to allow detection of QTc interval prolongation or frank arrhythmias. This can occur with

overdose of tricyclic antidepressants, certain phenothiazines (e.g. mesoridazine and thoridazine), diphenhydramine and other agents with anticholinergic properties.

Grade D, Level 3

D Urine analysis/microscopy and serum creatinine kinase: rhabdomyolysis in anti-cholinergic toxicity can occur secondary to prolonged seizures or may be atraumatic in doxylamine and diphenhydramine poisoning.

Grade D, Level 3

D Serum drug levels of anticholinergic agents are not helpful or readily available in the clinical setting; the diagnosis of anticholinergic toxicity is based on clinical findings and less often the result of a diagnostic/therapeutic trial of physostigmine.

Grade D, Level 2+

7.6 Management

7.6.1 Resuscitation

Management of the poisoned patient must always begin with stabilisation of the airway, breathing, and circulation.

D Patients should have intravenous access, supplemental oxygen, cardiac monitoring and continuous pulse oximetry.

Grade D, Level 3

General discussions of the basic facets of resuscitation are found under Chapter 2: Principles of management of acute poisoning.

D Patients with severe anticholinergic toxicity and/or treated with physostigmine should be monitored in an intensive care unit for observation.

Grade D, Level 3

7.6.1.1 *Other considerations in resuscitation*

(1) Cardiotoxicity:

Sodium bicarbonate should be used in the treatment of prolonged QRS or QTc intervals; or for arrhythmia related to anticholinergic

poisoning. The use of sodium bicarbonate, including dosing, in the treatment of poison-related cardiotoxicity is discussed elsewhere (refer to section 8.4.6.3 on pharmacologic treatment of arrhythmia under Chapter 8: Psychotropics; or Hypertonic Sodium Bicarbonate monograph under Annex A).²³⁰⁻²³¹

(2) Neurotoxicity:

- Agitation and seizures should be initially treated with benzodiazepines.
- Physostigmine may be considered for use in agitation and delirium.
- Phenothiazines and butyrophenones have anticholinergic effects and should not be used to sedate patients with anticholinergic toxicity.

Hyperthermia should be treated in typical fashion, including evaporative cooling for moderate to severe cases.

7.6.2 Decontamination

Although systemic anticholinergic toxicity has been reported from cutaneous and ocular absorption, most anticholinergic toxicity results from ingestion.²³²

7.6.2.1 Gastrointestinal decontamination

(3) Gastric lavage:

D May be considered in patients with history of significant overdosing and potential for high morbidity as gastric emptying may be delayed.

Grade D, Level 3

(4) Activated charcoal:

D If the patient's mental status is intact and ingestion of an anticholinergic agent is likely, activated charcoal (1 g/kg; maximum 50 g) should be given.

Grade D, Level 2+

Charcoal should be withheld in obtunded patients with an unprotected airway, unless the airway is secured first.

Endotracheal intubation, however, should not be performed solely for the purpose of giving charcoal.

7.6.3 Antidote therapy

7.6.3.1 *Physostigmine*²³³⁻²³⁴

Its use in anticholinergic poisoning is still controversial.

D The main management for most patients with cholinergic toxicity is supportive care alone, but some literature report benefit in selected patients.

Grade D, Level 3

C Physostigmine may be indicated when patients manifest isolated moderate to severe agitation/delirium secondary to anticholinergic toxicity.

Grade C, Level 2+

D Physostigmine should not be given if a condition other than a purely anticholinergic poisoning is suspected (e.g. tricyclic antidepressant overdose) as it is associated with cardiac adverse events and deaths.

Grade D, Level 3

D Before physostigmine is given, the patient should be placed on a cardiac monitor; and atropine and resuscitative equipment should be available.

Grade D, Level 3

Indications:

D Physostigmine may be superior to benzodiazepines in the management of agitation and delirium due to anticholinergic toxicity in selected patients.

Grade D, Level 2+

D Diagnostic trial in patients presenting with agitation and delirium with suggestive history which may avoid the use of many invasive and radiological investigations.

Grade D, Level 2+

(2) Contraindications:

- Physostigmine should not be used when tricyclic antidepressant poisoning is known or suspected; or when the duration of the QRS interval is at or above 100 ms as asystole have been reported post administration.
- Caution should be used when giving physostigmine to patients with reactive airway disease, intestinal obstruction, epilepsy and cardiac conduction abnormalities.

(3) Recommended dose of physostigmine:

- Paediatric patients: 0.02 mg/kg IV, up to a maximum of 0.5 mg per dose.
- Adults: 0.5 to 2 mg.
 - The drug should be given by slow IV push generally over 5 minutes as overly rapid infusion may result in cholinergic symptoms or seizures.
- The half-life of physostigmine is approximately 15 minutes, but its effects may last significantly longer.
- The initial dose may be repeated after 20-30 minutes, if necessary.

8 Psychotropics

8.1 Benzodiazepines

8.1.1 Introduction

Benzodiazepines are used as sedatives/hypnotics, muscle relaxants, antianxiety agents and anticonvulsants. Their action is on the central nervous system, and these effects appear to be mediated through the inhibitory neurotransmitter, gamma-aminobutyric acid (GABA).²³⁵

8.1.2 Epidemiology

Benzodiazepines rank as one of the most commonly overdosed drugs, which can lead to fatalities, especially in multi-agent overdoses.

From 2001 to 2003, benzodiazepines accounted for 8.4% (849 out of 10,063) of total toxin exposures seen at the emergency departments of 3 public hospitals locally.²

In 2007, a total of 72,978 Benzodiazepine exposures were reported to US poison control centres, of which 269 cases (0.37%) resulted in major toxicity, and 7 resulted in death.²³⁶

The newer non-benzodiazepine sedatives, including zolpidem and zopiclone, act on the benzodiazepine subtype receptor, and have similar activity as typical benzodiazepines (e.g. diazepam, lorazepam, midazolam, alprazolam).²³⁷

8.1.3 Mechanism of toxicity²³⁸⁻²⁴⁵

Drug	Toxicity	Toxic level	Fatalities	Dose associated with fatalities
Alprazolam	Lethargy, heart block.	12 mg	Yes (Patient had multiple medical problems)	7.5 mg
Bromazepam	Hypothermia	420 mg	No	NR
Chlordiazepoxide	Nystagmus	50 mg	No	NR
Clonazepam	Drowsiness and ataxia.	60 mg	No	NR
Diazepam	Minor toxicity, diplopia, drowsiness, fatigue and ataxia.	30 mg	No	NR
Estazolam	Drowsiness, confusion, agitation.	60 mg	No	NR
Flunitrazepam	Respiratory arrest, hypotension and bradycardia, retrograde amnesia.	50 mg; 0.1 mg/kg	Yes	28 mg
Flurazepam	Impaired mental function.	15 mg	Yes	2.1 g
Ketazolam	-	-	No	NR
Lorazepam	Lethargy, combativeness.	20 mg	No	NR
Midazolam	Respiratory depression, cardiac arrest.	30 mg	Yes	IV 10 mg (2.4 mcg/mL)
Oxazepam	Coma	900 mg	No	NR
Temazepam	Amnesia, confusion, depression.	15 mg	Yes	0.885-14 mg/L
Triazolam	Apnea, lethargy, ataxia, and slurred speech; coma.	1 mg	Yes	12.5 mg

Abbreviation: NR = not reported.

Few fatalities have been clearly documented due to oral benzodiazepine ingestion alone. However, observation is recommended for overdoses more than double the therapeutic dose. Flunitrazepam overdose particularly places patient at risk for respiratory arrest.

8.1.4 Toxicokinetics²⁴⁶

- Benzodiazepines may be administered via the oral, nasal, intramuscular, intravascular or rectal route.
- Their action is on the central nervous system, and these effects appear to be mediated through the inhibitory neurotransmitter gamma-aminobutyric acid (GABA). They bind to the benzodiazepine receptor, resulting in the opening of chloride channels and potentiation of GABA activity.
- With appropriate supportive care, most patients recover within 12 to 36 hours following an acute overdose.
- Interaction with ETHANOL: In general, when given concurrently, benzodiazepine metabolism appears to be inhibited by ethanol. Clinically, concomitant administration of high doses of ethanol and benzodiazepines act to synergistically depress respiration.

8.1.5 Diagnosis

8.1.5.1 Presentation

Patients with intoxication or overdose may present with drowsiness, altered mental state, impaired attention or memory, speech incoordination and unsteady gait.

Physical signs include nystagmus, hypothermia, hyporeflexia, hypotension and shallow respiration.

Psychiatric manifestations include inappropriate behaviour, uncooperativeness, labile mood, impaired judgment and social functioning.

Severe overdoses may lead to coma and respiratory arrest.

8.1.5.2 Prognosis

The prognosis depends on interindividual differences in tolerance and dependency. Benzodiazepines and non-benzodiazepines (excluding barbiturates) generally have a high toxic to therapeutic ratio. Most

sedatives-hypnotics are unlikely to cause significant adverse effects within 5-10 times the hypnotic doses.²⁴⁷

Intravenous administration is associated with a greater degree of hypotension as compared to the other routes of administration. It is more likely to cause cardiac and respiratory arrest.²⁴⁸

Mortality from a pure benzodiazepine overdose is rare; it usually results from concomitant ingestion of alcohol or other sedative-hypnotics.²⁴⁹⁻²⁵¹

8.1.6 Special groups of patients

Elderly individuals and very young persons are more susceptible to the CNS depressant effects.^{248,252-254}

Benzodiazepines are excreted in breast milk and may produce effects in the nursing infant, such as lethargy, weight loss and withdrawal symptoms.^{235,255-257}

8.1.7 Investigations

Routine quantitative drug estimation is not readily available.

D Qualitative screening of urine or blood is not recommended. Screening rarely influences treatment decisions because of long turnaround time, lack of available or reliable tests, poor correlation clinically and may not alter emergency treatment options. However urine and blood screening may support evidence of exposure.²⁵⁸⁻²⁵⁹

Grade D, Level 3

Laboratory levels may not correlate with severity of poisoning.²⁶⁰⁻²⁶³

Screening tests usually detect benzodiazepines that are metabolized to desmethyldiazepam or oxazepam. Thus they may not detect triazolam, lorazepam, alprazolam or temazepam.²⁶³

GPP Monitor arterial blood gas if there is respiratory depression. Obtain serum electrolytes, glucose, BUN levels. Useful tests to exclude other causes of respiratory depression and predict severity of respiratory depression.

GPP

8.1.7.1 Criteria for diagnosis

D Diagnosis is usually based on a history of ingestion.²⁶⁴ Specific serum levels may confirm diagnosis. Urine and blood screens are also available.

Grade D, Level 3

8.1.8 Treatment

8.1.8.1 Decontamination

Refer to Chapter 3: Decontamination after poisoning.

8.1.8.2 Supportive management

Refer to Chapter 2: Principles of management of acute poisoning.

8.1.8.3 Antidotes

A Although flumazenil may be effective to reverse coma from suspected drug poisoning in patients presenting to the emergency department, its routine use is not recommended. Routine use of flumazenil is not recommended as benzodiazepine overdose is seldom fatal and flumazenil has side effects.

Grade A, Level 1+

A Flumazenil is not recommended in patients with epilepsy, benzodiazepine dependence or suspected multi-agent overdoses. Co-ingested substances, such as heterocyclic antidepressants, are known to produce seizures.

Grade A, Level 1+

8.2 Selective serotonin reuptake inhibitor (SSRI)

8.2.1 Introduction

SSRIs are potent inhibitors of serotonin re-uptake by central nervous system neurones, and may also alter sensitivity to serotonin. They include: citalopram (Cipram), escitalopram (Lexapro), fluoxetine (Prozac), fluvoxamine (Faverin), paroxetine (Seroxat) and sertraline (Zoloft).

8.2.2 Epidemiology

They belong to the class of antidepressants. Antidepressants accounted for 4% of toxic human exposures and 0.25% of fatalities in USA in 2007.²⁶⁵

8.2.3 Mechanism of toxicity²⁶⁶⁻²⁷⁰

They are relatively specific for the serotonin reuptake receptor, and thus have few other pharmacological effects, even in toxic doses. Most of the adverse effects can be explained by excessive concentrations of serotonin, particularly in the central nervous system. Toxicity is minimal, unless there is increased production of serotonin or inhibition of serotonin metabolism. In most cases, severe symptoms are not expected unless the SSRI overdose is large (25 to 50 times a single therapeutic dose). Toxic level is usually more than 5 times the therapeutic dose but rare cases of lower doses resulting in toxicities have also been reported.

Drug	Toxicity	Toxic level	Fatalities	Dose associated with fatalities
Citalopram	QTc interval and/or arrhythmia, seizure.	400 mg to 5 g. 5 times therapeutic dose.	Serotonin syndrome	840 mg
Escitalopram	Vomiting, sedation.	5 times therapeutic dose.	No	NR
Fluoxetine	Seizures, agitation, dyskinesia.	100 mg	Yes	260 mg

Drug	Toxicity	Toxic level	Fatalities	Dose associated with fatalities
Fluvoxamine	Seizures, abdominal pain, tremor, drowsiness, bundle branch block, bradycardia, prolonged prothrombin time.	250 mg	Yes	2500 mg
Paroxetine	Sedation, vomiting, mydriasis, drowsiness, and tachycardia.	100 mg	Yes	530–600 mg
Sertraline	Seizures, ECG abnormalities, Serotonin syndrome.	250 mg	Yes	1100 mg

Abbreviation: NR = not reported.

8.2.4 Toxicokinetics

SSRIs are usually administered orally, with good bioavailability. They have significant plasma protein binding and large volumes of distribution.

Most SSRIs and their metabolites are metabolised via P450 hepatic enzymes. These drugs may inhibit cytochrome P450 isoenzymes which may lead to increased concentrations of drugs such as TCAs, carbamazepine and haloperidol.

8.2.5 Diagnosis

8.2.5.1 Presentation

Symptoms observed following SSRI overdose are typically mild and manifest primarily as CNS depression.

They include drowsiness, tremor in upper extremities, giddiness, nausea, vomiting, diarrhoea, tachycardia (occasionally bradycardia), hypo/hypertension, dilated pupils, agitation, dry mouth and sweating.²⁷¹⁻²⁷⁴

Seizures and cardiac abnormalities (QTc interval prolongation) can occur, especially in overdoses with citalopram.^{266,269,275-277}

Onset and progression of clinical toxicity, including serotonin syndrome, is gradual over several hours. However, after a large overdose or with certain drug interactions, onset can be abrupt.²⁷⁸⁻²⁷⁹

8.2.5.2 Prognosis

Pure SSRI overdose is usually benign, unless a large overdose (more than 25 times therapeutic dose) or co-ingestion occurs.^{268,277,280-281}

SSRIs may interact with other drugs that cause serotonin release, and produce the life threatening serotonin syndrome: altered mental status (confusion, hypomania), agitation, myoclonus, hyperreflexia, sweating, shivering, tremor, diarrhoea, motor incoordination, muscle rigidity and fever.

Severe complications may include: hyperthermia, rhabdomyolysis, disseminated intravascular coagulation (DIC), convulsions, respiratory arrest and death.²⁷⁸

D Asymptomatic patients or those with mild effects following isolated unintentional acute SSRI ingestions of up to five times an initial adult therapeutic dose can be observed at home with instructions to seek medical attention if symptoms develop.²⁷⁹

The therapeutic index is wide and overdoses up to 5 times the therapeutic doses may be tolerated without serious toxicity.

Grade D, Level 4

D For patients already on an SSRI, those with ingestion of up to five times their own single daily therapeutic dose can be observed at home with instructions to seek medical attention if symptoms develop.²⁷⁹

Grade D, Level 4

8.2.6 Special groups of patients

SSRIs are not usually prescribed to treat conditions in paediatrics. However, sertraline has been used in children and adolescents for the treatment of obsessive compulsive disorder at dosages of 25 mg once daily for ages 6–12 years and 50 mg once daily for ages 13–17 years.

8.2.7 Investigations

Routine quantitative drug estimation is not readily available.

GPP

- Monitor arterial blood gas if there is respiratory depression.
- Monitor serum electrolytes, glucose, BUN.
- Useful tests to exclude other causes of respiratory depression and predict severity of respiratory depression.

GPP

8.2.8 Treatment

8.2.8.1 Decontamination

Refer to Chapter 3:Decontamination after poisoning.

8.2.8.2 Supportive management

GPP Cardiac monitoring is recommended in symptomatic cases. Some drugs can prolong QT and in overdoses, arrhythmias need to be excluded.

GPP

D Use intravenous benzodiazepines for seizures, and external cooling measures for hyperthermia (>104°F or >40°C) seen with SSRI-induced serotonin syndrome.²⁷⁹ Institute emergency and supportive measures as they occur.

Grade D, Level 4

Refer to Benzodiazepine antidote monograph under Annex A (page 201).

D Sodium bicarbonate may be used for QRS widening in patients with cardiac conduction abnormalities after SSRI poisoning.²⁸²⁻²⁸⁴ This reverses the sodium channel-dependent membrane depressant effects and may correct the cardiac conduction abnormalities.

Grade D, Level 4

Refer to Sodium Bicarbonate antidote monograph under Annex A (page 231).

GPP Provide IV fluids and maintenance of the airway and ventilation if required. Institute emergency and supportive measures as required clinically.

GPP

GPP Inotropic agents should be started for hypotension not responding to fluid resuscitation. Institute emergency and supportive measures as they occur.

GPP

8.2.8.3 *Antidotes*

D Cyproheptadine may be considered for suspected serotonin syndrome refractory to standard treatment measures.²⁸⁵⁻²⁹⁰ Cyproheptadine is a histamine H1 blocker which antagonises serotonin receptors. Anecdotal case reports have shown improved clinical symptoms with its use.

Grade D, Level 3

Refer to Cyproheptadine antidote monograph under Annex A (page 207).

D Chlorpromazine may be considered for suspected serotonin syndrome refractory to standard treatment measures.²⁹¹⁻²⁹⁴ Chlorpromazine is a serotonin receptor antagonist neuroleptic. Anecdotal case reports have shown improved clinical symptoms with its use.

Grade D, Level 3

D Dantrolene may be considered for suspected serotonin syndrome refractory to standard treatment measures.²⁹⁵⁻²⁹⁷ Dantrolene relaxes skeletal muscles and prevents hyperthermia. Anecdotal case reports have shown improved clinical symptoms with its use.

Grade D, Level 3

Refer to Dantrolene antidote monograph under Annex A (page 208).

8.2.8.4 *Enhanced elimination*

There are no known effective methods for enhanced elimination of SSRIs.

8.2.8.5 *Advice*²⁹⁸⁻³⁰⁵

D In the absence of an established toxic dose, the presence of more than mild clinical effects (vomiting, somnolence, mydriasis, diaphoresis, including those consistent with serotonin syndrome) should be used as an indication for emergency department referral, regardless of the dose reportedly ingested.

Patients who have unintentional SSRI ingestions and are asymptomatic may stay at home with poison centre follow-up. A patient suspected of a significant overdose is at risk of serious toxicity and serotonin syndrome.

Grade D, Level 3

8.3 Antipsychotics

8.3.1 Introduction

Antipsychotics may be divided into 2 types: Typical and Atypical. The critically poisoned patient should be managed according to standard advanced cardiac life support measures.

Toxicity profiles and fatal doses of some antipsychotic drugs³⁰⁶

Drug	Class	Toxicity	Fatalities reported	Doses associated with fatalities
Chlorpromazine	Phenothiazine	Tachycardia, sedation.	Yes	15-150 mg/kg ^a
Haloperidol	Butyrophenone	QT interval prolongation, paradoxical hypertension, drowsiness in children.	No	NR
Amisulpride	Benzamide	Cardiotoxicity, seizures, QT interval prolongation.	Yes	3 g
Quetiapine	Dibenzothiazepine	Hypotension, respiratory depression and coma.	Yes	NR
Olanzapine	Thienobenzodiazepine	QT interval prolongation.	Yes	150 mg
Trifluoperazine	Piperazine Phenothiazine	Coma	Yes	NR
Aripiprazole	Quinolinone derivative	Tremor, drowsiness, QRS and QT interval prolongation.	No	NR
Ziprasidone	Benzylisothiazolylpiperazine	QT interval prolongation.	Yes	NR
Clozapine	Tricyclic dibenzodiazepine	Coma, seizures, quinidine-like ECG changes	Yes	>1 g
Risperidone	Benzisoxazole	Drowsiness, QRS and QT interval prolongation	Yes	NR

^a *Children seem to be more sensitive to chlorpromazine*; 5 childhood deaths have occurred from ingestions of 20 to 74 mg/kg.

Abbreviation: NR = not reported.

8.3.2 Epidemiology

Antipsychotics have been used clinically for 60 years. Atypical antipsychotics are increasingly being prescribed as they cause less extrapyramidal side effects (EPSE) compared to typical antipsychotics. However, the atypical antipsychotic agents are associated with more metabolic adverse effects and CNS depression.

8.3.3 Mechanism of toxicity

Orthostatic hypotension results from alpha adrenergic receptor blockade, while the toxic-confusional state is attributed to muscarinic blockade. These agents may cause electroencephalographic (EEG) changes in the subcortical sites and thus cause seizures. They may cause QTc prolongation leading to cardiac arrhythmias and death.

8.3.4 Relevant toxicokinetics

Antipsychotics are generally lipid-soluble weak bases that are rapidly absorbed, and have high protein binding with large volumes of distribution. Anticholinergic effects associated with many of these drugs may delay absorption, and cause delayed peak concentrations.

Chlorpromazine causes significant drowsiness. Haloperidol causes less hypotension compared to chlorpromazine, but has a high incidence of EPSE.

Clozapine serum concentrations in deliberate overdose is usually 2-7 mg/L. It is metabolized by CYP 1A2 and 2D6. Olanzapine is also metabolized by CYP 1A2 and 2D6 but has less potential for significant drug interactions as there are also other metabolic pathways. Drugs that inhibit CYP 1A2, such as fluvoxamine, cimetidine and erythromycin, can cause substantial increases in clozapine and olanzapine.

8.3.5 Clinical presentations / diagnosis

B Clinical manifestations of atypical antipsychotic toxicity generally include varying degrees of central nervous system depression (drowsiness), agitation, anticholinergic effects, pupillary changes, seizures, hypotension or hypertension, and cardiac conduction abnormalities (prolongation of the QTc and QRS intervals). Clozapine has been shown to cause agranulocytosis in 1–2% of patients after

1 year of therapy. Morbidity usually results from cardiotoxicity (hypotension, ventricular arrhythmias or conduction delay); or neurotoxicity (respiratory depression, coma, seizures or delirium).

Grade B, Level 1-

D Patients with stated or suspected self-harm should be referred to an emergency department immediately. This is regardless of the dose reported.

Grade D, Level 4

C Asymptomatic patients without evidence of attempted self-harm are unlikely to develop symptoms if the time since ingestion is greater than 6 hours. They do not need referral into hospital.³⁰⁷

Grade C, Level 3

8.3.6 Atypical antipsychotics

8.3.6.1 Treatment

D All patients (12 years of age or older) who are naïve to atypical antipsychotic medications, and are experiencing no more than mild drowsiness can be observed at home, unless they have ingested more than five times the initial adult dose of the antipsychotic medication (i.e. if they ingested more than aripiprazole 50 mg, clozapine 62.5 mg, olanzapine 25 mg, quetiapine 125 mg, risperidone 5 mg, ziprasidone 100 mg).³⁰⁷

Grade D, Level 4

D If a patient on chronic atypical antipsychotic therapy ingested more than 5 times their current single dose (not daily dose), they should be referred to the emergency department.³⁰⁷

Grade D, Level 3

D Ipecac syrup should be avoided due to insufficient evidence of its effectiveness. (Olanzapine, ziprasidone).³⁰⁸⁻³⁰⁹

Grade D, Level 3

D Decontaminate with activated charcoal. Consider attempting gastric lavage if ingestion was within a few hours since anticholinergic action slows GI transit. (Olanzapine, quetiapine).³⁰⁹⁻³¹¹

Grade D, Level 3

D Hypotension should be treated with IV crystalloid infusions. If vasopressors are required, norepinephrine or phenylephrine is preferred. Agents with beta-agonist activity (dopamine, epinephrine) may worsen vasodilatory effects (hypotension) and should be avoided. Hypotension is due to atypical antipsychotic-induced alpha blockade.^{308,312}

Grade D, Level 3

D For drug-induced dystonia in the adult, give IV benztropine 1-2 mg or diphenhydramine 50 mg IV/IM over 2 minutes. For that in the child, give diphenhydramine 1 mg/kg/dose IV over 2 minutes (maximum 5 mg/kg/day or 50 mg/m²/day).^{307-308,313-317}

Grade D, Level 3

D Perform continuous cardiac monitoring. Monitor antimuscarinic effects, and check creatine kinase (CK) levels in patients with prolonged agitation, excessive rigidity or coma. In patients with neurologic symptoms, monitor for respiratory depression (pulse oximetry and/or ABGs).³⁰⁸

Grade D, Level 3

D Haemodialysis, haemoperfusion, forced diuresis and exchange transfusion are unlikely to be useful following overdose, because of the relatively large volume of distribution and high degree of protein binding. (Ziprasidone, clozapine).³⁰⁸

Grade D, Level 3

D Treat seizures with IV benzodiazepines.^{308,318}

Grade D, Level 3

Severe neuroleptic malignant syndrome (NMS) can lead to rhabdomyolysis, myoglobinuria and renal failure as well as long-term neuropsychiatric sequelae.

General supportive measures should be instigated including rehydration, cooling and the treatment of any intercurrent infection. Benzodiazepines may be used to facilitate muscle relaxation. Bromocriptine or amantadine has been used.

C Neuroleptic Malignant Syndrome should be treated with oral or parenteral dantrolene.³¹⁹⁻³²¹

Grade C, Level 2+

Refer to Dantrolene antidote monograph under Annex A (page 208).

8.3.6.2 Special populations at risk

C All patients less than 12 years of age who are naïve to atypical antipsychotics, and are experiencing no more than mild drowsiness (lightly sedated and can be aroused with speaking voice or light touch) can be observed at home. However, refer if they have ingested more than four times the initial adult dose; or a dose that is equal to or more than the lowest reported acute dose that resulted in moderate toxicity, whichever dose is smaller (i.e. aripiprazole 15 mg; clozapine 50 mg; olanzapine 10 mg; quetiapine 100 mg; risperidone 1 mg; or ziprasidone 80mg).³⁰⁷

Grade C, Level 3

8.3.7 Typical antipsychotics

8.3.7.1 Clinical presentations / diagnosis

C Clinical manifestations of typical antipsychotics poisoning generally include neuroleptic malignant syndrome, rigidity, dystonia, fever and widened QRS interval.³²²

Grade C, Level 2+

8.3.7.2 Treatment

Treatment of typical antipsychotic poisoning does not differ from that of atypical antipsychotic poisoning. *Refer to that section for treatment.*³¹²

D The primary treatment of cardiotoxicity is plasma alkalinisation with sodium bicarbonate and hyperventilation.³²³

Grade D, Level 4

Refer to Sodium Bicarbonate antidote monograph under Annex A (page 231).

GPP Patients with altered mental state or persistent tachycardia despite intravenous fluids should be closely monitored.³¹⁸ Benzodiazepines or physostigmine could be administered to manage tachycardia.

GPP

8.4 Tricyclic antidepressants

8.4.1 Introduction

Tricyclic antidepressants (TCA) are used clinically to treat a range of disorders such as depression, panic disorder, social phobia, bulimia, narcolepsy, attention deficit disorder, obsessive compulsive disorder, childhood (nocturnal) enuresis, and chronic pain syndromes.

Available TCAs in Singapore include amitriptyline, clomipramine, doxepin, dothiepin, imipramine, nortriptyline and trimipramine.

8.4.2 Epidemiology

Tricyclic antidepressants were first discovered in the early 1950s and were subsequently introduced later in the decade. For many years, the TCAs were the first choice for pharmacological treatment of clinical depression. Although they are still considered to be highly effective, TCAs have been increasingly replaced by SSRIs and other new antidepressants.

There are no specific statistics for TCA overdoses and associated outcomes:

- In the USA, antidepressants as a class accounted for 8.2% of toxic adult human exposures and implicated 7.8% of 1315 overdose-related fatalities³²⁴
- In an earlier study² conducted in 3 public hospitals in Singapore from 2001-2003, 215 cases of overdose with an antidepressant (2.1% of total exposures) presented to the hospital emergency departments during the study period.

8.4.3 Mechanism of toxicity³²⁵

TCAs are highly lipophilic, are extensively bound to plasma proteins, and also bind to tissue and cellular sites. They have a large volume of distribution and long elimination half-lives.

TCAs have actions at numerous receptors. These include (i) anticholinergic and alpha-antagonistic activities; (ii) serotonin, norepinephrine and dopamine reuptake inhibition; and (iii) sodium and potassium channel blockade.

Therapeutic doses may initially cause drowsiness, and difficulty in concentrating and thinking. The dulling of depressive ideation may explain the efficacy of TCAs in depressive disorders. Hallucinations, excitement, and confusion have occurred in a small percentage of patients during antidepressant therapy with TCAs.

In moderate overdose, drowsiness, sedation, sinus tachycardia, hallucinations and other anticholinergic effects may be observed.

In severe toxicity, coma, seizures, QRS prolongation with ventricular dysrhythmias, respiratory failure, and hypotension are the primary life-threatening symptoms.

8.4.4 Relevant toxicokinetics

Table 1. Basic kinetics of TCAs

Drug	Oral Bioavailability ³²⁵	Protein binding ³²⁶	Vol of distribution ³²⁶	Cytochrome P450 metabolism ⁺	Elim half life (hr)**
Amitriptyline	30 to 60%	96.4 +/- 0.8%	8.3 +/- 2 L/kg	1A2, 2C19, 3A4, 2D6,	9–25
Clomipramine	20 to 78%	97%	7 to 20 L/kg	1A2, 2C19, 3A4, 2D6	21, (36)
Dothiepin	30%	84%	11 to 78 L/kg	-	14–24 (23–46)
Doxepin	13 to 45%	79 to 84%	20 +/- 8 L/kg	2D6	8–24
Imipramine	22 to 77%	85.7%	15 +/- 6 L/kg	1A2, 2C19, 3A4, 2D6	18–34 (12–30)
Nortriptyline	45 to 70%	93 to 95%	18 +/- 4 L/kg	2D6	16–36
Trimipramine	Unknown	95%	30.9 +/- 3.5 L/kg	2D6	23

* *Metabolic pathways are not fully established for all drugs.*

** *Numbers in parentheses represent the half-life of the metabolites.*

A precise toxic threshold is difficult to determine from the literature. However an evidence-based consensus guideline³²⁷ has recommended TCA exposure levels which should be referred for management in a hospital emergency department:

- Amitriptyline > 5 mg/kg.
- Clomipramine > 5 mg/kg.
- Doxepin > 5 mg/kg.
- Imipramine > 5 mg/kg.
- Nortriptyline > 2.5 mg/kg.
- Trimipramine > 2.5 mg/kg.

TCA blood levels are generally thought to be of little or no value in treating patients with known TCA overdose.³²⁸⁻³³⁰ The best predictor of seizures and cardiac arrhythmias in TCA overdose is thought to be a QRS duration of greater than 0.10 seconds on an electrocardiogram.³³¹

8.4.4.1 Physical findings

Findings in overdose situations relate to the anticholinergic, cardiovascular and CNS effects of TCAs.

TCAs exert toxic effects in 4 main ways:

- Blocking the neuronal reuptake of norepinephrine, serotonin, and dopamine.
- Anticholinergic effects.
- Direct alpha-adrenergic blockade.
- Blockade of fast sodium channels in myocardial cells, resulting in quinidine-like membrane stabilising effects.

Recently, a sodium channel blockade toxidrome has been proposed and described, using the mnemonic “S-A-L-T” (i.e. shock, altered mental status, long-QRS interval duration, terminal R wave in aVR).³³²

8.4.4.2 Drug interactions

The TCAs are highly metabolised by the hepatic cytochrome P450 microsomal enzyme system.

- Drugs which inhibit P450 enzymes (e.g. cimetidine, methylphenidate, fluoxetine, certain antipsychotics and calcium channel blockers) may produce decreases in TCA metabolism, leading to increases in TCA blood concentrations and accompanying toxicity.
- Drugs which prolong the QT interval, including antiarrhythmics (e.g. quinidine); antihistamines (e.g. terfenadine); and some antipsychotics, may increase the chance of ventricular dysrhythmias.
- TCAs may enhance response to alcohol and the effects of barbiturates and other CNS depressants.
- Adverse effects of TCAs may also be enhanced by other drugs that have antimuscarinic properties.

8.4.5 Clinical presentation / diagnosis

Toxicities of TCAs are mostly via exaggeration of pharmacologic activity, including CNS depression; seizurogenicity; sodium channel blockade; and alpha-adrenergic blockade.

Initially, anticholinergic effects predominate, including dry mouth; blurred vision; urinary retention; constipation; dizziness; and emesis.

Other signs and symptoms associated:

- Anticholinergic effects: altered mental status (e.g. agitation, confusion, lethargy etc), resting sinus tachycardia, mydriasis (pupil dilation), fever.
- Cardiac effects: hypertension (early and transient; should not be treated), tachycardia, orthostasis and hypotension, arrhythmias (including ventricular tachycardia and ventricular fibrillation), ECG changes (prolonged QRS, QT and PR intervals).
- CNS effects: syncope, seizure, coma, myoclonus, hyperreflexia.
- Pulmonary effects: hypoventilation resulting from CNS depression.
- Gastrointestinal effects: decreased or absent bowel sounds.

C Consider referral to a hospital emergency department if ingested either of the following amounts (whichever is lower):

- An amount that exceeds the usual maximum single therapeutic dose;

OR

- An amount equal to or greater than the lowest reported toxic dose
 - For amitriptyline, clomipramine, doxepin and imipramine: 5 mg/kg.
 - For nortriptyline and trimipramine: 2.5 mg/kg.

This recommendation applies both to patients who are naïve to the specific drug and to patients currently taking TCAs. For patients currently on TCAs, the extra doses should be added to the daily dose taken for comparison to the threshold doses stated above.³²⁷

Grade C, Level 2+

C For unintentional poisonings, asymptomatic patients do not need referral to an emergency department facility if more than 6 hours have elapsed since the ingestion of the TCA. These patients are unlikely to develop symptoms.³²⁷

Grade C, Level 2+

B ECG readings are recommended over serum TCA drug level to predict seizure and arrhythmia.³³³

Grade B, Level 1+

8.4.6 Treatment

8.4.6.1 Pre-hospital Triage

TCA overdose cases can be managed at home as per the following algorithm³²⁷ :

Table 2. Pre-hospital triage algorithm for TCA ingestion.

Is suicidal, abuse, or malicious intent suspected? No ↓	→ Yes → Refer to ED
Is the home situation of concern? (e.g. patient lives alone or family/caregiver seems unreliable) No ↓	→ Yes → Refer to ED
Is the patient symptomatic? (e.g. weak, drowsy, dizzy, tremulous, palpitations) No ↓	→ Yes → Refer to ED
Have more than 6 hours elapsed since the TCA ingestion and the patient is still asymptomatic? No ↓	→ Yes → Continue to follow closely at home
Does the patient have significant underlying cardiovascular or neurological disease, or is he/she taking a cardiodepressant drug or MAO inhibitor? No ↓	→ Yes → Consider referral to ED
Can you estimate the maximum amount ingested? YES ↓	→ NO → Refer to ED
Has the patient ingested a potentially toxic dose? Amitriptyline > 5 mg/kg Clomipramine > 5 mg/kg Doxepin > 5 mg/kg Imipramine > 5 mg/kg Nortriptyline > 2.5 mg/kg Trimipramine > 2.5 mg/kg No ↓	→ Yes → Refer to ED
Observe at home. Instruct caregiver to call physician or poison centre if symptoms appear. Consider follow-up within 4 hours of initial call. Consider referral to emergency services should new symptoms develop.	
*Algorithm applies only to ingested TCAs, not to parenteral use or other routes of exposure. Algorithm applies only to acute ingestions. †A toxic dose for dermal exposures could not be established from available evidence. The dose represents the ingestion of a dermal preparation.	

8.4.6.2 Decontamination and elimination^{325,334}

D Gastric lavage may be considered for massive ingestions, up to 2-4 hours post-ingestion in potentially toxic TCA overdoses. Gastric emptying time may be delayed due to anticholinergic effects of the TCAs.

Grade D, Level 3

D Activated charcoal may be used for gastric decontamination. However, the routine use of multiple-dose activated charcoal is not recommended.

Activated charcoal slurry 1 g/kg may be administered as soon as possible after a potentially toxic ingestion in a healthcare setting (due to the risk of aspiration), as TCAs are known to undergo enterohepatic recirculation. Administration of subsequent doses should be considered in patients with serious toxicity, because of the possibility of desorption of TCA from charcoal. It should also be considered in patients who ingest modified-release formulations.^{325,335-336}

Grade D, Level 3

GPP Haemodialysis and haemoperfusion may be considered in patients with very severe TCA poisoning. Due to the very large volume of distribution and high protein binding of TCAs, haemodialysis and haemoperfusion are not as effective in enhancing drug removal.

GPP

8.4.6.3 Pharmacologic treatment

(1) Arrhythmia:

C Sodium bicarbonate is the mainstay of therapy in TCA overdose. Bolus doses of 1-2 mEq/kg should be given to achieve and maintain a QRS width of 100 milliseconds or less. In patients with dysrhythmia, serum pH should be maintained at 7.45 to 7.55. Other causes of widened QRS should be considered if the patient fails to respond to sufficient doses of sodium bicarbonate therapy.³³⁷⁻³³⁸

Grade C, Level 2-

Refer to Sodium Bicarbonate antidote monograph under Annex A (page 231).

GPP Use of physostigmine as an antiarrhythmic is not recommended.

In the setting of TCA overdose, it has been associated with the development of seizures and fatal dysrhythmias.³²⁵

GPP

GPP Avoid antiarrhythmic drugs from class Ia (quinidine, procainamide, disopyramide), class Ic (flecainide), class II, and class III (bretylium, amiodarone). These agents may prolong depolarisation, QTc interval and predispose to arrhythmias.

The correction of hypotension, hypoxia and acidosis will reduce the cardiotoxic effects of tricyclics. Ventricular arrhythmias refractory to sodium bicarbonate may require treatment with lidocaine, magnesium sulphate, or both.^{337,339}

GPP

(2) Hypotension:

D Hypotension refractory to fluid resuscitation and sodium bicarbonate may require vasopressor support (norepinephrine, phenylephrine). Inotrope support (dopamine) may not be as effective.³³⁷⁻³⁴⁰

Grade D, Level 3

(3) CNS Complications:

GPP For TCA-associated convulsions, benzodiazepines are recommended. The efficacy of phenytoin is not proven.³²⁷

GPP

GPP Flumazenil is not recommended in patients who have co-ingested TCA and benzodiazepines.^{327,337}

GPP

8.4.6.4 Monitoring

D Symptoms of TCA toxicity generally present within 2 hours of ingestion.

All patients with suspected significant cyclic antidepressant exposure should undergo cardiac monitoring for a minimum of 6-8 hours. Major complications (such as seizures and arrhythmias) typically occur in the first 6 hours after ingestion. Monitoring in symptomatic patients should continue until the ECG findings have been normal for 12-24 hours. Patients may be discharged then if there are no signs of toxicity and no significant ECG abnormalities (QRS < 100 milliseconds).^{337,339,341}

Grade D, Level 3

C While serum TCA levels may be used to confirm suspected poisoning, the levels do not correlate with toxic effects and are not predictive. ECG is recommended over serum TCA levels to predict seizure and arrhythmia risk.³⁴²⁻³⁴³

Grade C, Level 2+

9 Organophosphates

9.1 Introduction

Organophosphorus (OP) compounds are generally used as pesticides. Hence, they are widely found in agricultural communities, national parks and environmental agencies and homes. The use of such agents in the military setting as nerve agents and more recently in chemical terrorism incidents such as the sarin incident in the Tokyo subways^{344,345} have added on to their portfolio. Some OPs which are used as flame retardants have no anticholinesterase activity and hence do not pose a direct risk to humans.

Carbamates are pesticides that produce the same clinical manifestations as OP toxic exposures although they tend to be milder and shorter in duration. There is no way of distinguishing carbamate and OP poisoning in the clinical setting. Carbamate cholinesterase inhibition is reversible; hence the routine use of oximes in carbamate poisonings is unnecessary.

9.2 Epidemiology

Most toxic exposures to OP occur in developing countries with a predominant agricultural industry. The World Health Organization (WHO) has estimated that approximately 200,000 deaths from OP poisonings worldwide following intentional poisoning.³⁴⁶ In countries such as India, it is the commonest agent involved in poisoning.³⁴⁷ In the Asia-Pacific region, especially in rural Asia, there is an estimated 500,000 deaths from deliberate self harm³⁴⁸, with approximately 60% due to self-poisoning with pesticides.³⁴⁹ In developed countries where pesticides are highly regulated, accidental occupational poisonings are rare. However, the incidence of accidental occupational exposure is noted to be high in developing countries with less regulation and legislation on pesticide use.³⁵⁰

A local study in Singapore², has noted that pesticide poisoning accounted for only 0.7% of all toxic exposures, possibly reflecting the limited availability of these agents in developed countries with small agricultural industry. Although the incidence of OP poisoning is noted to be low locally, the potential for accidents involving workers handling these agents and the unconventional use of such agents in

terrorism linked incidents remain high with possible high morbidity and mortality as evidenced from literature.³⁵¹⁻³⁵²

The case-fatality rate for OP pesticide self poisoning is 10% to 20% despite standard treatment, and may be as high as 50-70% for some pesticides.³⁵³⁻³⁵⁵ The outcomes are no different in developed countries with more experienced clinicians and better resources.³⁵⁶

The health impact of chronic low level occupational exposures are beyond the scope of this practice guidelines and are not covered.

GPP The diagnosis of anticholinesterase poisoning is made by a combination of suspected exposure to a pesticide / insecticide and clinical signs and symptoms of a cholinergic crisis. Acetylcholinesterase levels, if available, should be used as supporting evidence of such poisonings.

GPP

9.3 Mechanism of Toxicity

Organophosphorus compounds primarily inhibit esterase enzymes, including acetylcholinesterases present in synapses, red blood cell membranes, and butyrylcholinesterases in plasma. This results in accumulation of acetylcholine at synapses of the autonomic, neuromuscular and central nervous systems, causing overstimulation of effectors organs. They may be absorbed via various routes, including inhalation, ingestion and through the skin.

The interaction between acetylcholinesterase and the organophosphorus compound is initially reversible but a process of aging occurs beyond which the acetylcholinesterase and OP compound bonding becomes stable and inseparable. The time frame for this aging varies with different OP compounds. Once this irreversible process has occurred, the use of oximes as antidotes to separate the complex and regenerate the acetylcholinesterase becomes unsuccessful. Thereafter, the body will need to resynthesize new acetylcholinesterase at its own endogenous rate (approximately 1% per day) to resume bodily functions.

There are hundreds of OP compounds with wide variations in their clinical toxicity.³⁵⁷ For example, chemical warfare nerve agents have a high potency and are capable of producing severe toxicity at low concentrations exposure.³⁵⁸

The chemical nature of the OP influences the severity of the poisoning and the response to antidotes. There are generally 3 classes of OP: dimethyl, diethyl and atypical (alkyl) organophosphorus compounds. The rate of inhibition of acetylcholinesterase and rate of aging process is slowest in the diethyl group, fastest in the atypical group, with the dimethyl group intermediate. Hence, the timing of oxime use is critical for management.

Most patients will become symptomatic immediately following exposure. However, some parent OP compounds are inactive (e.g. parathion) and need to undergo endogenous activation via the cytochrome P450 enzymes to their active metabolites (e.g. paraoxon) before developing toxicity. The activation rates of the different OP compounds vary; some are very fast (e.g. conversion of parathion to paraoxon occurs in 10 to 20 minutes), whereas others such as dimethoate takes hours. This can delay the onset of symptoms, though ultimately it should still occur within 8 hours of OP exposure.

Furthermore, highly lipid soluble OP, such as fenthion, are likely to have slower onset of toxicity, but with more prolonged effects that sometimes last for days. This is likely attributed to its rapid absorption and distribution to the fatty tissues forming a store, with slow sustained release thereafter.³⁵⁹ Hence, there is a relapse of the cholinergic crisis following initial recovery, contributing to the intermediate syndrome seen in OP poisoning.

Besides the chemical nature of the pesticide, the solvent (e.g. xylene, naphtha, cyclohexanone) used in the formulation may have a potentially significant impact on the clinical outcome. However, there are no studies that have determined the possible contribution of these solvents to the final outcome of OP poisoned patients.

9.4 Clinical presentation and diagnosis

9.4.1 Diagnosis

The diagnosis of acute OP poisoning is based on a combination of clinical suspicion and recognition of the spectrum of clinical features of cholinergic manifestations. The onset of clinical toxicity is variable and may occasionally be delayed.³⁶⁰

Clinical manifestations include cholinergic crisis in the acute phase, an intermediate syndrome and delayed neurologic sequelae.³⁶⁰ However, the clinical syndrome may vary according to the precise pesticide involved. The main cause of death in the acute phase is respiratory arrest and failure.³⁶¹ Complications from prolonged ICU stays are responsible for late deaths including hypoxic brain damage, aspiration pneumonia and subsequent septicaemia³⁶²⁻³⁶⁴, Acute Respiratory Distress Syndrome³⁶⁵⁻³⁶⁷, and deep vein thrombosis (DVT) / pulmonary embolism (PE) from prolonged immobility and morbidity (physical deconditioning).

Clinical features of organophosphorus pesticide poisoning^{360-362,368}

Muscarinic effects can be summarised as **DUMB³ELS³** –

D = Diarrhoea (with Abdominal pain)
U = Urination (Incontinence)
M = Miosis
B = Bradycardia, Bronchorrhoea, Bronchoconstriction
E = Emesis
L = Lacrimation
S = Salivation, Sweating & Increased Secretions (Rhinorrhoea)

Overstimulation of nicotinic receptors in the sympathetic system cause:

- Hypertension
- Mydriasis
- Sweating
- Tachycardia

Overstimulation of nicotinic receptors at the neuromuscular junction cause:

- Fasciculation
- Muscle weakness
- Paralysis

CNS effects include:

- Agitation
- Coma
- Confusion
- Convulsion or seizures
- Respiratory failure

Patients usually present with features of parasympathetic overstimulation and manifest cholinergic crisis. A few might show signs of sympathetic stimulation, including tachycardia. Tachycardia can also be caused by hypovolemia, hypoxia and treatment with atropine. Respiratory failure can be due to bronchospasm, bronchorrhoea (both reversible with atropine), and dysfunction of neuromuscular junctions and the CNS.

Paediatric OP poisoning may manifest differently from adults. A review of 31 cases in Israel suggests that the classic nicotinic and muscarinic symptoms were seen less, with the major clinical manifestation neurological. Most paediatric patients presented with coma and/or seizures.³⁶⁹

The use of red cell acetylcholinesterase levels as a prognosticating tool is recommended. However, it is limited by the lack of resource availability and turnaround times for acute poisonings.

The main differential diagnosis of OP poisoning is poisoning with carbamates.

9.4.2 Intermediate Syndrome (IMS) and its management

The intermediate syndrome (IMS) from OP poisoning is noted to occur following the initial successful treatment of acute cholinergic syndrome with atropine.³⁷⁰ It is noted to be a major contributor to morbidity and mortality following OP poisoning. IMS is typically a syndrome of muscular paralysis that occurs in conscious patients, without cholinergic signs and symptoms, generally between 24 to 96 hours post ingestion. The muscles affected are generally the proximal limb muscles, motor cranial nerves and muscles of respiration, progressing to respiratory failure in the worst case scenario.^{364,371-373}

The actual pathophysiology of IMS is unknown, but is secondary to accumulation of acetylcholine at the neuromuscular junctions with persistent over-stimulation of the nicotinic receptors. This is followed by a period of desensitization³⁷⁴ or down regulation³⁷⁵ or conformational transformation³⁷⁶ of the post synaptic receptors, resulting in reduced neuromuscular transmission and thus muscle weakness. Inadequate treatment with oximes may play a role in the development of IMS but the evidence is still lacking.³⁷⁷

The management of IMS involves prompt recognition of the condition and the institution of good supportive care and ventilatory support. Delays in instituting ventilation will result in death. Depolarising muscle relaxants, such as suxamethonium, are contraindicated in OP poisoning. Subsequently, weaning from ventilatory care is best carried out in stages, with provision of continuous positive airway pressure prior to complete weaning. With appropriate therapy, complete recovery occurs 5–18 days later without any sequelae.³⁷⁸⁻³⁷⁹

GPP The management of IMS involves prompt recognition of the condition and the institution of good supportive care, including ventilatory support as appropriate.

GPP

A high index of suspicion with early recognition and prompt treatment of acute OP poisoning is expected to reduce the incidence of IMS.

9.5 Clinical predictors / indicators for ICU care for acute OP poisonings

- (1) **Intentional ingestions** are more likely to result in significant toxicity compared to accidental exposures which usually occur via the cutaneous and inhalational route and in limited amounts.
- (2) **Increasing age** was predictive of higher mortality rate from OP poisoning with odds ratio of 5.59 when comparing someone below 50 years old and someone above 50.³⁸⁰
- (3) **Early onset of symptoms (< 6 hours) following exposure.** In contrast, patients remaining asymptomatic for 12 hours after exposure are unlikely to develop any major clinical toxicity.³⁸¹⁻³⁸² However, exceptions to this include poisoning by lipophilic OPs, such as fenthion.³⁸³⁻³⁸⁵
- (4) **Specific agent type** (see above under mechanisms of toxicity).
- (5) **A GCS (Glasgow Coma Score) < 6.** A GCS score of less than 6 was predictive of in-hospital mortality in OP poisoning.³⁸⁶
- (6) **ECG showing prolonged QTc intervals.**

(7) **A pH < 7.2 at initial presentation.**⁴²⁶ Acid-base disturbances at presentation are predictive of mortality with an odds ratio of 10.1 for a pH of < 7.2 compared to pH > 7.2 at presentation. Mortality rates of patients with OP poisoning were 6.25%, 25%, 50% & 80% for no acidosis, metabolic acidosis, respiratory acidosis and mixed acidosis, respectively.

(8) **Red blood cell cholinesterase activity less than 20% of normal** i.e. a reduction of more than 80%.^{381,387-388} However, plasma butyrylcholinesterase level has no relation to severity of clinical toxicity.^{387,389-390}

9.6 Investigations for OP poisoning

The main investigation is measurement of cholinesterase activity. This comprises red cell acetylcholinesterase or serum butyrylcholinesterases.³⁹¹ However, the interpretation of these investigations is complex,³⁸⁷ and treatment should be instituted based on exposure history and clinical presentation.

9.6.1 Red cell acetylcholinesterase versus plasma/serum butyrylcholinesterase (pseudocholinesterase)

- Some pesticides inhibit butyrylcholinesterase more effectively than acetylcholinesterase.³⁸⁵
- Butyrylcholinesterase can be used to indicate the presence of OP or carbamate exposure as it is rapidly inactivated, usually within a few minutes of exposure.
- Butyryl cholinesterase is produced by the liver and is produced at an average rate of 7% a day once OP has been eliminated from the body. When monitored daily for trends, they are a useful marker for monitoring progress of the OP poisoned patient.³⁹² When enzyme levels start to rise again, this suggests recovery and that the organophosphorus compound has been eliminated
- However, depressed butyrylcholinesterase activity may not be the result of enzyme inhibition. Other reasons for reduced enzyme activity include genetic variability, physiological changes (early pregnancy), pathological states involving the liver (cirrhosis, hepatitis, malnutrition, chronic alcoholism) and toxins (cocaine, carbon disulphide, organic mercury compounds, benzylkonium salts, oral contraceptive pills, metoclopramide).³⁹³⁻³⁹⁵ Ideally

serum butyrylcholinesterase level should be interpreted in relation to a baseline for the individual. In the context of poisoning exposure with no baseline levels and where the nature of the chemical is uncertain, the clinician must base his treatment decision on clinical signs and symptoms of OP poisoning.³⁹⁶

- Red cell acetylcholinesterase is a good marker of severity of OP poisoning, and is reflective of the synaptic function and atropine needs in OP poisoned patients.^{387,397} Patients with acetylcholinesterase level of at least 30% of normal have normal muscle function and no need for atropine, while those with less than 10% activity had grossly deranged muscle function and needed high dose atropine therapy. Those with levels in between had varying degrees of muscular function impairment and requirements for atropine.
- Once aged, the red cell acetylcholinesterase and OP complex becomes permanently inactivated. Recovery of acetylcholinesterase activity is dependent on erythropoiesis and progresses at a rate of 1% per day. Hence, it is less useful as a marker for recovery.
- Red cell acetylcholinesterase is less likely to be affected by factors other than OP poisoning, except in rare conditions with haemolytic anaemia.

9.6.2 Electrocardiograph

ECG changes in patients with OP poisoning include sinus tachycardia or bradycardia, prolonged QTc, PR intervals, ST/T wave changes and arrhythmias.³⁹⁸⁻⁴⁰⁰ Causes may be multifactorial, including sympathetic and parasympathetic overactivity, hypoxemia, acidosis, electrolyte derangements and direct toxic effects on the myocardium⁴⁰¹ and coronary vasospasm.⁴⁰² The commonest ECG abnormality was prolonged QTc (55.2%) and sinus tachycardia (32.9%),

9.6.3 Arterial blood gas

Arterial blood gas may be useful to assess severity of OP poisoning.

9.6.4 Other useful investigations

Other useful investigations include electrolytes, glucose levels, blood urea/nitrogen (BUN), creatinine, amylase, liver function tests, and chest X-ray.

9.7 Treatment of organophosphorus poisoning

Management of OP poisoning has been fraught with many controversies and many treatment options have been contentious. The lack of randomised controlled trials (RCTs) for this poisoning contributes to the paucity of evidence-based guidelines.

The clinical toxicity from OP poisoning ranges from mild to severe. Only moderate and severe poisoning from exposure to OP compounds need to be admitted for management. The subsequent section relates to management of these cases.

9.7.1 Resuscitation and stabilization

Resuscitation, including ventilation and circulatory support as appropriate, as well as symptomatic and supportive care are indicated in all patients.

The risk of secondary poisoning of health care workers from handling contaminated patients and property is of concern.⁴⁰³ However, the likelihood of severe poisoning is reportedly low.⁴⁰⁴ Some of the reported symptoms in healthcare workers managing these patients include headache and nausea, which are likely secondary to anxiety, and possibly the organic solvent in which the OP is mixed.⁴⁰⁵ Hence, healthcare workers should not compromise patient care by withholding treatment due to fear of secondary exposure.

The current recommendation is for simple protective measures: use of universal precautions, properly ventilated care areas and proper containment measures (including removal and containment of contaminated items and clothing), and prompt decontamination of patients as needed.⁴⁰⁴⁻⁴⁰⁵

GPP

- Resuscitation should proceed according to standard BCLS/ACLS protocols as indicated in all patients.
- The risk of secondary poisoning of health care workers from handling contaminated patients and property is of concern. However, the likelihood of severe poisoning is reportedly low. We recommend the use of simple protective measures: use of universal precautions, properly ventilated care areas and proper

containment measures (including removal and containment of contaminated items & clothing) and prompt decontamination of patients as needed.

GPP

9.7.2 Decontamination

Skin exposure should be irrigated with copious amount of water and liberal use of soap. It is important for health care workers to wear appropriate protective gear before removing contaminated clothing and items from patients.⁴⁰⁶

Eye exposure should be irrigated with copious amount of normal saline. Refer cases to the ophthalmologist for further management. There is no RCT comparing the effectiveness of eye irrigation and atropine eye drops for relief of ocular symptoms. Atropine eye drops for symptomatic relief should be given on an individualised case basis after consultation with a clinical toxicologist or ophthalmologist.

Gastric decontamination from oral exposure involves the use of activated charcoal. There are no RCTs specifically on use of activated charcoal in organophosphate poisoning, thus general recommendations for its use are to be followed. It should only be considered after the patient has been fully resuscitated and stabilized. For gastric lavage, there is no evidence that it helps in the final outcome of OP poisoned patients,⁴⁰⁷ and its use is compounded by complications such as aspiration, laryngeal spasm, oesophageal perforation and hypoxia.⁴⁰⁸ Hence it is not recommended unless it satisfies the general criteria for gastric lavage.

D

- Skin exposure would require irrigation of the skin with copious amounts of water and liberal use of soap. It is important for health care workers to wear appropriate protective gear before removing contaminated clothing and items from patients.
- Eye exposure should be irrigated with copious amount of normal saline. In all cases refer to ophthalmologist for further management. The routine use of atropine eye drops for relief of ocular symptoms is not recommended.

- General recommendations for gastric decontamination from oral exposure should be followed.

Grade D, Level 3

Refer to section 3.2 on Gastric Lavage under Chapter 3: Decontamination after poisoning.

9.7.3 Antidotes

9.7.3.1 Muscarinic antagonists (Atropine, Glycopyrronium bromide)

C Muscarinic antagonist: Atropine or glycopyrronium bromide. Atropine use reverses the cholinergic effects. In particular, aim to dry bronchial secretions and reverse bronchospasm and to facilitate ventilation and oxygenation. Glycopyrronium bromide can be an alternative for peripheral symptoms.

Grade C, Level 2+

Atropine

Atropine is the most commonly used anti-muscarinic agent for this indication.⁴⁰⁹ This is mainly because of its wide availability, low cost and moderate penetration into the CNS.

Early and sufficient atropinisation is important, as delay may lead to death from central respiratory depression, bronchospasm, bronchorrhoea, severe bradycardia and hypotension. The main aim of atropinisation is to reverse the cholinergic effects, particularly to dry bronchial secretions and reverse bronchospasm so as to facilitate ventilation and oxygenation.⁴¹⁰ Atropine has little effect on neuromuscular junction and muscle weakness.⁴¹¹

There are no randomized controlled studies in humans comparing the effectiveness of different dosing regimens for loading and maintenance. A systematic comparison of these regimens suggest that the initial regimen used should allow doses to be administered fast enough to avoid delay in achieving atropinisation, as large amounts of atropine may be required.⁴¹⁰ In a Sri Lankan study, a mean dose of 23.4 mg and a maximum dose of 75 mg were used.⁴¹⁰

(1) Mechanism of action

Atropine is an anticholinergic agent that competitively blocks the action of acetylcholine at muscarinic receptors. It crosses the blood-brain barrier.

(2) Route & Dosage

Intravenous boluses of 1-5 mg, repeated every 5-10 minutes until satisfactory atropinisation;

OR

Initial dose of 1-2 mg. Double the dose every 5 minutes until response. Cease doubling the dose once parameters have improved. Similar or lowered doses can be continued until satisfactory atropinisation.³⁶⁸

Paediatric patients can start at 0.02 -0.05 mg/kg.

Severe poisoning may require very large doses administered quickly (e.g. up to 100 mg over several hours). Total doses of several grams have been reported, given via continuous infusion or large bolus doses, or with more frequent intervals of 3-5 minutes. If the amount of atropine given is too little, cholinergic symptoms will re-emerge.

Atropine may be given undiluted. For small doses, dilute dose in at least 10 mL water for injection (WFI) for easier administration

The half-life of distribution of atropine is about 1 minute.⁴¹²⁻⁴¹³ The peak effect is seen within 3 minutes in anaesthetized patients given intravenous atropine.⁴¹⁴ Hence, there is no need to wait more than 5 minutes before checking for a response and giving another bolus dose if no response has occurred.

After the patient is stable, an atropine infusion (giving an hourly dose about 10%-20% of the total dose needed to stabilize patient initially) can be continued.

In mass casualty situations, the dose may also be given intramuscularly (IM) or as commercially available auto-injectors. It can also be given via the intra-tracheal, ophthalmic or inhalation routes.

Formulation: Available as 12 mg/2mL ampoule.

- **Alternative:** Glycopyrronium bromide can be used as an alternative for peripheral cholinergic effects without causing atropine-induced delirium. It is a synthetic quaternary amine with poor CNS penetration. Thus, it is ineffective for reversing coma and decreased respiration.³⁶⁸

Formulation: Glycopyrronium Br 0.4 mg/2mL ampoule.

(3) Contraindications / Special precautions⁴¹⁵

- Patients with hypertension, tachyarrhythmias, thyrotoxicosis, CHF, coronary artery disease, valvular heart disease and other conditions that are adversely affected by a rapid heart rate. In severe cholinesterase poisoning, atropine may reduce tachycardia by improving oxygenation.
- Myasthenia gravis.
- Closed-angle glaucoma.
- Partial or complete obstructive uropathy.
- GI obstruction.

(4) Adverse effects

Dry mouth, blurred vision, mydriasis, cycloplegia, arrhythmia, palpitations, tachycardia, urinary retention and constipation. CNS anticholinergic adverse effects (e.g. delirium) may occur when large doses of atropine are used.

Low doses (less than 0.5mg for adults) can cause a paradoxical decrease in heart rates.

Tachycardia in ischemic patients (especially in the elderly) could lead to myocardial infarction and deaths.

(5) Monitoring parameters / Therapeutic endpoints

The aim is to reverse cholinergic effects without resulting in atropine toxicity. The drying of bronchial secretions and reversal of bronchospasm can facilitate ventilation and oxygenation.

Target end points⁴¹⁰:

- Clear chest on auscultation.
- Heart rate > 80 beats per min (WHO recommends >100bpm).
- Systolic BP > 80 mmHg.
- Pupils no longer pinpoint.
- Dry axillae.

Aim to attain at least 4 end-points, including all of the first three, before patients is considered atropinised.

HR > 120bpm and dilated pupils suggest excessive atropine was administered. Other signs include absent bowel sounds and urinary retention. Atropine toxicity can cause confusion, agitation and hyperthermia. In severe cases, it can lead to cardiac arrest.

(6) Other considerations

- Pregnancy: FDA Category C, drug readily crosses placenta. Should still be used for symptomatic patients.
- Lactation: May decrease lactation. Should still be used for symptomatic patients.
- Paediatric: Weight-based dosing. Dose for nerve agent poisoning may be higher, especially with the use of auto-injectors⁴¹⁶
- Glycopyrronium bromide may be used as an alternative if patient is allergic to atropine or has atropine toxicity.⁴¹⁷

9.7.3.2 Oximes

We recommend using pralidoxime for OP poisoning with **caution** until further evidence becomes available. It should be given in consultation with a clinical toxicologist, or an expert in the care of poisoned patients

The main mechanism of action of oximes is thought to be the reactivation of the acetylcholinesterase from the OP–acetylcholinesterase complex. This has to be done before the complex ages, and the acetylcholinesterase becomes permanently inactivated. Hence, prompt administration of oximes is thought to be crucial.

Despite the theoretical benefits, controversy surrounds its use. Clinical evidence have been conflicting; some RCTs concluded that it did not offer clinical benefits and in some situations may cause higher mortality rates, especially with obidoxime⁴¹⁸; a study using large doses of pralidoxime administered promptly after OP exposure suggests reduced case fatality.⁴¹⁹ Systematic reviews did not offer a conclusive risk-benefit profile.⁴²⁰⁻⁴²¹ As there are multiple variables involved in the management of OP poisonings such as the type of OP, formulation, toxin load, time to start therapy and dose and rate of oxime use, it is difficult to derive conclusions from the studies. Hence, the clinical benefits of oxime use remain unclear.⁴²²⁻⁴²³

Nevertheless, WHO currently recommends the use of oximes in all symptomatic patients who require atropine and to continue till atropine is no longer required.^{409,424}

A Pralidoxime should be used with caution for OP poisoning. It should be given in consultation with a clinical toxicologist or an expert in the care of poisoned patients.

Grade A, Level 1+

Pralidoxime chloride (2-PAM)

(1) Mechanism of action

Pralidoxime reactivates acetylcholinesterase enzymes by removing the phosphoryl group deposited by the organophosphate. This reverses the inhibition of acetylcholinesterase and allows the breakdown of accumulated acetylcholine. It can also protect the enzyme from further inhibition by OP. The clinical effects are most apparent at nicotinic receptors, with rapid reversal of skeletal muscle weakness and muscle fasciculations.

The chloride salt has the highest amount of oxime activity compared to other salt forms (e.g. iodide).

Nerve agents used as chemical warfare agents (e.g. sarin, soman, tabun and VX) are much more potent than OP pesticides and may be responsive only to specific oximes.

(2) Route & Dosage

Pralidoxime should be given early to prevent aging of the cholinesterase enzyme which can render the antidote ineffective. It must be given in sufficient amounts; inadequate dosing could result in the intermediate syndrome, with prolonged muscle weakness. Reversal at muscarinic receptors can be hastened if atropine and pralidoxime are administered concurrently.

Intravenous route is preferred, although IM or subcutaneous route may be used (e.g. by autoinjectors). Peak plasma concentrations are reached 5-15 minutes after IV dose is given.

- Initial dose 30 mg/kg (i.e. 1-2 g for adults) in 100 mL normal saline over 15-30 minutes.
- Followed by an 8mg/kg/hr infusion (about 0.5-1 g/hour for adults) in normal saline.

Paediatric patients can use weight-based dosing.

Pralidoxime has a short half-life of 1-3 hours, hence repeated boluses or continuous infusions may be required. For continuous infusions, dilute to give a concentration of 1-2 g in 100 mL normal saline.

Late therapy with pralidoxime may be indicated (even several days post-exposure) especially in patients poisoned with diethylating compounds and by fat-soluble compounds that can be released from tissue stores over days, causing prolonged or recurrent symptoms.

Formulation: Available as 500 mg/20mL injection (500 mg vials with 20 mL diluent ampoules).

(3) Contraindications / Special precautions

- Myasthenia gravis (may precipitate a myasthenic crisis). In severe poisoning, the benefit may exceed this possible risk.
- Use with caution or in reduced doses for patients with renal impairment. Pralidoxime can accumulate due to reduced renal excretion.

(4) Adverse effects

Nausea, headache, dizziness, drowsiness, blurred vision, diplopia, muscle rigidity and weakness, and hyperventilation may occur.

Rapid IV administration may cause vomiting, diastolic hypertension, tachycardia, laryngospasm, muscle rigidity, and transient neuromuscular blockade.

(5) Monitoring parameters / Therapeutic endpoints

Minimum therapeutic level: 4 mcg/mL.

Pralidoxime infusion may be continued until atropine has not been required for 12-24 hours and the patient is extubated.

(6) Other considerations

- Pregnancy: FDA Category C; should still be used for symptomatic patients.
- Lactation: Use with caution.
- Paediatric: Weight-based dosing. Dose for nerve agent poisoning may be higher, especially with the use of auto-injectors.⁴¹⁶

9.7.3.3 Benzodiazepines

We recommend benzodiazepines for control of seizures and agitation in patients poisoned by organophosphorus compounds.

Benzodiazepines are the mainstay of treatment for patients who have seizures or agitation following organophosphorus poisoning. Seizures are however uncommon in patients exposed to industrial organophosphorus compounds who are well oxygenated^{385,425} compared to chemical warfare nerve agents.⁴²⁶ Currently, there are limited human studies,³⁶⁰ but animal studies have shown that diazepam reduces neuronal damage⁴²⁷ and prevents respiratory failure and death.⁴²⁸

C Benzodiazepines are recommended to control seizures and agitation in patients poisoned by organophosphorus compounds.

Grade C, Level 2-

9.7.3.4 Alternative antidotes

We do **not** recommend the routine use of alkalinisation for OP poisoning.

There have been several published reports of benefits from treatment with serum alkalinisation.⁴²⁹⁻⁴³¹ They suggest that the relative risk of death, total dose of atropine use, length of hospital stay were seemingly reduced in patients who were treated with alkalinisation (using sodium bicarbonate). The rationale for its use is based on increased rate of spontaneous hydrolysis of OP compounds. However, only one of the reports was a randomized controlled clinical trial, albeit with a small sample size and poor concealment methods.

The Cochrane review on serum alkalinisation for organophosphorus poisoning had concluded that there are potential clinical benefits using alkalization for OP poisoning, but there is insufficient evidence to support its routine use.⁴³²

B The routine use of serum alkalization using sodium bicarbonate is currently not recommended.

Grade B, Level 1-

9.7.4 Enhanced elimination

We do **not** recommend haemodialysis, haemoperfusion or haemofiltration for managing poisonings with OP.

Charcoal haemoperfusion has been noted to be effective in a study on poisoning with dichlorvos which has low fat solubility and a small volume of distribution.⁴³³ However, this study was not randomized and hence the evidence for its recommendation is limited.

C Charcoal haemoperfusion or haemodialysis or haemofiltration are not recommended for managing poisonings with OP.

Grade C, Level 2-

9.7.4.1 Supportive care and monitoring

Patients with OP poisoning are fluid depleted due to excessive sweating, GI and urinary loss. Hence it is important to give adequate fluid resuscitation, and correct electrolyte disturbance (mainly hypokalaemia), from diarrhoeal losses. There is no evidence that aggressive fluid resuscitation in patients with bronchorrhoea is dangerous, provided atropine is also given simultaneously to dry the pulmonary secretions.

GPP

- There should be adequate fluid resuscitation and correction of acid-base and electrolyte disturbances as is deemed appropriate.
- Patients with OP poisoning tend to be fluid depleted due to the excessive sweating, gastrointestinal and urinary loss.
- There is no evidence that aggressive fluid resuscitation in patients with bronchorrhoea is dangerous provided atropine is also given simultaneously to dry the lung secretions.

GPP

9.7.5 Preventive measures

Prevention of OP poisoning is best achieved by selection of or substitution with OP pesticides that have the least toxicity. This is evident from the drastic fall in deaths from OP exposures in Sri Lanka, following regulatory control on the import and sale of pesticides that are particularly toxic to humans.⁴³⁴

For accidental exposures in the workplace, it is important to remove the victim from further exposure, and take measures to investigate and mitigate the source of exposure.

GPP

- For accidental exposures in the workplace, it is important to remove the victim from further exposure and take measures to investigate and mitigate the source of exposure.
- It is mandatory to report occupational toxic exposure to Ministry of Manpower – *Refer to Annex D: Resources for industrial chemical exposure.*

GPP

9.8 Carbamates

9.8.1 Carbamates and the differences in the management of carbamate poisoning

Carbamates are pesticides that produce the same clinical manifestations as OP toxic exposures, although they tend to be milder and shorter in duration.⁴¹¹ There is no way of distinguishing carbamate and OP poisoning in the clinical setting.

Carbamate cholinesterase inhibition is reversible, and hence the routine use of oximes in carbamate poisonings is unnecessary. However, in unknown toxic exposures presenting with cholinergic crisis with suspicion of anticholinesterase pesticide poisoning, the use of oximes may be warranted. There is currently no evidence of harm in humans from using oximes in such an approach.

In Singapore, a retrospective study of toxic exposure cases seen in the Emergency Department of 3 major hospitals over a 3-year period identified 747 cases of accidental industrial toxic exposures from various chemicals.²

For effective and appropriate management of patients who have been exposed to industrial chemicals, it is essential to know the nature of the chemical. This information is available from the Safety Data Sheet (SDS). You should request for a copy from the workplace representative. If not available, please refer to **Annex D** for other possible sources of information and interpretation of pictograms to assist in identification of the potential health effects.

To assist diagnosis of poisoning, depending on the type of chemical, a sample of urine and/or blood should be collected for toxicological analysis as soon as possible from the patient(s). Please refer to **Annex D** for the list of toxicological laboratories.

This chapter will focus on the management of persons exposed to hydrofluoric acid.

Hydrofluoric acid (HF)

10.1 Introduction

Hydrofluoric acid (HF) is also known as hydrogen fluoride, fluoric acid, hydrofluoride and fluorine monohydride.

HF is used for the production of various types of chemicals for etching, frosting and polishing glass, brick cleaning, for etching silicon wafers in the semi-conductor industry and as catalyst in production of high-octane fuels. The concentration used ranges from 20-99%. It can also be found in some household products like automotive cleaning products, aluminium brighteners, water spot and rust removal agents, at a concentration of 6-12%.

10.2 Epidemiology

In the 2007 AAPCC report,²³⁶ there were 6 case fatalities from exposure, with a total of 1280 cases out of 2.8 million exposures.

10.3 Mechanism of toxicity

HF causes local cellular destruction and systemic toxicity.⁴³⁵⁻⁴³⁷ It is readily absorbed through intact and damaged skin because it is a weak acid and has a high permeability coefficient. Once in the tissue, the fluoride ion (F^-) causes extensive liquefactive necrosis of the soft tissues and decalcification and corrosion of bones, continuing for several days if untreated.

F^- is the most electronegative ion known and is able to chelate calcium, magnesium and other cations. The systemic effects of HF are due to increased F^- concentrations in the body, which causes hypocalcaemia, hypomagnesaemia, and hyperkalaemia.

Ingestion of even a small amount of HF is likely to produce systemic effects and may be fatal. The surface area of the burn is not entirely predictive of its effects and other factors like concentration, duration of exposure should be accounted for. Anhydrous HF, which has a boiling point at 19.5°C, poses inhalational risks. Most industrial HF exposures occur by inhalation of HF gas and dermal contact with liquid HF.

10.4 Relevant toxico-kinetics

HF is a colourless gas and has a strong irritating odour, discernable at 0.04 parts per million (ppm).⁴³⁸ At the Permissible Exposure Level (PEL) Short Term (Singapore)⁴³⁹ of 3 ppm, there is mild irritation to eyes and throat.⁴³⁸ The NIOSH IDLH (Immediately Dangerous to Life and Health)⁴⁴⁰ level is 30 ppm. In children, an oral fluoride dose of 5.0 mg F/kg of body weight should be regarded as the probably toxic dose.⁴⁴¹

F^- is eliminated by sequestration in bones and by the renal route. The elimination half-life is between 5.1 and 9 hours.⁴³⁵

10.5 Clinical presentation / diagnosis

HF is irritating to skin, eyes, and mucous membranes. Burns can occur at higher concentration.

Systemic effects can occur for all routes of exposure. Effects are related to electrolyte disturbance, hypocalcaemia, hypomagnesaemia, hyperkalaemia and acidosis, leading to disturbance of cardiac, renal and hepatic function. Symptoms and signs may include nausea, vomiting, gastric pain, tetany, seizure, hypotension, ventricular fibrillation and death. Diagnosis of systemic HF poisoning is based on presence of symptoms, history of HF exposure and evidence of effects like hypocalcaemia, hypomagnesaemia, and hyperkalaemia.

(1) Inhalation of HF mist or vapour:

- Effects may be immediate or delayed in onset (12 – 36 hours).
- Mild effects include irritation of nose, throat and eyes, cough and narrowing of bronchi.
- Severe effects include immediate narrowing and swelling of throat, causing upper respiratory obstruction, pulmonary oedema, partial or complete lung collapse and haemorrhage.

(2) Effect of HF on skin:

- Intensity of pain does not correlate with clinical findings. Tenosynovitis and osteolysis may result.

> 50% concentration solution and anhydrous HF	→	Immediate severe throbbing pain and whitish discoloration of skin, forming blisters.
20 – 50% concentration solution	→	Fairly rapid onset of pain and swelling (can be delayed up to 8 hours).
< 20% concentration solution	→	No immediate pain; delayed serious injury up to 12 – 24 hours.

(3) Ingestion of HF:

- Corrosion of mouth, throat, and oesophagus. Inflammation of the stomach with bleeding occurs commonly.
- Nausea, vomiting, diarrhoea, and abdominal pain may occur.
- Aspiration may lead to pulmonary complications.
- Ingestion of HF carries a high risk of systemic toxicity and airway injury.

(4) Eye splashes:

- From mild irritation to permanent clouding of eye surface, developing immediately or delayed.

10.5.1 Diagnosis

(1) In cases where systemic toxicity is suspected (cases of inhalation, ingestion or significant dermal exposure), the following investigation should be done:

- Serum calcium, magnesium and potassium.
- ECG – look out for prolonged QT, T wave changes and dysrhythmias.

(2) For very ill patients, to exclude complications:

- Urea and electrolytes.
- Urine FEME – look for proteinuria, hematuria, etc.
- Liver function test.

(3) If there are respiratory symptoms, to do:

- Arterial blood gas.
- Chest X-ray.
- Pulmonary function tests.

(4) To confirm and quantify absorption of HF⁴⁴²:

- Serum fluoride (use EDTA tube)
 - Normal < 0.2 µg/mL;
 - Toxic serum fluoride is > 2 µg/mL;
- Urine fluoride – Normal < 2 µg/mL.

10.6 Treatment

10.6.1 Personal protective equipment

If victims' clothing or skin is contaminated with HF liquid or solution, protect hospital staff from direct contact or off-gassing vapour by wearing chemical protective clothing and multiple layers of rubber or latex gloves and eye goggles. Facemask with appropriate chemical canister may be needed if the concentration of HF is high.

Note: Victims of HF vapour do not pose substantial risks of secondary contamination.

10.6.2 ABC and other supportive measures

Patients with systemic fluoride toxicity should be managed in the critical care area and standard resuscitation measures applied. The patient should be placed on cardiac monitoring.

Analgesia should be administered as needed but giving local anaesthetic agents like lidocaine is controversial as this would remove the ability to monitor treatment endpoint, i.e. pain relief, with the use of the calcium antidote.

10.6.2.1 Decontamination

GPP Dermal and ocular decontamination should be immediately performed using water or saline.⁴⁴³⁻⁴⁴⁴ The clothes should be removed and the exposed area washed by copious irrigation for at least 30 minutes.

GPP

Do not induce emesis or administer activated charcoal. Gastric decontamination by large bore orogastric lavage is contraindicated. For dilute solution of HF, a small-bore nasogastric tube can be inserted and the gastric contents aspirated. At the site of incident, if the patient is conscious and the HF ingested is dilute, give 120-240 mL of water or milk or 60-120 mL of antacid containing magnesium or calcium.

10.6.2.2 Enhanced elimination

D Dialysis could be used for patients with severe systemic fluoride poisoning to lower F⁻ and potassium levels.⁴⁴⁵

Grade D, Level 3

10.6.2.3 Antidote

Calcium (Ca²⁺) is the antidote for HF poisoning. Calcium gluconate is commonly used because it is less concentrated and has less irritant effects compared to calcium chloride. Calcium chloride, which has 3 times the amount of calcium ions per unit mass compared to calcium gluconate, should only be administered via a central line and not via any other route.

10.6.2.4 Relief of pain is an important guide to the success of treatment.

(1) Dermal burns

Follow the following sequence of treatment for dermal burns until adequate alleviation of pain is achieved.

D Apply calcium gluconate gel 2.5%[‡] liberally over the exposed dermal area and rub.⁴⁴⁶⁻⁴⁴⁸ Allow it to remain in place for a minimum of 30 minutes. Reapply gel every 4-6 hours.

Grade D, Level 3

D Burns involving the fingers can be treated by placing the hands and gel in tight-fitting impervious gloves. Continue for at least 15 minutes after relief of pain.

Grade D, Level 3

D Perform subcutaneous infiltration of calcium gluconate⁴⁴⁹ by injecting 0.3-0.5 mL/cm² of 5% calcium gluconate with a 27G to 30G needle when local gel application therapy fails, the site has sufficient tissue space and is not amenable for regional perfusion therapy (e.g. the thigh).

Grade D, Level 3

D Use the Bier block method for intravenous regional application of 2.5% calcium gluconate.⁴⁵⁰⁻⁴⁵² A volume of 40 mL of 2.5% solution calcium gluconate is given via the regional intravenous anaesthesia route after the pressure cuff is inflated. The cuff is left inflated for about 20 minutes.

Grade D, Level 3

D If intravenous regional perfusion therapy fails to relieve pain, intra-arterial application of 2.5% calcium gluconate should be tried.⁴⁵³⁻⁴⁵⁶ Usually the brachial or radial artery is cannulated depending on the site of injury and about 40 mL of 2-2.5% calcium gluconate is infused over 4 hours. May repeat cycle 4 hours later. About 1 – 3 cycles may be needed.

Grade D, Level 3

[‡] The gel can be constituted by mixing 2.5 g of calcium gluconate powder in 100 mL water-soluble lubricant e.g. K-Y Jelly or 1 ampoule of 10% calcium gluconate per 30mL of K-Y Jelly.

Splitting or removal of nail for subungual burns may need to be performed if adequate access by the calcium gluconate gel cannot be adequately achieved for severe pain.^{436,457} However, this practice is contentious and some practitioners have managed patients without doing so.⁴⁵⁸ We do not recommend routine removal of nails for subungual burns. Excision of burn skin has been advocated for life-threatening exposures but it is a controversial practice and should not be performed without specialist consultation.

(2) Inhalational injury

Inhalational injury should be suspected under the following conditions:⁴⁵⁷

- Involving HF concentration of 50% or greater.
- HF burn covering > 5% body surface area.
- Burns involving head and neck.
- Where clothing is soaked or where there is delay in removing the clothing.
- Occurring in confined spaces.

D Administer bronchodilators for victims with bronchospasm together with parenteral corticosteroids as part of supportive treatment for respiratory irritation.^{457,459-460} Nebulisation using 1 mL of 10% calcium gluconate and 3 mL of normal saline (2.5% calcium gluconate) has been advocated. It has been shown that there are minimal side-effects when used at that concentration.

Grade D, Level 3

(3) Eye injury

D Do not use calcium gluconate gel for eyes and do not irrigate with calcium salts. If pain persists after irrigation, consider administration of 1% calcium gluconate eye drops every 2 – 3 hours for several days.⁴⁶¹

Grade D, Level 3

(4) Systemic toxicity

The following carries a high risk of systemic toxicity:⁴³⁶

- Dermal burn involving 5% or more BSA to any HF concentration;
- 1% BSA burn from 50% or greater HF concentration;
- Any inhalational injury; or
- Ingestion of HF.

A Treat hypocalcaemia using intravenous 10% calcium gluconate infusions with doses of 0.1 to 0.2 mL/kg up to 10 mL.⁴⁶² Infusions can be repeated until serum calcium, ECG, or till symptoms improve. Calcium levels should be checked hourly.

Grade A, Level 1+

Very large doses of calcium may be required.⁴⁶³⁻⁴⁶⁴

Treat hypomagnesaemia with 2 to 4 mL of 50% of magnesium sulphate intravenously over 30 minutes.

11 Caustics and detergents

11.1 Introduction

Caustics can be defined as toxicants that cause damage on contact with tissue surfaces. Agents that can cause caustic injuries include acids, alkaline, oxidizing agents, exothermic agents and some hydrocarbons.

11.2 Epidemiology

In general, the occurrence of caustic exposure varies from country to country being determined by the range of product (usually household products) available. Generally, the rate of exposures do not exceed beyond 5-10% of all toxic exposures.

- In Singapore, over a 2 year period, 314 cases of domestic cleaning products exposure were reported in three public emergency hospitals, making up 3.1% of toxic exposures from these three hospitals.²
- AAPCC 2006 report 191,046 cleaning chemical and detergents exposures of which there were 11 deaths and 215 major effects. This is out of 1,325,308 non-pharmaceutical exposures, or about 14.4% of all non-pharmaceutical exposures.⁴⁶⁵
- The Taiwan national poison centre reported 1,606 cases of cleaning substances exposures over a period of 8 years. This was about 6.9% of all exposure recorded, but cleaning substances exposures resulted in 20% of paediatric exposures.⁴⁶⁶
- A Chinese hospital reported 7 cases out of 698 exposures over a one- year period.⁴⁶⁷
- In Iran there were 38 cases of caustic exposure over a 7-year period reported from one centre. This makes up 0.5% of all toxic exposure from that centre.⁴⁶⁸

11.3 Pathophysiology

Various substances have been reported to cause corrosive injuries on ingestion. Acids desiccate epithelial cells leading to coagulation of cellular protein and necrosis. This result in eschar formation and may limit depth of penetration. However, deep penetrating damage can still occur. In cases of ingestion, the oesophagus may be spared while severe damage can occur in the stomach. Acid-induced pyloric spasm

can result in antral pooling and perforation. They generally cause significant injuries when pH is below 3.

Alkalis cause protein dissolution, collagen destruction, fat saponification with deeply penetrating injuries resulting in liquefaction of tissue and necrosis. This result in deep penetration and the risk of perforation and complications are higher. They generally cause significant injuries when pH is above 11.

Determinants of injuries in acid or alkaline exposures include:

- Titratable acid or alkaline reserve (TAR) – this is the amount of neutralizing substances that is required to bring the pH back to physiologic pH. The higher the TAR, the more severe the injury.
- Concentration of caustics.
- Contact time of caustics with tissue.
- pH – generally the more acidic or alkaline, the more severe the injury.

Other agents cause injuries after contact with tissue by chemical reaction like alkylation, oxidation, denaturing of protein and defatting of tissue or exothermic burns from exothermic reactions.

Common problems associated with caustic exposure include local surgical complications of the aerodigestive tracts like acute perforation, fistula formation, severe haemorrhage or chronic problems of stricture formation and carcinoma of the oesophagus.

Systemic complication can also arise due to systemic absorption of toxicants. Hypotension can occur from tissue oedema and haemorrhage. Metabolic acidosis can arise due to lactic acidosis from tissue necrosis and from the absorption of acids.

Some caustic agents can cause other systemic effects due to their unique toxicities, some important examples are:

- Hydrofluoric acid exposure and oxalic acid ingestion can cause hypocalcaemia and accompanying arrhythmia.
- Zinc and mercuric chloride can give rise to heavy metal toxicity.
- Phenol can cause seizure, methemoglobinemia, haemolysis, renal failure and hepatotoxicity.
- Cationic surfactant when absorbed can result in acidosis, seizure, hypotension, coma and death.
- Paraquat causes pulmonary fibrosis.
- Phosphorus is renal and hepatotoxic.

- Permanganate and silver nitrate causes methemoglobinemia.
- Tannic acid cause hepatic injuries.

11.4 Clinical features

Inhalation of caustic fumes can give rise to:

- Upper respiratory tract injury manifesting as stridor, hoarseness and airway oedema.
- Lower respiratory tract injury manifesting as acute lung injuries.

Contact with skin and eye results in pain, blistering and burns.

In cases of ingestion, patients may present with pain, swelling and lesions of upper aerodigestive track, and/or substernal chest pain and epigastric pain. Dyspnoea, dysphagia, drooling, vomiting and frank haematemesis can occur. Oropharyngeal oedema and burns can lead to airway obstruction. Epigastric tenderness may be present from stomach burns. Abdominal rigidity may indicate frank perforation⁴⁶⁹.

Stricture is the most common complication of caustic ingestion and occurs in about 24 % of all caustic ingestion.⁴⁷⁰

11.5 Determinants of severity and predictors of outcome in caustic ingestions

Determination of severity in caustic ingestion is important in that it allows for prognostication of injury and determination of the need for various intervention and follow-up. Most patients do not die acutely from severe caustic exposure; hence the most worrisome outcome is stricture formation in the upper digestive tract.

It is found that these factors are associated with more severe injury, where oesophageal-gastro-duodenoscopy (OGD) is recommended and patients should be monitored for stricture formation:

- Suicidal ingestion.⁴⁷¹⁻⁴⁷²
- Respiratory distress after ingestion.⁴⁷¹
- Prolonged dysphagia, vomiting and drooling in children.⁴⁷³⁻⁴⁷⁴
- Strong acid and lye ingestion.^{473,475}
- Haematemesis.⁴⁷⁶
- The more symptoms that a patient report, the more severe the injury.⁴⁷⁷

B Patients with suicidal ingestion or are persistently symptomatic after caustic ingestion should be referred for further investigations. Suicidal ingestion, ingestion of concentrated acid or alkaline, or persistent symptoms predicts severe injury to the aerodigestive tract.

Grade B, Level 2+

Almost all investigators found that oropharyngeal burns do not predict upper digestive tract injuries or stricture formation and should not be used to determine severity of injury.⁴⁷⁸⁻⁴⁸⁴

The extent and depth of acute oesophageal and gastric injury is found to accurately predict stricture formation. Most investigators use Zarger system of classification, but any system of gradation can be used.

- Zarger grades oesophageal injuries into:

O	No injuries seen.
I	Oedema and hyperaemia of the mucosa.
IIa	Superficial ulceration, friability and blisters.
IIb	Grade IIa and circumferential ulceration.
III	Multiple deep ulcerations and area of extensive necrosis.

- Grade IIb and III are predictive of stricture formation and patients with these injuries need to be monitored closely for stricture formation and are to be treated aggressively.^{469,471,473,478,481,485}

11.6 Investigation for caustic ingestion

B Assessment of severity of corrosive injuries should not be based on degree of oropharyngeal burns.

The degree of oropharyngeal burns does not predict upper digestive tract injuries or stricture formation.

Grade B, Level 2+

B Assess degree of injury in both adult and children with a flexible oesophageal-gastro-duodenoscope (OGD).

The extent and depth of acute oesophageal and gastric injury are found to accurately predict stricture formation. OGD is the instrument of choice and it has been shown that it can be safely performed up to 48 hours after caustic ingestion.

Grade B, Level 2+

GPP Perform contrast imaging studies with water-soluble contrast if OGD cannot be completed.

GPP

11.6.1 Role of Oesophageal-gastro-duodenoscopy (OGD) in caustic ingestions

Oesophageal-gastro-duodenoscopy (OGD) using a flexible scope is the investigation of choice to assess degree of injury in both adult and children.

- (1) **Indications for OGD** – this is the most controversial and debated aspect of caustic ingestion management. One camp argues that in asymptomatic ingestions, sequelae almost never arise, so OGD need not be done in such patients.^{469,473-474,480-481,485-486} Another camp argues that the absence of symptoms is not reliable in indicating absence of severe injuries and so OGD should be performed in all patients.^{472,478,487-488}
- (2) Generally OGD is recommended in:
 - Patients with intentional ingestion.
 - Patients with persistent symptoms.
 - Patients who are unable to tolerate diet.
- (3) In patients with unintentional ingestions and who are asymptomatic and who are able to tolerate diet well, OGD may not be indicated if the patient can be follow-up for potential stricture formation.
- (4) Timing of OGD – in most reports, OGD is done within 24 hours^{469,472,475,482,488}, 36 hours⁴⁷⁸, and 48 hours^{471,477,487,489-491} from time of ingestion. However, OGD had been done in up to 96 hours⁴⁷³ from time of ingestion.
- (5) Complications of OGD – There have not been any reports of any complications arising from the use of OGD in the literature.

11.6.2 Imaging

- (1) X-ray imaging of the chest and abdomen can be used to look for perforation, which will show up as pneumomediastinum, pneumothorax, pneumoperitoneum or pneumopericardium. These studies are not sensitive. Some authors performed these studies

before OGD and OGD is not performed if there are signs of perforation on these imaging studies; however such practice is not universal. One author reported that such practice do not add information to that obtained from OGD.⁴⁷⁴

- (2) CT imaging is more sensitive than X-rays in detecting perforation.
- (3) Contrast imaging allows visualization of extent of injury and should be performed when endoscopy cannot be completed. Water-soluble contrast should be given if perforation is suspected, as they are less irritating if extravasations occur. Some authors use contrast studies as follow-up tool to assess for oesophageal stricture formation.⁴⁹⁰⁻⁴⁹¹

11.6.3 Laboratory investigations

One group of investigators have shown that elevated white blood cell count at admission ($> 20,000$ units/mm³) in caustic ingestion is a predictor of mortality.⁴⁷⁵

11.7 Management

Resuscitation, symptomatic and supportive care are indicated in all patients. Skin exposure should be irrigated with copious water.

GPP Skin exposure should be irrigated with a copious amount of water. Eye exposure should be irrigated with a copious amount of normal saline. In all cases of eye exposure, promptly refer to an ophthalmologist.

GPP

In addition, for corrosives, therapy should be directed to reduce oesophageal stricture formation.

Eye exposure should be irrigated with copious amounts of normal saline until pH return to 7.4 (test with litmus paper), retest after 15-30 minutes to allow for caustics to leech out from tissue. In all cases refer to ophthalmologist for further management.

Attention should be paid to airway in patient with features of possible upper airway involvement. In such cases direct visualization of the vocal cord can aid in management. IV Dexamethasone 10 mg (0.6 mg/kg up to 10 mg in children) may be given to reduce swelling.

When intubation is considered, smaller sized ETT tube should be considered and surgical airway should be on standby.

Gastric decontamination is **not** indicated as there is a risk of reintroduction of the caustics into the upper aerodigestive track and aspiration. Activated charcoal is **not** indicated as most caustic are not absorbed and endoscopic management is hampered.

- Cautious aspiration with a narrow nasogastric tube may be indicated with large acidic ingestion presenting within 30 minutes, zinc and mercuric chloride ingestion.

GPP Gastric decontamination and activated charcoal are **not** recommended. Dilution with milk and water may be attempted in patients who are able to tolerate fluid. Neutralization of caustics is contraindicated.

GPP

Dilution with milk and water may be attempted in patients who are able to tolerate fluid. Neutralization of caustics is contraindicated as the exothermic reaction produces more tissue injury.

Specific antidote can be used for specific agents – like calcium for hydrofluoric burns.

Refer to section 10.6.2.3 on Antidote under Chapter 10: Industrial chemicals.

GPP To reduce stricture formation, the following treatments may be considered - bowel rest, proton pump inhibitor, intravenous antibiotics and intravenous steroids.

GPP

Therapies used to reduce stricture formation include bowel rest, proton pump inhibitor, intravenous antibiotics and intravenous steroids⁴⁹⁰⁻⁴⁹¹. However, there are no studies to evaluate their effectiveness.

12 Bites and stings

12.1 Snakebites in Singapore

Snakebites are not common. The commonest venomous snakebite in Singapore is from the Black Spitting Cobra (*Naja sumatrana*). Other possible venomous snakebites include Wagler's Pit Viper (*Tropidolaemus wagleri*), Blue Malayan Coral Snake (*Calliophis bivirgatus*), Banded Malayan Coral Snake (*Calliophis intestinalis*), Shore Pit Viper (*Cryptelytrops purpureomaculatus*), King Cobra (*Ophiophagus hannah*) and sea snakes.

12.1.1 Clinical presentation

The spectrum of the symptoms and signs of snakebite envenoming is wide. Local signs of envenoming include intense local pain, fang marks, local swelling, purpura, lymphadenopathy, lymphangitis, bleeding, bruising, inflammation, blistering, infection and necrosis. Conjunctivitis, corneal ulceration and scarring may occur from cobra venom spat at the eyes.

Systemic signs of envenoming include nausea, vomiting, and abdominal pain. Cobra envenoming is generally neurotoxic (paralysis, drowsiness, ptosis, external ophthalmoplegia, cranial nerve palsy, aphonia, weakness of respiratory and bulbar muscles, paraesthesia, fasciculations and generalised flaccid paralysis). Do not assume that patients have irreversible brain damage because they are areflexic, unresponsive to painful stimuli or have fixed dilated pupils. Shock, cardiac arrhythmia, and pulmonary oedema can occur.

Sea snake envenoming causes generalised myotoxicity. Cardiac arrest can be precipitated by hyperkalaemia resulting from rhabdomyolysis after sea snake bite. Generalised pain, tenderness and stiffness, pseudotetanus can occur as early as in 30 minutes in sea snake envenoming. Rhabdomyolysis (mainly in sea snake bites) may give rise to renal failure. Viper envenoming is vascular and haematotoxic. Coagulopathy and renal failure can occur.

If expertise is available, identify if the snake is venomous. However, do not handle the snake. A severed snake's head can still bite and envenomate.

12.1.1.1 First aid

D Ensure that the snake is no longer a threat before instituting first aid. Keep calm. Do not attempt to incise the bite wound or suck the venom out. Transport to hospital as soon as possible.⁴⁹²

Grade D, Level 3

12.1.1.2 Pressure Immobilisation Bandage (PIB) method

D Bind the crepe bandage firmly around the entire bitten limb, as tightly as for a sprained ankle. It should be loose enough to allow a finger to be easily slipped between its layers, and not occlude the peripheral pulse. Include a rigid splint or sling to avoid any muscular contraction of the bitten limb. Avoid tight tourniquets that may occlude circulation.

Movement or muscular contraction increases absorption of venom into the bloodstream and lymphatics.

Grade D, Level 3

D In clinically significant envenoming, compression bandages should not be released until the patient is under medical care in hospital, resuscitation facilities are available and antivenom treatment has been started.⁴⁹³

Grade D, Level 3

D PIB is not recommended in cases of viper bites.

PIB may increase the danger of local necrotic effects of viper venom.

Grade D, Level 3

12.1.2 Snakebite wound management

In general, exclude foreign bodies, update tetanus status and institute broad-spectrum antibiotics if signs of infection appear. Consider opiates for analgesia. Avoid NSAIDs or aspirin analgesics due to their anti-platelet effect.

Movement or muscular contraction increases absorption of venom into the bloodstream and lymphatics.

Traditional treatment, such as inflicting local incisions or sucking out the venom, does not confer any benefits and could lead to serious complications.

Tight arterial tourniquets may occlude circulation and add ischemic injuries.

12.1.3 Investigations

Clinical syndromes will aid in the diagnosis of envenoming.

- **Haemoglobin concentration/haematocrit:** a transient increase due to haemoconcentration, or a decrease reflecting blood loss or haemolysis.
- **Plasma/serum** may be pinkish or brownish if there is gross haemoglobinaemia or myoglobinaemia.
- **Platelet count:** this may be decreased in victims of viper bites.
- **White blood cell count:** an early neutrophil leucocytosis is evidence of systemic envenoming.
- **PT/PTT** prolongation indicates coagulopathy.
- **Blood film** may show microangiopathic haemolysis. Perform a blood group and cross-match in anticipation of bleeding complications.
- **Aminotransferases and muscle enzymes** (creatinine kinase, aldolase etc) will be elevated if there is severe local damage or rhabdomyolysis.
- **Mild hepatic dysfunction** is reflected in slight increases in other serum enzymes. Bilirubin is elevated following massive haemolysis.
- **Creatinine or urea levels** are raised in renal failure. Early hyperkalaemia may be seen following extensive rhabdomyolysis.
- **Arterial blood gases and pH** may show evidence of respiratory failure (risk of coagulopathy with Viperidae bites).
- Perform **dipsticks and microscopic urine examination** for blood, red cell casts, proteinuria, as these may point to rhabdomyolysis and/or renal involvement.
- **ECG** may reveal presence of hyperkalaemia or arrhythmia.
- Diagnostic kits are not available for local snakebites.

D The pressure immobilisation may be removed if the clinical examination is normal and clinically insignificant envenoming is suspected.

Re-evaluate 1-2 hours later with laboratory tests. If laboratory tests are normal, repeat at least twice.

Grade D, Level 4

12.1.3.2 Monitoring

D Observe all cases of probable venomous snake bite for at least 12 hours, after the bite or after removal of PIB. Monitor vital signs, limb circulation, wound infection, including urine for output and myoglobinuria. Monitor for an increase in girth and leading edge of oedema.

Grade D, Level 4

D Secure airway and assist ventilation if required. Treat shock, renal failure, myoglobinuria or haemoglobinuria. Correct coagulopathy.

Grade D, Level 4

12.1.4 Antivenom

Specific anti-venom against the local black spitting cobra does not exist. The Haffkine polyvalent antivenom from India exhibits paraspecific activity against *Naja sumatrana* envenoming in animal studies. There is no specific antivenom for Wagler's Pit Viper, Blue Malayan Coral Snake, Banded Malayan Coral Snake and Shore Pit Viper.

D In systemic envenoming, an appropriate antivenom is indicated. Antivenom therapy should be repeated after 1-2 hours, if there is persistent or recurrent coagulopathy or bleeding or deteriorating neurotoxic or cardiovascular signs along with full supportive treatment. Antivenom may reverse systemic envenoming even when this had been present for several days. Antivenom is effective in reversing signs of local envenoming only if it is given within the first few hours after the bite.

Grade D, Level 4

D Signs of local envenoming that indicate antivenom therapy include rapid extension of swelling (within a few hours of bites), local swelling involving more than half of the bitten limb, swelling after bites on the digits, enlarged tender lymph node draining the bitten limb.

Grade D, Level 4

D Administer antivenom intravenously. Local or intramuscular administration of antivenom is not recommended. The initial dose of antivenom is usually empirical.⁴⁹² Children are given exactly the same dose of antivenom as adults.

Grade D, Level 4

B Pre-treatment with subcutaneous epinephrine [0.25 mL (1:1000)], reduces acute adverse reactions to antivenom.⁴⁹⁴ Patients with high-risk of developing allergic reaction may be pre-treated **empirically** with subcutaneous epinephrine, intravenous antihistamines (both anti-H₁ and anti-H₂) and corticosteroid.

Grade B, Level 1+

D In asthmatic patients, prophylactic use of an inhaled adrenergic β_2 agonist may reduce the risk of bronchospasms.

Grade D, Level 4

D Skin Tests for antivenom hypersensitivity are not recommended as skin tests are not predictive and may delay treatment and can themselves be sensitizing.

Grade D, Level 4

12.1.4.1 Compartment syndrome

D Rarely, compartmental syndrome could develop despite aggressive antivenom therapy, and if so, an orthopaedic referral is needed. The compartment pressure should be measured before resorting to fasciotomy.

Grade D, Level 4

12.1.5 Corneal injury from the black spitting cobra

The black spitting cobra also defends itself by spitting venom, usually at the attacker's eyes. This can result in keratitis, corneal ulceration, scarring and subsequently blindness.

Death from respiratory depression following venom exposure in the cornea has been observed in experimental models. Immediate irrigation of the exposed eye with water, followed by instillation of topical heparin (5000 IU/mL) without delay, several drops every 2 to 5 minutes for the first 1 to 2 hours have shown improvement in visual outcomes in experimental models.⁴⁹⁵

D Fluorescent staining and slit lamp examination should be performed to diagnose corneal ulceration.

Topical antimicrobials (tetracycline or chloramphenicol) should be applied to prevent endophthalmitis or blinding corneal opacities.

Use a dressing pad to close the eye.

Grade D, Level 4

12.2 Bees and wasps stings

12.2.1 Introduction

There are 2 main types of bees⁴⁹⁶ in Singapore: solitary bees and eusocial bees - both are from the Apidae family.

- Solitary bees:
 - *Xylocopa (Platynopoda) latipes (Drury)*
 - *Xylocopa (Koptorthosoma) aestuans (Linne)*
 - *Xylocopa (Koptorthosoma) bryorum Fabricius*
- Eusocial bees:
 - *Apis (Hegapis) dorsata Fabricius (wild honey bee)*
 - *Apis (Apis) javana Enderlein (common honey bee)*
 - *Apis (Micropis) florea Fabricius (small honey bee)*

Common wasps species in Singapore include: *Vespa affinis indosinensis*, *Vespa analis analis Fabricius* and *Vespa tropica leefmansi van der Vecht*, the commonest being *V. affinis*. *V. tropica* is most closely associated with man, building its nests mostly on undisturbed portions of buildings.⁴⁹⁷

12.2.2 Epidemiology

A study in Brazil reported 149 cases of honeybee stings in the period of 1994 - 2006, of which 1 death resulted.⁴⁹⁸ In Costa Rica, from 1985 - 2006, 52 fatalities due to Hymenoptera stings were recorded. Annual mortality rates varied from 0-1.73 per 1 million inhabitants. The majority of deaths occurred in males (88.5%), representing a male to female ratio of 7.7:1. A predominance of fatalities was observed in the elderly (50 years of age and older), as well as in children less than 10 years of age.⁴⁹⁹

In the 2007 annual report of the American Association of Poison Control Centre, 3 deaths were reported for bite / stings.⁵⁰⁰

From January 2006 - December 2008, 126 cases of arthropod bites and stings were identified at six major regional hospitals in Hong Kong. 52% of these were due to bees and wasps.⁵⁰¹

In Singapore, there were 2 fatalities out of 38 reported stings by *Vespa affinis* species of wasp in 1970.² From 2002 - 2003, National Skin Centre saw 1085 bite cases from miscellaneous insects such as wasps, bees, hornets, ants, mosquitoes, sand flies, fleas, lice and ticks.⁵⁰² In a study of 31 patients referred to Clinical Immunology

/ Outpatient allergy service at Tan Tock Seng hospital from 1998 - 2002, anaphylaxis occurred in 22 (71%) cases, constituting 30.1% of all cases of anaphylaxis referred to that service during the study period. Honeybee was identified as the causative insect in 12 cases (38.7 %) and wasp in 3 cases (9.7 %).⁵⁰³

Bites and stings (from miscellaneous insects) form 16.1% of toxic exposures presented to the Department of Emergency Medicine of 3 local hospitals in a retrospective study in Singapore from 2001-2003.²

12.2.3 Mechanism of toxicity

Wasp venom contains

- Hyaluronidase, histamine.
- 5-hydroxytryptamine .
- A substance resembling bradykinin.

High concentration of histamine and 5-hydroxytryptamine accounts for some features of skin reaction following wasp stings.

Bee venom contains many toxins, including:

- Haemolytic enzyme (phosphatidase).
- A neurotoxic factor which paralyses adjacent nerve endings to cause localised oedema.
- Histamine.
- Peptides (lytic peptide melittin, neurotoxic apamin and mastocyte degranulating peptide).

Hypersensitisation to bee, wasp and ant venoms is a common cause of anaphylaxis but mass attacks by African killer bees can kill by direct envenoming.

12.2.4 Relevant toxico-kinetics

Large amounts of hyaluronidase in wasp venom would enhance diffusion of toxic substances in the skin. Rhabdomyolysis and elevated lactate dehydrogenase; elevated liver enzymes and thrombocytopenia may occur. Oliguria and acute renal failure secondary to acute tubular necrosis may occur too; they are usually reversible, responding well to dialysis.⁵⁰⁴

For multiple stings with honey bees, the toxic dose (LD50) is 4 stings per kg body weight.⁵⁰⁵

12.2.5 Clinical presentations / diagnosis

Clinical manifestations of bee and wasps stings can be broadly classified into 2 types - those exhibiting from direct effect on the venous system or allergic reactions. They generally include: itch, pain, erythema and swelling. Allergy or hypersensitivity can occur even after one sting. Hypersensitivity to venom may lead to anaphylaxis. Initial symptoms of massive envenomation include: oedema, fatigue, nausea, vomiting, fever and unconsciousness. Endogenous histamine response can cause quick onset of diarrhoea or incontinence.

Toxic reactions happen immediately after the bite and they are a response to the venom constituents that induce mast cell degranulation. Usually painful burning papules form at the site of envenomation, with progression to erythematous wheal- and-flare reactions that begin to subside within 24 hours. Up to 50% of cases progress to larger oedematous local reactions that may mimic cellulitis or become vesicular or bullous. Up to 5% of patients experience systemic reactions, including anaphylaxis from foreign protein (implanted barb of the bee and pollen) injected with the venom. Symptoms of systemic reactions may include nausea, vomiting, and dizziness in a dose-response fashion after multiple stings.

Mass envenomation with bee or wasp stings presents with nausea, vomiting, diarrhoea, light-headedness, lethargy, oedema, and seizures secondary to histamine-mediated inflammation, hypotension, and direct toxic effects of venom components. These clinical signs are not immune-mediated. Haemolysis, rhabdomyolysis, hemoglobinuria, and myoglobinuria may evolve over several hours to days after envenomation.⁵⁰⁶

12.2.6 Treatment

D Stingers should be removed by forceps or scraping with care to avoid breaking the venomous sac as soon as possible.⁵⁰⁷⁻⁵⁰⁸

Grade D, Level 3

GPP Treatment is symptomatic. Oral or injectable antihistamines may be used to reduce itching and swelling. Cool compress (ice should not be placed directly on the skin), elevations to limit oedema and local wound care have been recommended. Patients with severe symptoms, including airway, cardiovascular, or pulmonary

compromise, or persistent symptoms should receive a short course of corticosteroids.⁵⁰⁸

GPP

D In cases of anaphylactic reaction, epinephrine should be given and repeated after 5 minutes in the absence of clinical improvement.⁵⁰⁹

Grade D, Level 4

D Patients with multiple stings may warrant extended observation at least 24 hours after envenomation, with close monitoring of serum chemistries, haemoglobin, myoglobin and creatinine phosphokinase.⁵¹⁰⁻⁵¹¹

(Healthy adults with > 50 stings, the elderly and in those with underlying medical problems and > 1 sting per kg in children)

Grade D, Level 3

D When there is severe systemic reaction of massive envenomation, careful monitoring for: rhabdomyolysis, thrombocytopenia, cardiac arrhythmias, renal failure and possible dialysis should be instituted.⁵⁰⁴

Grade D, Level 3

D In cases of corneal bee stings, pain relief should be provided. An urgent referral to the ophthalmologist should be done to rule out infection, uveitis and inflammatory glaucoma. Broad-spectrum topical antibiotics could be given to prevent secondary infection. Surgical removal of the embedded stinger is controversial.^{508, 512-513}

Grade D, Level 3

12.2.7 Special populations at risk

Army personnel (NS men), Civil Defence officers, staff who work at National Parks and pest controllers are at increased risk of being poisoned by bee/ wasp venom.^{504, 514-515}

GPP Individuals who are aware they are allergic to stings should be advised to carry epinephrine auto injector.^{508, 516}

GPP

GPP Immunotherapy is indicated in adults and children who had life threatening reactions to bee or wasp stings including cardiovascular and respiratory symptoms, provided that either skin test or serum IgE is positive.⁵¹⁶

GPP

12.3 Marine Envenomation

Marine envenomations are fairly common in Singapore. Due to the circumstances of marine envenomation, the marine creature responsible is often unknown.

12.3.1 Clinical Presentation

Following a painful encounter with a marine animal, the presentation includes collapse, anaphylaxis, neurotoxicity, cardiotoxicity, myolysis, coagulopathy, renal failure, pain and local necrosis.

12.3.1.1 Immediate symptoms

Jellyfish stings are generally non-lethal, but may however be responsible for cases of collapse, near drowning or diving accidents. Box jellyfish stings are rare in Singapore, but they can be fatal. They cause immediate pain, sometimes with confusion, agitation, loss of consciousness, breathlessness, paralysis, respiratory failure, A-V conduction disturbances and cardiac arrest. Multiple erythematous lines on the skin occur from contact with tentacles may progress to wheals, vesicles and subsequent skin necrosis.

A series of linear puncture marks (e.g. stone fish, scorpion fish), or single puncture (e.g. stingray) is caused by stinging fish; with local swelling, sometimes with foreign bodies embedded in the wound from the spine. Immediate severe pain, rapid local swelling, subsequent tissue necrosis, nausea, vomiting, abdominal pain, fever, dyspnoea, delirium, shock and paralysis may occur in severe stone fish stings.

Stings from the stingray causes significant local trauma with increasing local pain, swelling, nausea, vomiting, diarrhoea, salivation, sweating, muscle cramps, fasciculations, syncope, seizures, paralysis, arrhythmias and death.

Sea snakes produce scratches or uneven paired, puncture marks.

Refer to the section 12.1.1 on Clinical presentation (snakebites) under Chapter 12: Bites and stings for the clinical presentation.

A cone snail sting also causes immediate pain, but the initial cutaneous signs are scant initially.

12.3.1.2 Delayed symptoms

Small puncture mark or initially no marks with mild or no local pain may be due to Irukandji syndrome (jellyfish sting) or sponge stings. In Irukandji syndrome, the pain progresses to the back, abdominal, limbs or joint pains after about 30 minutes later, including nausea, vomiting, sweating and agitation, paraesthesia, hypertension and tachycardia.

The pain is delayed minutes to hours, with itch and burning sensation, associated with an erythematous rash-like appearance, vesiculation, desquamation and dermatitis occur in sponge bites. Severe pain may develop over 10 to 30 minutes and may recur, intermittently over days.

Identification of the sea creature by a picture guide may help.

12.3.1.3 Other circumstances

A painful but non-fatal shock can occur when touching a live electric ray. A variety of biting fish may inflict physical injuries.

Scombrototoxin poisoning occurs from consuming decaying fish, due to the histamine-like content. Patients experience flushing, abdominal cramps, nausea, diarrhoea, palpitations, tachycardia, wheezing, and hypotension within minutes.

Puffer fish are also known to contain tetrodotoxin, poisoning from puffer fish can occur in restaurants as raw puffer fish is consumed as a delicacy. Poisoning could also occur from eating improperly prepared puffer fish caught off the coast. Ciguatera poisoning is unknown in Singapore.

12.3.2 Resuscitation and general management.

Rinse the area of jellyfish stings in sea water. If available, first aid for tropical jellyfish stings consists of large quantities of dilute (3-5%) acetic acid (i.e. vinegar) to inactivate undischarged nematocysts.⁵¹⁷ Vinegar is recommended for box jellyfish, Irukandji stings or for unknown tropical stings.⁵¹⁸

This is followed by removal of tentacular material with forceps or gloved fingers. Washing with fresh water or physical rubbing may intensify the pain as this may encourage the firing from nematocysts.

⁵¹⁸⁻⁵¹⁹

D Resuscitate and manage cardiorespiratory arrest (from stonefish, stingray, jellyfish, blue-ringed octopus envenomation).

- Treat anaphylaxis, if present.
- Tetratoxin envenoming or neurotoxicity from jelly fish stings will require intubation and ventilation, if respiratory paralysis occurs.
- Treat any major haemorrhage.

Grade D, Level 4

D Administer analgesics, including local anaesthetics where indicated.

- Update the tetanus immunisation status.
- Relevant radiological investigations, surgical removal of foreign material and surgical debridement may be required to address the local lesion.

Grade D, Level 4

D Secondary infection, chronic ulcer and osteomyelitis can occur. Prophylactic antibiotic should be given in contaminated wounds.

Grade D, Level 4

Stonefish and Stingray envenoming

B First aid for stingray and stonefish stings is hot, non-scalding (not higher than 45°C) water immersion as the venom is heat labile.⁵²⁰⁻⁵²¹

Grade B, Level 2++

A Hot water immersion may be useful for pain relief following jellyfish stings after the tentacles have been removed.

Grade A, Level 1-

Annex A Commonly-used antidotes

Certain antidotes listed in the table may not be readily available and may require special order.

Name of Antidote	Chapter / Annex	Page Number
Atropine	Chapter 9	162
Benzodiazepines	Chapter 9; Annex A	168; 201
Benztropine	Annex A	203
Calcium Gluconate and Chloride	Annex A	205
Chlorpromazine	Chapter 8	135
Cyproheptadine	Chapter 8; Annex A	135; 207
Dantrolene	Chapter 8; Annex A	135; 208
Desferrioxamine (DFO, deferoxamine)	Annex A	210
Digoxin-specific antibodies (Digitalis antidote, Digibind, digoxin-specific Fab)	Annex A	212
Dimercaprol or British Anti-Lewisite (BAL)	Annex A	215
Edetate Calcium Disodium (ECD) or CaNa_2EDTA (Ethylenediamine Tetraacetic Acid)	Annex A	217
Ethanol	Annex A	219
Flumazenil	Chapter 8	130
Folinic Acid (Leucovorin or citrovorum factor)	Annex A	221
Glucagon	Annex A	223

Name of Antidote	Chapter / Annex	Page Number
High Dose Insulin Euglycemia (HIE)	Annex A	225
Hydroxocobalamin (<i>exemption</i>)	Annex A	227
Hyperbaric Oxygen Therapy (HBOT)	Annex A	229
Hypertonic Sodium Bicarbonate (NaHCO ₃)	Annex A	231
Methionine	Chapter 6	112
Methylene Blue	Annex A	233
N-Acetylcysteine	Chapter 6	110
Naloxone	Chapter 6	92
Octreotide	Annex A	235
Penicillamine	Annex A	237
Physostigmine	Chapter 7; Annex A	124; 239
Pralidoxime	Chapter 9	166
Protamine	Annex A	241
Pyridoxine (Vitamin B ₆)	Annex A	243
Sodium Nitrite	Annex A	245
Sodium Thiosulphate	Annex A	247
Succimer or 2,3-dimercaptosuccinic acid (DMSA) (<i>exemption</i>)	Annex A	249
Thiamine (Vitamin B ₁)	Annex A	251
Vitamin K ₁ (Phytomenadione)	Annex A	253

Main References:

- (1) Kent Olsen. Poisoning and Drug Overdose. 5th edition. McGraw-Hill Companies 2006.
- (2) Goldfrank LR, Flomenbaum NE, Lewin NA, et al. Goldfrank's Toxicologic Emergencies. 7th edition. McGraw-Hill New York 2002.

Benzodiazepines (example: Diazepam, Lorazepam)

1. Indications

- Treatment of acute seizures or status epilepticus.
- Treatment of anxiety and agitation e.g. due to hallucinogens.
- Excessive muscle rigidity.
- Alcohol and sedative-hypnotic withdrawal.

2. Mechanism of action

Potentiate GABA inhibitory effects on CNS.

3. Route & Dosage

- *Anxiety/Agitation and muscle relaxation*
Diazepam: IV 0.1-0.2 mg/kg.
Usual dose for adult and children > 5 years: 2-10 mg.
Repeat as needed every 1-4 hours. Oral doses may also be used.

Lorazepam: IV 0.05 mg/kg in children (adults 1-2 mg).
IM: 0.05 mg/kg (maximum 4 mg).

Repeat as needed every 1-4 hours. Oral doses may also be used.
- *Seizures*
Diazepam: IV 0.1-0.2 mg/kg, repeat if needed every 5-10 minutes.

Maximum total doses of 30 mg (adults), 10 mg (older children) or 5 mg (infants and younger children up to 5 years old).
Diazepam rectal tubes may also be used.

Lorazepam: IV 0.04 mg/kg (adults 1-2 mg), repeat if needed every 5-10 minutes.
IM: same dose as IV but not preferred unless IV route is unavailable.
- *Alcohol withdrawal:*
Diazepam: IV 5-10 mg initially, then 5 mg every 10 minutes if needed.
Oral: 10mg every 6 hourly x 4 doses, then 5-10 mg every 6 hourly.

Lorazepam: IV 1-2 mg initially, then 1 mg every 10 minutes if needed.

Oral: 2 mg every 6 hourly for 4 doses, then 1-2 mg every 6 hourly.

Note that there are many different recommended regimens for benzodiazepine use in alcohol withdrawal.

IV Diazepam should not be injected faster than 5 mg/min.

IV Lorazepam should not be injected faster than 2 mg/min.

Injection rate for children should be slowed.

- ***Formulation***

Diazepam available as 10 mg/2mL amp, 5 mg rectal tube, 2 mg, 5 mg and 10 mg tab.

Lorazepam available as 4 mg/mL amp, 0.5 mg and 1 mg tab.

4. Contraindications / Special precautions

Known hypersensitivity to benzodiazepines.

5. Adverse effects

CNS depression, amnesia, disorientation, respiratory depression.

6. Monitoring parameters / Therapeutic endpoints

Onset of action within a few minutes if given via IV route. Monitor sedation, respiratory rate and other vital parameters.

7. Other considerations

- **Pregnancy:**
 - FDA Category D.
 - Can be used short-term for severely symptomatic patient.
- **Lactation:**
 - Diazepam and its metabolite accumulate in breast milk with repeated doses. Other agents are generally preferred.
 - Lorazepam has low levels in the breast milk, and a relatively shorter half-life. After a single dose, it is advised to wait 6-8 hours before resuming breastfeeding.
- **Paediatric:** Weight based dosing.

Benztropine (COGENTIN®)

1. Indications

Treatment of acute dystonia (e.g. oculogyric crisis) associated with antipsychotics and metoclopramide.

2. Mechanism of action

Exhibit antimuscarinic, antihistaminergic effects. It is also a dopamine reuptake inhibitor.

3. Route & Dosage

- *IV or IM*
Adults: 1-2 mg.
Children 3 years and above: 0.02 mg/kg to maximum of 1 mg.
May repeat dose in 15 minutes if unresponsive.
- *Oral*
Adults: PO 1-2 mg every 12 hourly.
Children 3 years and above: 0.02 mg/kg to maximum of 1 mg every 12 hourly.
Can continue for 2-3 days to prevent recurrence.

Has a longer duration of action compared to diphenhydramine, and can be given twice daily.

- *Formulation*
Available as 2 mg/2mL amp or 2 mg tab.

4. Contraindications / Special precautions

- Closed-angle glaucoma
- Bladder neck obstruction
- Myasthenia gravis
- Tardive dyskinesia
- Tachycardia
- Hyperthermia

5. Adverse effects

Sedation, blurred vision, tachycardia, urinary retention, dry mouth.

6. Monitoring parameters / Therapeutic endpoints

Improvement should be seen within minutes of IV administration. Monitor pulse rate and temperature.

7. Other considerations

- Pregnancy:
 - FDA Category C.
 - Can be used in acute treatment of severely symptomatic patient.
- Lactation:
 - No data, but single dose is unlikely to interfere with breastfeeding.
- Paediatric:
 - For child below 3 years old, use of diphenhydramine is recommended instead.
 - Benztropine may be reserved for symptomatic child unresponsive to diphenhydramine.

Calcium Gluconate and Chloride

1. Indications

- Hypocalcaemia.
- Antidote for hydrofluoric acid (HF) burn (*refer to Chapter 10: Industrial Chemicals*).
- Calcium-channel blocker medication overdose.
- Hyperkalaemia.

2. Mechanism of action

- Replace the ionic calcium that is depleted by hydrofluoric acid.
- Overcome the blockade of slow calcium channel by calcium-channel blocker poisoning.
- Stabilize the cardiac cell membrane during hyperkalaemia.

3. Route & Dosage

- *Life threatening hypocalcaemia, calcium-channel blocker overdose and hyperkalaemia:*
IV calcium gluconate (10%) 10-20 mL over 5-10 minutes
(Paediatric dose: 0.2-0.3 mL/kg).
IV calcium chloride (10%) 5-10 mLs over 5-10 minutes
(Paediatric dose: 0.1-0.2 mL/kg).

Repeat as needed every 5-10 minutes.

- ***Formulation***

Available as Calcium Gluconate 10% (10 mL = 1g) and Calcium Chloride 10% (10 mL = 1g).

Calcium chloride contains three times the amount of calcium ions compared to calcium gluconate and should preferably be given via a central line because it is highly concentrated.

Precipitates can form if calcium salt is given with other medications containing carbonates, sulphates and phosphates.

4. Contraindications / Special precautions

- Hypercalcaemia
- Hyperphosphatemia
- Digoxin toxicity

5. Adverse effects

- Hypercalcaemia.
- Vasodilatation, arrhythmia, hypotension, bradycardia and syncope (caused by rapid IV administration).
- Nephrolithiasis.
- Tissue necrosis with extravasation.
- Hypomagnesaemia.
- Constipation.
- Flushing, dizziness.

6. Monitoring parameters / Therapeutic endpoints

- Calcium level should be monitored. Target a high normal calcium level for calcium-channel blocker overdose.
- Cardiac monitoring.

7. Other considerations

- Pregnancy: FDA Category C.
- Lactation: Probably safe.
- Paediatric: Use weight-based dosing.

Cyproheptadine

1. Indications

- Serotonin syndrome. Usually mild to moderate toxicity.

2. Mechanism of action

It is an antiserotonergic, anticholinergic and antihistaminergic agent that competitively blocks the serotonin 5HT_{2A}, 5HT_{1A} and histamine H₁ receptors.

3. Route & Dosage

Oral dose

Adults: 12 mg is given stat followed by 8 mg every 8 hourly for 24 hours.
Paediatric dose is not well established.

Formulation

Available as 4 mg tablets.

4. Contraindications / Special precautions

- Acute asthma
- Close angle glaucoma
- Bladder neck obstruction
- Stenosing peptic ulcer

5. Adverse effects

- Sedation
- Thickening of bronchial secretions
- Anticholinergic effects
- Leucopenia and thrombocytopenia

6. Monitoring parameters / Therapeutic endpoints

Monitor the clinical state of the patient.

7. Other considerations

- Pregnancy: FDA Category B.
- Lactation: Safety unknown.
- Paediatric: Insufficient information on dosing.

Dantrolene

1. Indications

- Malignant hyperthermia.
- Hyperthermia and rhabdomyolysis due to drug-induced muscular hyperactivity.
- Neuroleptic malignant syndrome.

2. Mechanism of action

Inhibit release of calcium from the sarcoplasmic reticulum, hence relaxing skeletal muscle.

Dantrolene is not a substitute for temperature-cooling measures.

3. Route & Dosage

IV: 1 mg/kg via rapid IV bolus over 2-3 minutes or infused over 30-60 minutes.

Repeated every 5-10 minutes till a maximum of 10 mg/kg.

Can also continue as an IV infusion till a maximum daily dose of 10 mg/kg/day.

Maintenance dose of 1 mg/kg once to four times daily for 2-3 days may be given to prevent recurrence. Oral doses may be used if available.

Formulation

Available as a 20 mg vial. Each vial is to be diluted with 60 mL of water for injection (WFI), and the resulting solution is stable for 6 hours after reconstitution.

4. Contraindications / Special precautions

- Known hypersensitivity to dantrolene.
- Caution in patient with muscular weakness or respiratory depression.

5. Adverse effects

- Muscle weakness, including muscles used in respiration.
- Sedation, fatigue, dizziness, diarrhoea.
- Venous irritation and thrombophlebitis upon extravasation.

6. Monitoring parameters / Therapeutic endpoints

Muscle hyperactivity is expected to normalize within 30 minutes of an effective dose.

7. Other considerations

- Pregnancy: FDA Category C. May be used in severely symptomatic patient.
- Lactation: After short-term use, the drug is expected to be eliminated from breast milk in 1 to 2 days after stopping dantrolene.
- Paediatric: Weight-based dosing.

Desferrioxamine (DFO, deferoxamine)

1. Indications

- Acute iron poisoning with features of systemic toxicity like metabolic acidosis, altered mental state and shock. Also indicated if the level of iron is > 500 mcg/dL at 4-6 hours post ingestion.
- Chronic iron overload.

2. Mechanism of action

It chelates free iron and loosely bound iron to form ferrioxamine which is water soluble and is then excreted in the urine. The urine changes to vin-rose colour.

3. Route & Dosage

Intravenous dose: Initially 1 g, give at rate not more than 15 mg/kg/h, then 0.5 g every 4 hours. Maximum rate for subsequent infusions is 125 mg/h. Should not exceed > 6 g per 24 hours. The duration of therapy should be limited to 24 hours.

Intravenous route is preferred for patients with acute poisoning.

Intramuscular route: 1 g initial dosing followed by 0.5 g every 4 hours and should not exceed > 6 g per 24 hours.

Formulation

Available as Desferrioxamine B (Desferal) 500mg vials.

500 mg of DFO can be diluted in 100 mL of normal saline or D5% water.

4. Contraindications / Special precautions

- Anuria
- Severe renal failure

5. Adverse effects

- Hypotension (rate-related).
- Acute lung injury presenting as acute respiratory distress syndrome may develop with infusion > 24 hours.
- Yersinia sepsis.
- Chronic: Auditory, ocular, pulmonary toxicity.

- Hypersensitivity reaction.
- Hypocalcaemia.
- Seizures, dizziness, neuropathy.

6. Monitoring parameters / Therapeutic endpoints

Avoid prolonged infusion of > 24 hours. Continue treatment until serum iron < 350 mcg/dL and patient clinically well. Vin rose-coloured urine should be observed.

7. Other considerations

- Pregnancy: FDA Category C. DFO should not be withheld from pregnant patients with severe iron toxicity.
- Lactation: Safety unknown.
- Paediatric: For children > 3 year old, same as adult dose.

Digoxin-specific antibodies (Digitalis antidote, Digibind, digoxin-specific Fab)⁵²²

1. Indications

Life-threatening arrhythmias or hyperkalaemia (> 5 mmol/L) due to toxicity related to digoxin, digitoxin and other cardiac glycosides. Natural sources of cardiac glycosides include oleander, foxglove and toad venom (bufotoxin). During chronic poisoning, consider its use if patients are symptomatic with cardiac arrhythmias and have impaired renal function.

2. Mechanism of action

The antibodies bind to free digoxin, and the resulting complex is pharmacologically inactive, hence reversing the toxic effects of digoxin. There is a high binding affinity to digoxin, and sufficient cross-reactivity with digitoxin and other cardiac glycosides.

3. Route & Dosage

Known amount of digoxin ingested:

80 mg of digoxin-specific Fab for each 1 mg of digoxin absorbed. The 38 mg vial can be considered equivalent to a dose of 40 mg.

The approximate dose absorbed is an estimate of the total body load of digoxin

Dose ingested (mg of digoxin)	Approx. dose absorbed (mg of digoxin)	Recommended dose of antidote (mg)
1.25	1	80
2.5	2	160
6.25	5	400
12.5	10	800
18.75	15	1200

Or dose ingested (in mg) x 0.8 x 80 = Dose of antidote recommended
Doses should usually be rounded up to the next whole vial.

If steady-state digoxin level is known:

Approx. total body load of digoxin (mg)

= serum conc. (in ng/mL) x 0.001 x 5 x body weight (in kg)

(Assume volume of distribution = 5 L/kg)

Refer to the table for dose of antidote required (i.e. 80 mg of antidote for each 1 mg of digoxin)

Unknown amount of digoxin absorbed:

Acute poisoning: 400 mg of digoxin-specific Fab (children, use lower dose if < 20 kg body weight)

Chronic toxicity: 120-240 mg (adults), 40-80 mg (children: use lower dose if < 20 kg body weight)

Repeat dose if symptoms do not resolve in 1 hour, or if they recur.

Reconstitute as recommended in package insert.

Administer as slow IV infusion over 30 minutes. Longer infusion times (1-7 hours) have been used.

May be given as a rapid IV bolus for life-threatening arrhythmias.

Formulation

Available as 38 mg or 80 mg vials.

4. Contraindications / Special precautions

- Caution if known hypersensitivity to sheep products.
- May contain traces of papain.

5. Adverse effects

- Hypokalemia.
- Exacerbation of congestive heart failure or increased ventricular rate in patients using digoxin for therapeutic effects.
- Serum sickness.
- Rare: allergic reactions.
- Rebound increase in free digoxin levels may occur in patients with renal impairment due to delayed clearance of digoxin-Fab complex.

6. Monitoring parameters / Therapeutic endpoints

Monitor potassium levels, ECG and digoxin levels.

Measure steady state serum digoxin concentration at least 6-8 hours after last digoxin dose, prior to start of antidote. Subsequently, total serum digoxin levels will rise greatly after the use of antidote and is not an accurate indicator of body stores. The digoxin will be mostly bound to the Fab fragments and is not considered active.

Serum potassium levels are a better indicator of acute toxicity and should be closely monitored. Serial levels are recommended as onset of hyperkalaemia may be delayed up to 12 hours.

Initial response to antidote should occur within 60 minutes, and complete reversal 30-360 minutes (average 88 minutes) after administration of digoxin-specific Fab.

7. Other considerations

- Pregnancy: FDA Category C. Therapy should not be withheld because of pregnancy.
- Lactation: Likely to be safe.
- Paediatric: Based on amount of digoxin absorbed. Empiric doses may be lower than adult doses.

Dimercaprol or British Anti-Lewisite (BAL)

1. Indications

Poisoning by heavy metals:

- Lead
- Gold
- Inorganic arsenic (including lewisite blistering agent)
- Inorganic mercury

2. Mechanism of action

Binds metal ions to form stable dimercaptides, which are excreted in the urine.

3. Route & Dosage

Via deep intramuscular injection

- Severe inorganic arsenic or mercury poisoning
 - IM 3 mg/kg every 4 hours for 48 hours, followed by
 - IM 3mg/kg every 12 hours for 7-10 days according to clinical response.
- Lead encephalopathy
 - 4 hours before commencing EDTA.
 - IM 4 mg/kg every 4 hours for 5 days.

Formulation

Available as 100 mg/2 mL (5%) amp (formulated in peanut oil).

4. Contraindications / Special precautions

- Peanut allergy.
- G6PD deficiency.
- Hepatic insufficiency (except in post-arsenical jaundice).
- Caution in patients with oliguria.

5. Adverse effects

High incidence of adverse effects occurs at therapeutic dosing (up to 50%). For life-threatening adverse effects, subsequent doses should be reduced.

- Hypertension and tachycardia.
- Chest pain.
- Headache, nausea, vomiting.
- Peripheral paresthesia, burning sensation of lips, mouth, throat and eyes.
- Lacrimation, rhinorrhea, and excessive salivation.
- Intravascular haemolysis (G6PD deficiency).
- Pain and sterile abscess formation at injection site.
- Fever and myalgia.
- Nephrotoxicity.
- Hypertensive encephalopathy.

6. Monitoring parameters / Therapeutic endpoints

Keep urine alkaline as chelate dissociates in acid media.

7. Other considerations

- Pregnancy: FDA Category C.
- Lactation: Safety not established.
- Paediatric: Weight-based dosing.

Edetate Calcium Disodium (ECD) or CaNa₂EDTA (Ethylenediamine Tetraacetic Acid)

1. Indications

- Serious lead poisoning and lead encephalopathy together with dimercaprol (BAL).
- Possibly: Poisonings with cadmium, cobalt, copper, uranium, zinc (insufficient evidence).

2. Mechanism of action

Calcium is displaced by divalent or trivalent metals to form water soluble complexes that are readily excreted by kidney.

3. Route and dosage

Intravenous and Intramuscular routes only. Not for oral route.

- Lead encephalopathy
 - BAL and ECD combined therapy.
 - Start BAL 4 hours before commencing ECD.
 - 1500 mg/m²/day (30 mg/kg/day) for 5 days.
 - Give as continuous infusion or as deep IM injection 2-3 times a day (of total daily dose).
 - If via IM route, use a separate injection site from BAL injection
 - For intravenous infusion, dilute to 2-4 mg/mL in normal saline or 5% dextrose solution.
 - Repeat with 2nd and 3rd courses if lead level rebounds 48 hours after termination of treatment.
- Symptomatic lead poisoning without encephalopathy
 - BAL and ECD combined therapy.
 - Start BAL 4 hours before commencing ECD.
 - 1000 mg/m²/day (20-30 mg/kg/day) for 5 days.
 - Continuous infusion or deep IM injection 2-3 times a day (divide the total daily dose).
 - If via IM route, use a separate injection site from BAL injection.
 - Stop BAL when blood lead level < 50 mcg/dL.
 - Repeat 2nd and 3rd courses if needed.

Formulations

Edetate calcium disodium in 1g/5mL ampoules – 200 mg of CaNa_2EDTA per mL.

4. Contraindications / Special precautions

- Patients with cerebral oedema, increased intracranial pressure (IM route or more concentrated solutions preferred for this group of patients).
- Patients with renal failure.

5. Adverse effects

- Initial systemic symptoms:
 - Numbness, tingling.
 - Yawning, nasal congestion, prolonged sneezing.
 - Malaise, fatigue, excessive thirst.
- Nephrotoxicity (limit total daily dose to 500 mg/m²/day).
- Acute febrile reaction - peaks at 3-6 hours and resolves after 12-24 hours.
- Mucocutaneous lesions: sore throat, sore mouth, tongue.
- Others: thrombophlebitis (give at < 0.5% conc), glycosuria, decreased systolic and diastolic pressure, decreased Hb level and cardiac rhythm irregularities.

6. Monitoring parameters / Therapeutic endpoints

- Blood lead levels at baseline, during infusion and after infusion. Stop infusion 1 hour before taking blood lead level to avoid falsely elevated blood lead levels.
- Monitor renal function.
- ECG monitoring with IV infusion route.

7. Other considerations

- Pregnancy: FDA Category B (limit use to severe, symptomatic lead poisoning).
- Lactation: Safety unknown.
- Paediatric: 1000-1500 mg/m²/day.

For patients who are asymptomatic but have elevated blood lead level, the use of succimer 2,3 dimercaptosuccinic acid (DMSA) may be considered.

Ethanol

1. Indications

Methanol or ethylene glycol poisoning, with history of ingestion, metabolic acidosis or serum concentration ≥ 20 mg/dL.

2. Mechanism of action

Ethanol acts as a competitive substrate for alcohol dehydrogenase, thus preventing the metabolism of methanol or ethylene glycol to toxic metabolites.

3. Route & Dosage

Intravenous:

Loading dose: 750 mg/kg, infused over 30 minutes.

Maintenance: 100-150 mg/kg/h continuous infusion.

Higher maintenance doses are used for chronic alcoholics (150-200 mg/kg/h) and during haemodialysis (175-250 mg/kg/h).

Oral:

Loading and maintenance doses same as IV.

If the patient's serum ethanol level is greater than zero, reduce the loading dose in a proportionate manner.

Omit the loading dose if the ethanol level is > 100 mg/dL.

Adjusted loading dose

= calculated loading dose \times $[100 - (\text{measured serum ethanol level})] / 100$

Formulation

Available as Ethanol (Alcohol, dehydrated) 100% w/v (1 g/mL) 20 mL vial.

IV: Dilute to 10%w/v (50 g in 500 mL) = 50 mL of 100% ethanol added to 450 mL 5% dextrose solution.

Oral: Dilute to 20% w/v (20 g in 100 mL) = each 20 mL added to 80 mL of juice.

4. Contraindications/ Special precautions

- Patient on drugs that may induce a disulfiram-like effect (e.g. metronidazole).

- Caution in head trauma or altered mental state, or in patients on other CNS depressants.
 - Caution in epilepsy.
 - Contraindicated in diabetic coma.

5. Adverse effects

- Sedation, hypoglycaemia, flushing, palpitations, and postural hypotension.
- Oral use may cause nausea, vomiting and gastritis.
- IV use may cause local phlebitis, and hyponatremia due to large volumes of sodium-free infusates.

6. Monitoring parameters / Therapeutic endpoints

Monitor serum ethanol levels after loading dose and every 1-4 hours during maintenance therapy to target a concentration of 100-200 mg/dL. Treatment may continue until osmolar and anion gaps are corrected or when toxic alcohol levels are < 20 mg/dL. Monitor CNS depression, respiratory rate, and liver function tests for toxic effects.

7. Other considerations

- Pregnancy: FDA Category D. Can be used for pregnant women with toxic alcohol poisoning.
- Lactation: Hold off breastfeeding till ethanol is fully metabolised.
- Paediatric: Weight-based dosing.

Fomepizole (if available) is an alternative antidote for methanol or ethylene glycol poisonings.

Folinic acid (Leucovorin or citrovorum factor)⁵²³

1. Indications

- Poisoning by methotrexate and other folate antagonist (trimethoprim and pyrimethamine – large overdoses).
- Methanol poisoning.

2. Mechanism of action

Folinic acid is a reduced folate and bypasses the inhibition of dihydrofolate reductase by methotrexate and other folate antagonist. The reduced folate is required for purine synthesis and formation of DNA and RNA which are needed for cell replication.

Folate or folinic acid enhance the metabolism of formic acid to a non-toxic metabolite in methanol poisoning.

3. Route & Dosage

- *Intravenous route (for methotrexate poisoning):*
 - Administer a dose equal to or greater than the dose of methotrexate overdose as soon as possible (preferably within 1 hour). This dose is repeated every 3-6 hours for 1-3 days depending on methotrexate serum concentration.
 - For leucovorin rescue, leucovorin can be administered at 15 mg (or 10 mg/m²/dose for paediatrics) every 6 hours until the serum methotrexate level is <10⁻⁸ M.
 - Dose will need to be adjusted according to methotrexate level and renal function. Higher doses may be required (up to 100 mg/m²), and given more frequently based on methotrexate levels.
- *Other folic acid antagonists:*
Administer 5-15 mg/day IM, IV, or PO for 5-7 days.
- *Methanol poisoning:*
For adults and children, give 1 mg/kg (up to 50-70 mg) IV every 4 hours for one to two doses. Oral folic acid is given thereafter at the same dosage every 4-6 hours.

Formulation

Parenteral formulation: 50 mg/5mL vials.

Oral: Leucovorin calcium 15 mg tablets.

4. Contraindications / Special precautions

- The rate of IV administration should not be greater than 160 mg/min (since it contains calcium).
- Should not be administered intrathecally.

5. Adverse effects

- Anaphylactoid reactions
- Seizures
- Syncope
- Urticaria
- Nausea, vomiting, stomatitis, diarrhoea
- Hypercalcaemia

6. Monitoring parameters / Therapeutic endpoints

Methotrexate levels, renal function, fluid and electrolyte status will guide need for further therapy.

7. Other considerations

- Pregnancy: FDA Category C.
- Lactation: Safety unknown.
- Paediatric: Give according to body surface area as listed above.

Glucagon

1. Indications

- Beta- blocker overdose with haemodynamic instability. (Used as second-line agent).
- Calcium-channel blocker overdose. (Also used as second-line antidote. Evidence for its use is not as strong compared to its use in beta-blocker overdose).

2. Mechanism of action

Glucagon is a counter-regulatory polypeptide hormone secreted by the alpha cells of the pancreas. Glucagon receptors stimulation activate adenylyl cyclase via a Gs protein in myocardium leading to an increase in cyclic AMP level. This increases inotropy and chronotropy in myocardium. In the liver and adipose tissue, it causes an increase in glycogenolysis, gluconeogenesis and ketogenesis.

3. Route & Dosage

Initial 3-10 mg IV over 30-60 seconds.

If there is no response, the dose can be repeated after 5 minutes (up to maximum of 10 mg).

This is followed by a maintenance dose of about 2-5 mg/h in Dextrose 5%.

Paediatric dose: IV 0.15 mg/kg followed by 0.05-0.1 mg/kg/h= in Dextrose 5%.

Formulation

Available as 1 mg vial.

4. Contraindications / Special precautions

- Insulinomas
- Pheochromocytoma
- Glucagonoma

5. Adverse effects

- Vomiting and nausea.
- Hyperglycemia especially in diabetics and during infusion.

- Hypokalemia.
- Allergic manifestation.
- Headache.

6. Monitoring parameters / Therapeutic endpoints

Blood pressure and blood glucose levels. Glucagon can be withdrawn when haemodynamic status improves.

7. Other considerations

- Pregnancy: FDA Category B.
- Lactation: Safety unknown.
- Paediatric: Weight-based dosing.

High Dose Insulin Euglycemia (HIE)

1. Indications

Calcium-channel blocker overdose after poor response to fluids, calcium salts and inotropic agents. Can also be used for beta-blocker overdose although the evidence is not as well established.

2. Mechanism of action

Calcium-channel blockers cause decrease in inotropy, chronotropy and dromotropy as well as decreased insulin secretion from pancreatic islet cells. Insulin promotes cellular uptake of glucose in muscle and adipose tissue. It promotes inotropy by stimulating myocardial energy production and increases aerobic metabolism. This metabolic effect optimizes heart function under stress condition.

3. Route & Dosage

Insulin is given as an IV bolus 1 unit/kg, followed by 0.5-1 unit/kg/h titrated to clinical response. It should be started early as it can take 1 hour to reach peak inotropic effect.

Dextrose is started when the glucose level drops below 10 mmol/L, and can be given as an IV bolus of 25 g (50 mL of Dextrose 50%) followed by 25 g/h infusion. This is titrated to maintain euglycaemia.

Potassium is also replaced as required.

Formulation

Available as regular insulin 100 units per 10mLs vials.

4. Contraindications / Special precautions

Nil.

5. Adverse effects

- Hypoglycaemia
- Hypokalemia

6. Monitoring parameters / Therapeutic endpoints

Blood pressure, heart rate, glucose and potassium levels are monitored hourly. Therapy can be stopped when the blood pressure is > 100mmHg systolic and the heart rate is more than 50 beats per minute.

7. Other considerations

- Pregnancy: FDA Category B.
- Lactation: Safety unknown.
- Paediatric: Weight-based dosing.

Hydroxocobalamin

1. Indications

- Cyanide toxicity: Known or suspected.
- Prophylaxis against cyanide toxicity during sodium nitroprusside infusion.

2. Mechanism of action

Hydroxocobalamin is the precursor of vitamin B12. It is a cobalt-centred metalloprotein which avidly complexes with cyanide to form cyanocobalamin (vitamin B12). This is then eliminated in the urine or the cyanide is released at a rate sufficient to allow detoxification by rhodanese route. Five grams of hydroxocobalamin can bind up to 100 mg of cyanide.

3. Route & Dosage

- Intravenous route:

Adults: Give 5 g diluted in 200 mL of normal saline over 15 minutes.

May repeat a second 5 g dose (maximum cumulative dose 15 g), depending on state of patient.

It is usually given together with sodium thiosulphate.

Paediatric: give 70 mg/kg (max of 5g), may repeat 2nd dose if needed.

Formulation

Cyanokit 5 g—2 vials of 2.5 g powder (Drug not registered in Singapore).

4. Contraindications / Special precautions

Avoid excessive sunlight or ultraviolet light exposure.

5. Adverse effects

- Allergic reactions.
- Hypertension.
- Red urine, skin and mucous membrane. Discolouration of body fluids may interfere with certain laboratory investigations that use colorimetric methods.

6. Monitoring parameters / Therapeutic endpoints

Blood pressure and heart rate during and after infusion, pre-treatment serum lactate and venous-arterial PO₂ gradient. Monitor clinical state of patient.

7. Other considerations

- Pregnancy: FDA Category C, but likely a safer choice compared to sodium nitrite/thiosulphate combination.
- Lactation: Safety unknown.
- Paediatric: Weight-based dosing.

Hyperbaric Oxygen Therapy (HBOT)

1. Indications

Carbon monoxide (CO) poisoning

- Especially indicated in those poisoned patients with high risk features: significant loss of consciousness, coma, persistent neurological dysfunction, abnormal cerebellar examination, metabolic acidosis, myocardial ischemia, and pregnancy.
- ACEP position statement (2008) states that 'HBOT is a therapeutic option for CO-poisoned patients; however, its use cannot be mandated'. High flow oxygen therapy with 100% oxygen administered via a tight fitting mask under normal atmospheric condition can be used where HBOT is not readily available.

2. Mechanism of action

- The half-life of carboxyhemoglobin is reduced from 60 minutes in ambient pressure with 100% oxygen to about 23 minutes under HBOT.
- It blunts the cascade of vascular injury and diminishes injuries associated with a number of pathologic process characterized by oxidative stress.

3. Route & Dosage

100% oxygen is administered under 2-3 atmospheric pressure in a mono or multi-place chamber. There are chambers available at SGH, TTSH and the naval base but logistical arrangement need to be made for transfer of these patients.

4. Contraindications / Special precautions

- Unvented pneumothorax.
- Claustrophobia.
- Sinus congestion.
- Scarred or non-compliant structures in middle ear e.g. otosclerosis.

5. Adverse effects

- Middle ear barotraumas.
- Sinus pain or bleeding.
- Immediate deafness or tinnitus, vertigo, nystagmus.

- Transient near sightedness.
- Oxygen toxicity resulting in seizure (rare).

6. Monitoring parameters / Therapeutic endpoints

Monitor for clinical improvement.

7. Other considerations

- Pregnancy: As foetal haemoglobin binds more readily to carbon monoxide, risk of foetal toxicity in carbon monoxide poisoning increases and HBOT use is encouraged.
- Lactation: Safe.
- Paediatric: Care should be taken to keep the child warm in chamber as temperature in chamber may fluctuate. Tympanostomy tubes may need to be placed if the child cannot equalise his ear pressure.

Hypertonic Sodium Bicarbonate (NaHCO₃)

1. Indications

- Cardiotoxicity from sodium channel blocking drug overdose e.g. tricyclic antidepressant (TCA), type Ia and Ic antiarrhythmics.
- Correction of metabolic acidosis (not discussed here).
- Urine alkalinisation (described in *Chapter 4: Enhancing the elimination of toxic substances from the body*).
- Hyperkalaemia (not discussed here).

2. Mechanism of action

Use in tricyclic antidepressant poisoning:

- Provide sodium load to overcome the membrane-depressant effect of sodium-channel blockade.
- Direct effect on myocardial contractility by correcting the metabolic acidosis present.
- Alkalinize the serum to decrease drug receptor binding and accelerate recovery of the sodium channel.

3. Route & Dosage

- Given IV 1-2 mEq/kg over 1-2 minutes when there is widened QRS (> 100 milliseconds), hypotension or ventricular arrhythmia from TCA overdose.
- For 8.4% w/v sodium bicarbonate, 1 mL = 1 mEq.
- Further administration may be required and should be guided by blood gas result.

Formulation

Available as hypertonic sodium bicarbonate 8.4%w/v - 20 mL ampoule or 500 mL infusion bag. Sodium bicarbonate 4.2%w/v (0.5 mEq/mL) is available for paediatric use.

4. Contraindications / Special precautions

- Fluid overload from congestive cardiac failure.
- Renal failure.
- Metabolic and respiratory alkalosis.
- Severe hyponatremia.
- Hypocalcaemia.

5. Adverse effects

- Excessive alkalization (pH > 7.6).
- Fluid overload.
- Hyponatremia and hyperosmolarity.
- Extravasation cellulitis (hypertonic solution).
- Hypokalemia, hypocalcaemia.

6. Monitoring parameters / Therapeutic endpoints

- Endpoint of treatment is narrowing of widened QRS in the ECG.
- Cardiac monitoring and repeat ECG.
- Serial arterial pH monitoring. Keep pH < 7.55.
- Check electrolytes frequently for hypokalemia.

7. Other considerations

- Pregnancy: FDA Category C.
- Lactation: Safety unknown.
- Paediatric: Weight-based dosing.

Methylene Blue⁵²⁴

1. Indications

Methaemoglobinemia, with signs and symptoms of hypoxia or methaemoglobin levels > 30%.

2. Mechanism of action

Increase the conversion of methaemoglobin to haemoglobin. Therapeutic effects may be seen in 30 minutes.

3. Route & Dosage

Intravenous: 1-2 mg/kg (0.1-0.2 mL/kg of 1% injection). Slow IV injection over 5 minutes.

May repeat in 30-60 minutes.

Flush IV line with 15-30 mL normal saline to reduce injection pain.

Patients with continued production of methaemoglobin from a persistent oxidant stress may require dosing every 6-8 hours for 2-3 days.

Formulation

Available as 50 mg/5mL (1%) ampoule.

4. Contraindications / Special precautions

- G6PD deficiency – treatment with methylene blue is ineffective and can cause haemolysis.
- Methaemoglobin reductase deficiency.
- Severe renal failure.
- Reversal of nitrite-induced methaemoglobinemia for treatment of cyanide poisoning.
- Known hypersensitivity to methylene blue.

5. Adverse effects

- GI upset, headache and dizziness.
- Large doses (> 7 mg/kg) can cause methaemoglobinemia. Doses > 15 mg/kg linked to haemolysis, especially in neonates.
- Extravasation can cause local tissue necrosis.

6. Monitoring parameters / Therapeutic endpoints

Do not repeat if no response after 2 doses, and consider G6PD deficiency or methaemoglobin reductase deficiency.

7. Other considerations

- Pregnancy: FDA Category C, human data suggest some risk in 2nd and 3rd trimesters. Can still be used for severely symptomatic patient.
- Lactation: Safety not established, probably compatible.
- Paediatric: Weight-based dosing.

Octreotide

1. Indications

- Refractory hypoglycaemia from oral hypoglycaemic agent overdose e.g. sulphonylurea, and quinine overdose. Usually administered when hypoglycaemia is refractory to standard therapy with dextrose.
- Non-poisoning use include: acromegaly, pituitary adenoma, pancreatic islet cell tumour, carcinoid tumours, oesophageal varices and secretory diarrhoea (not discussed here).

2. Mechanism of action

Octreotide is a long-acting somatostatin analogue that suppresses insulin, glucagon, and other hormones. It inhibits insulin secretion via G protein-mediated decrease in calcium entry through voltage-dependent calcium channel.

3. Route & Dosage

Subcutaneous route: 75 mcg every 8 hours for 3 doses.

Paediatric: 1 mcg/kg (every 8 hours for 3 doses).

Formulation

Available as 50 mcg/mL, 100 mcg/mL and 1000 mcg/5mL (Octreotide acetate - Sandostatin).

4. Contraindications / Special precautions

None in short term acute use.

5. Adverse effects

- Pain at injection site.
- Anaphylactoid reactions.
- Early transient nausea.
- Late-appearing but longer-lasting diarrhoea or abdominal pain.

6. Monitoring parameters / Therapeutic endpoints

Glucose level should be closely monitored.

7. Other considerations

- Pregnancy: FDA Category B.
- Lactation: Safety unknown.
- Paediatric: Weight-based dosing.

Penicillamine

1. Indications

- Copper toxicity (Wilson's disease).
- Second line for chelation of arsenic, iron, lead, mercury and zinc.
 - Lead poisoning: Used for mild to moderate lead toxicity but has been replaced by succimer in the US.

Non-poisoning indications include use for rheumatoid arthritis and scleroderma (not discussed here).

2. Mechanism of action

It is derived from penicillin. It binds to various heavy metals and the complex formed is water-soluble, which is then excreted by the kidney as sulphide conjugates.

3. Route & Dosage

Oral:

- 4-7 mg/kg/dose - 4 times a day. Usual adult dose is 250 mg four times a day.
- Maximum adult daily dose is 2 g.
- Months of therapy may be required.
- Start at lower dose range and titrate upwards if needed.

Formulation

Available as 250 mg capsules. Supplement with pyridoxine (when used in Wilson's disease).

4. Contraindications / Special precautions

- Penicillin allergy.
- Pregnancy.
- Renal failure.
- Cadmium poisoning.

5. Adverse effects

- Cutaneous hypersensitivity: Erythematous skin reaction.
- Systemic hypersensitivity: Fever, proteinuria, hematuria, erythema multiforme.

- Haematological: Bone marrow hypoplasia – thrombocytopenia, leucopenia, fatal agranulocytosis.
- Neurological: Myasthenia gravis, peripheral neuropathy.
- Others: Goodpasture’s syndrome, hepatotoxicity, pancreatitis.

6. Monitoring parameters / Therapeutic endpoints

- Weekly blood counts and urinalysis.
- Weekly urine and blood testing for metal concentration for titration to target value.

Therapy should be ceased if significant cutaneous reactions, abnormal urinalysis or falling WBC or platelet counts occurs.

7. Other considerations

- Pregnancy: FDA Category D.
- Lactation: Unsafe.
- Paediatric: Same as adults, use lower doses (4 mg/kg/dose) to minimize adverse effects.

Physostigmine

1. Indications

Severe anticholinergic syndrome characterized by urinary retention, severe sinus tachycardia, hyperthermia with absent sweating, delirium and agitation.

2. Mechanism of action

Reversible inhibitor of acetylcholinesterase, thereby increasing concentration of acetylcholine and its effects on nicotinic and muscarinic receptors.

3. Route & Dosage

Adult: 0.5- 2 mg via slow IV bolus (not faster than 1 mg/min).

Usual adult total dose: 4 mg.

Children: 0.02 mg/kg slow IV bolus (not faster than 0.5 mg/min).

May repeat dose every 10-30 minutes if inadequate response, or to prevent recurrence due to the short half-life of physostigmine.

Rapid administration may cause bradycardia, hypersalivation, respiratory difficulties and seizures.

Do not administer as IM injection or as a continuous IV infusion.

Atropine should be available to correct excessive muscarinic activity.

Formulation

Available as 2 mg/2mL ampoule.

4. Contraindications / Special precautions

- Use in cyclic antidepressant overdose.
- Concurrent use with depolarizing neuromuscular blockers.
- Known hypersensitivity to physostigmine.
- Caution in asthma, peripheral vascular disease, intestinal or bladder obstruction and cardiovascular disease.
- Bradyarrhythmias, intraventricular block, AV block and bronchospasm.

5. Adverse effects

- Asystole, bradycardia, heart block.
- Seizures (with rapid administration).
- Diarrhoea, nausea, vomiting, hypersalivation.
- Bronchospasm, bronchorrhoea.
- Muscle weakness, twitching.

6. Monitoring parameters / Therapeutic endpoints

Onset of action usually within minutes. Monitor ECG, respiratory rate, muscarinic and antimuscarinic symptoms. Therapeutic endpoint is resolution of delirium.

7. Other considerations

- Pregnancy: FDA Category C. Transient muscular weakness has been observed in newborns of mothers with myasthenia gravis given physostigmine.
- Lactation: Safety not established.
- Paediatric: Weight-based dosing.
- Drug interactions: Potentiate effects of depolarizing neuromuscular blockers. Additional slowing of cardiac conduction in cyclic antidepressants, beta-blocker and calcium-channel blocker overdoses.

Protamine

1. Indications

Reversal of anticoagulant effects of unfractionated heparin or low molecular weight heparins (LMWH).

2. Mechanism of action

Cationic protein that rapidly binds to heparin, forming an inactive complex. May also act as an anticoagulant by inhibiting thromboplastin.

3. Route & Dosage

Unfractionated heparin

One mg of protamine will neutralize about 100 units of unfractionated heparin. However, dose also depends on time elapsed since heparin administration.

Time elapsed	Dose of protamine (per 100 units of heparin)
Immediate	1-1.5 mg
30-60 minutes	0.5-0.75 mg
2 hours or longer	0.25-0.375 mg

- If heparin was given by continuous infusion: 25-50 mg of protamine.
- If heparin was given by subcutaneous injection: 1-1.5 mg of protamine per 100 units of heparin. Give a portion (25-50 mg) as a slow IV bolus, with the remainder as a continuous infusion over 8-16 hours.
- Unknown dose of heparin: 25-50 mg of protamine initially, and check aPTT to determine need for additional doses.

Low molecular weight heparins

- Protamine neutralizes about 60% of anti-factor Xa activity of LMWH.
- Within first 8 hours: 1 mg of protamine per 100 anti-factor Xa units of LMWH.
- (For enoxaparin [Clexane], 1 mg of protamine per 1 mg of enoxaparin). Smaller doses may be used if the LMWH was injected more than 8 hours ago.
- If bleeding continues after 1st dose of protamine, a second dose of 0.5 mg per 100 anti-factor Xa units should be given.
- Effects of LMWH may be prolonged in patients with renal impairment.
- Protamine may be given as a slow IV bolus injection, at a rate not exceeding 5 mg/min.

Formulation

Available as 50 mg/5mL ampoule.

4. Contraindications / Special precautions

- Known hypersensitivity to protamine.
- Diabetic patients on protamine-containing insulins (e.g. NPH, Insulatard, Mixtard, Novomix) may be at increased risk for hypersensitivity reaction.

5. Adverse effects

- Rapid administration can lead to hypotension, bradycardia, flushing and anaphylactoid reactions.
- Heparin rebound effect with bleeding may occur within 8 hours of protamine use.
- Excessive protamine doses can increase anticoagulation.

6. Monitoring parameters / Therapeutic endpoints

Onset of action is almost immediate and lasts for about 2 hours. Monitor aPTT (for unfractionated heparin) and signs of bleeding.

7. Other considerations

- Pregnancy: FDA Category C. Maternal benefit outweighs foetal risks.
- Lactation: Likely compatible.
- Paediatric: Dosed based on amount of heparin or LMWH.

Pyridoxine (Vitamin B₆)

1. Indications

- To control seizures due to isoniazid, hydrazine or monomethylhydrazine overdoses.
- Adjunct therapy for ethylene glycol overdose.

2. Mechanism of action

Pyridoxine is a co-factor in many enzymatic reactions. Overdose of isoniazid and hydrazine interfere with pyridoxine utilization in the brain, which ultimately leads to seizures because of GABA depletion. Administration of high doses of pyridoxine can overcome this.

In ethylene glycol poisoning, pyridoxine can enhance the conversion to non-toxic metabolites.

3. Route & Dosage

Isoniazid overdose:

Intravenous: 1 g of pyridoxine for each gram of isoniazid ingested.

If unknown amount ingested, give 4-5 g and repeat every 5-20 minutes if needed. The total dose given should be monitored.

May dilute in dextrose or normal saline and run at 0.5-1 g/min until seizures stop. Remainder of dose can then be infused over 4-6 hours.

Monomethylhydrazine overdose:

Intravenous: 25 mg/kg, repeat as needed.

Ethylene glycol poisoning:

Intravenous/IM: 50 mg every 6 hourly until intoxication resolved.

Pyridoxine should be given together with a benzodiazepine to achieve rapid control of seizures.

Formulation

Available as 100 mg/mL ampoule.

4. Contraindications / Special precautions

Known hypersensitivity to pyridoxine.

5. Adverse effects

Large doses may induce sensory neuropathy and seizures. A safe maximum dose has not been established.

6. Monitoring parameters / Therapeutic endpoints

Monitor seizure control in isoniazid and hydrazine poisoning. Monitor for acidosis and ethylene glycol levels in ethylene glycol poisoning.

7. Other considerations

- Pregnancy: FDA Category A.
- Lactation: Compatible.
- Paediatric: Recommended initial dose not to exceed 70 mg/kg.

Sodium Nitrite

1. Indications

Cyanide toxicity.

2. Mechanism of action

Nitrite oxidizes the iron moiety in haemoglobin to form methaemoglobin. Cyanide binds preferentially to methaemoglobin to form cyanomethemoglobin, which is then converted to thiocyanate by rhodanese enzyme. The sulfur moiety is supplied by sodium thiosulphate and the thiocyanate compound is then excreted via the kidneys.

3. Route & Dosage

Intravenous route

- Adults: Give 300 mg over 2-4 minutes. (10 mL of 3%w/v injection.)
- Paediatric: Give 0.33 mL/kg to maximum dose of 10 mL.

A second dose (full or half dose) may be given if there is ongoing cyanide toxicity. This depends on the haemoglobin level, methaemoglobin level and the clinical state of the patient.

Amyl nitrite pearls

Glass ampoules are crushed and intermittently inhaled until intravenous sodium nitrite is available.

Formulation

Available as 300 mg, 3% w/v 10 mL ampoules.

Amyl nitrite pearls, sodium nitrite and sodium thiosulphate ampoules are available together in commercial cyanide antidote kits.

4. Contraindications / Special precautions

Severe anaemia

5. Adverse effects

- Hypotension.
- Severe methaemoglobinemia.

6. Monitoring parameters / Therapeutic endpoints:

Monitor the clinical state of the patient and the methaemoglobin level.

7. Other considerations

- Pregnancy: FDA Category C.
- Lactation: Safety unknown.
- Paediatric: Weight-based dosing.

Sodium Thiosulphate

1. Indications

- Cyanide poisoning: Can be used alone for mild poisoning cases but should be used with sodium nitrite in severe poisoning cases.
- Prophylaxis against cyanide poisoning during rapid sodium nitroprusside infusion. (Infusion of sodium nitroprusside at rates greater than 2 mcg/kg/min generates cyanide ion faster than the body can normally eliminate it.)

2. Mechanism of action

Supplies the sulfur needed in the rhodanese mediated conversion of cyanide to thiocyanate. Thiocyanate is then eliminated via the kidneys.

3. Route & Dosage

Intravenous route (*for acute cyanide toxicity*):

- Adults: Give 12.5 g (50 mL of 25% w/v solution) at 2.5-5 mL/min.
- Paediatric: Give 1.65 mL/kg up to 50 mL.

A second dose at half the initial dose may be required if the patient does not improve in 30 minutes.

Formulation

Available as 12.5 g ampoules. Can be found together with sodium nitrite and amyl nitrite in commercial cyanide antidote kit.

4. Contraindications / Special precautions

Thiocyanate toxicity can develop in patients with renal impairment.

5. Adverse effects

- Nausea and vomiting.
- Burning sensation at injection sites.
- Localized muscle cramps.

6. Monitoring parameters / Therapeutic endpoints

Monitor for clinical improvement of vital signs and patient's mental state from cyanide toxicity.

7. Other considerations

- Pregnancy: FDA Category C.
- Lactation: Safety unknown.
- Paediatric: Weight-based dosing.

Succimer or 2,3-dimercaptosuccinic acid (DMSA)

1. Indications

- Adult lead poisoning.
- Symptomatic or asymptomatic with blood lead level > 60 mcg/dL.
- Paediatric lead poisoning.
- Symptomatic or asymptomatic with blood lead > 45 mcg/dL.
- Other heavy metal poisonings: mercury, arsenic, bismuth, antimony and copper.

2. Mechanism of action

Succimer is a water-soluble analogue of dimercaprol. It binds to heavy metals ions and the complexes are excreted via the kidney.

3. Route & Dosage

Oral route

- 10 mg/kg three times daily for 5 days.
- Followed by 10 mg/kg twice daily for 14 days.
- Succimer is given after calcium disodium edetate for more severe poisonings.
- Repeat the course if there is rebound in blood lead level due to redistribution from bone stores. It is recommended that two weeks elapse between courses of chelation therapy unless blood concentrations indicate that a more rapid retreatment is necessary.
- Can be given as outpatient basis.

Formulation

Available as 100 mg tabs (not registered in Singapore).

4. Contraindications / Special precautions

- Hypersensitivity.
- Ongoing heavy metal exposure.

5. Adverse effects

- Hypersensitivity reactions.
- Gastrointestinal upset (diarrhoea, nausea, vomiting).
- Transient liver function test (LFT) abnormalities.
- Reversible neutropenia (rare).

6. Monitoring parameters / Therapeutic endpoints

Check blood lead level after completion of initial course. Monitor LFTs at baseline and at least weekly, particularly in patients with history of liver disease.

7. Other considerations

- Pregnancy: FDA Category C. (Consider using calcium disodium edetate in pregnant patients instead.)
- Lactation: Safety not established.
- Paediatric: Lower threshold for starting succimer.

Thiamine (Vitamin B₁)

1. Indications

- Empiric therapy to treat or prevent Wernicke-Korsakoff syndrome in alcoholic or malnourished patients, and patients with altered mental status of unknown etiology.
- Adjunctive treatment in patients poisoned with ethylene glycol.

2. Mechanism of action

Thiamine is an essential co-factor for carbohydrate metabolism, and also aids in the metabolism of glycolic acid that is produced in ethylene glycol overdoses. Deficiency results in beriberi and Wernicke-Korsakoff syndrome.

3. Route & Dosage

Slow IV (over 5 minutes) or IM injection.

Adults: 100 mg

May repeat every 8 hours if needed.

Doses of up to 1000 mg have been given over the first 12 hours in patients with persistent neurologic abnormalities.

Usually given together with dextrose infusions for patients with altered mental status.

Formulation

Available as 100 mg/mL ampoule and 10 mg tablet.

4. Contraindications / Special precautions

Known hypersensitivity to thiamine.

5. Adverse effects

Rare – anaphylactoid reactions (vasodilation, hypotension, weakness, angioedema) associated with rapid IV injections.

6. Monitoring parameters / Therapeutic endpoints

Monitor clinical signs and symptoms.

7. Other considerations

- Pregnancy: FDA Category C for therapeutic doses.
- Lactation: Likely compatible.
- Paediatric: Dosing is not well-defined.

Vitamin K₁ (Phytomenadione)⁵²⁵⁻⁵²⁶

1. Indications

Excessive anticoagulation caused by warfarin, and other coumarin and indanedione derivatives.

2. Mechanism of action

Increases hepatic synthesis of clotting factors II, VII, IX, X by reducing the inhibitory effect of the anticoagulants.

3. Route & Dosage

- *No significant bleeding*

INR 5-9: Oral Vitamin K 1-3 mg (Paediatric: 0.3 mg/kg, maximum 10 mg).

INR > 9: Oral Vit K 3-5 mg. Re-check INR and give additional Vit K if needed.

- *Serious bleeds*

10 mg in 50 mL dextrose 5% given as slow IV infusion over 30 minutes. May repeat every 12 hourly if needed.

High doses (e.g. 10 mg) are effective but may lead to warfarin resistance for more than a week. The use of smaller titrated doses for patients requiring therapeutic anticoagulation is recommended.

IV route should be reserved for patients who require rapid reversal of anticoagulation.

Formulation

Available as 10 mg/mL ampoule. Oral vitamin K is prepared by dilution of the ampoule. Not to be given IM.

4. Contraindications / Special precautions

Known hypersensitivity to phytomenadione.

5. Adverse effects

Anaphylactoid reactions with IV administration.

6. Monitoring parameters / Therapeutic endpoints

Onset of action: A few hours after parenteral administration, with peak activity 1-2 days later. Re-check INR at least 6 hourly if there was severe bleeding.

Concomitant blood product should be given if there is active bleeding and INR > 9.

7. Other considerations

- Pregnancy: FDA Category C. Can be used in a severely symptomatic patient.
- Lactation: The American Academy of Pediatrics classifies vitamin K₁ as compatible with breastfeeding.
- Paediatric: Dosed based on INR and clinical presentation. Usual dose: 0.3 mg/kg, maximum 10 mg.

Annex B Serum toxicity ranges and toxicology laboratory services in Singapore

Therapeutic and reported toxic concentrations of some common drugs⁵²⁷⁻⁵³⁷

Therapeutic level refers to the concentration of a drug attained in blood/plasma/serum following therapeutically effective dosage in humans.

Toxic concentration refers to the concentration of a drug/metabolite/chemical present in blood/plasma/serum that is associated with serious toxic symptoms.

Inter-individual deviation as a result of sex, age, adsorption difference, tolerance, condition of health, etc is high. Different laboratories may also use slightly varied reference levels. Therefore, the values listed in the table can only be taken as a guideline in evaluating a given case.

Level written as (10-) 20-35 (-50) means: normally between 20-35 µg/mL, but some authors or clinicians are using ranges between 10 and 50 µg/mL.

Compounds	Blood / Serum / Plasma	Normal / Therapeutic level (in µg/mL unless otherwise specified)	Critical / Reported Toxic level (µg/mL)	Service Provider*
Acetubtolol	S	0.2 – 1.5	>15	
Acetaminophen	See paracetamol			
Acetazolamide	P	10 – 15 (-20)	25 – 30	
Acetone (in mg/dL)	B	Diabetes: 0.5 – 2	10 – 40	
Alprazolam	S	0.005 – 0.05 (-0.1)	0.1 – 0.4	
Aluminium (in µmol/L)	S	> 12 years: 0 – 0.73	-	SGH
Amikacin	S	Trough: 0 – 5 (-10) Peak: (20-) 15 – 25 (-30)	Peak > 35; Trough > 5	AH, CGH, KKH, KTPH, SGH, TTSH
Amiodarone	P	(0.5-) 1 – 2 (-2.5)	2.5 – 3	
Amisulpride	P	<0.4 (1)	10	
Amitriptyline	-	0.05 – 0.3	0.5 – 0.6	

Compounds	Blood / Serum / Plasma	Normal / Therapeutic level (in µg/mL unless otherwise specified)	Critical / Reported Toxic level (µg/mL)	Service Provider*
Amphetamine	S	(0.02-) 0.05 – 0.15	0.2	
Atenolol	S/P	0.1 – 1	>2	
Atropine	S/P	0.002 – 0.03	0.1	
Benzhexol (=trihexyphenidyl)	S	0.05 – 0.2	0.5	
Bisoprolol	S	0.01 – 0.06	-	
Bromazepam	S/P	0.08 – 0.2	>0.3	
Brompheniramine	S	0.005 – 0.015	0.2 ^a	
Bupivacaine	P	(0.25-) 0.5 – 1.5 (-2)	2 – 4	
Buprenorphine	S	0.001 – 0.01	0.2	
Bupropion	B	0.05 – 0.1	>0.17	
Caffeine	S	3 – 15	-	HSA, SGH
Carbamazepine	S	4 – 12	>20	HSA, NUH, SGH, TTSH,
Carbinoxamine	P	~0.02 – 0.04	-	
Carboxyhemoglobin, HbCO	B	Non-smokers <3%; Smokers: 4 – 10%	25 – 35%	HSA, TTSH
Chloramphenicol	S	Trough: 5 – 10; Peak: 10 – 20	>25	
Chlordiazepoxide	P	0.4 – 4	>3	
Chloroquine	P	0.02 – 0.2	>0.6	
Chlorpheniramine	S/P	0.003 – 0.02	0.5 (B)	
Chlorpromazine	S/P	0.01 – 0.3; 0.5b 0.04 – 0.08 (child)	0.5 – 1; 1 (B)	
Chlorpropamide	S/P	30-150	>200	
Chlorthalidone	P	0.14 – 1.4; 5 – 10 (B)	~2	
Cholinesterase, serum	S	5500 - 12000 U/L (>12 years old)	-	SGH
Cholinesterase, RBCc	B	15000 – 24000 U/L RBC (>12 years old)	-	SGH

Compounds	Blood / Serum / Plasma	Normal / Therapeutic level (in µg/mL unless otherwise specified)	Critical / Reported Toxic level (µg/mL)	Service Provider*
Citalopram	P	0.02 – 0.2	-	
Clobazam	S	0.1 – 0.4	-	
Clomipramine	S/P	(0.02-) 0.09 – 0.25 (-0.4)	0.4 – 0.6	
Clonazepam	P	0.02 – 0.07	>0.1	
Clozapine	S/P	0.1 – 0.5	0.6	
Codeine	S	Trough: 0.01 – 0.05; Peak: 0.05 – 0.25	0.3 – 1	
Colchicine	S	0.0003 – 0.003	0.005	
Copper (in µmol/L)	S	11.8 – 22.8	-	SGH
Copper (in µmol/day)	U	0.2 – 0.9	-	SGH
Cyanide	B	“normal”: 0.001 – 0.006; smokers: 0.005 – 0.012 (-0.15)	>0.5	
Cyclosporine A Monoclonal	B	Renal Transplant (12hr after dose): 0.1 – 0.4 (24hr after dose): 0.1 – 0.2 Cardiac Transplant (12hr after dose): 0.1 – 0.3 (24hr after dose): 0.1 – 0.2 Hepatic Transplant (12hr after dose): 0.1 – 0.4 Bone Marrow Transplant (12hr after dose): 0.1 – 0.25	-	SGH
Cyproheptadine	P	<0.05	-	
Dapsone	S	0.5 – 5	10 – 20	
Desalkylflurazepam	B	0.04 – 0.06	>0.5	

Compounds	Blood / Serum / Plasma	Normal / Therapeutic level (in µg/mL unless otherwise specified)	Critical / Reported Toxic level (µg/mL)	Service Provider*
Dextromethorphan	S	0.01 – 0.04	>0.1	
Diazepam	B	0.055 – 0.55	>1.5	
Diclofenac	P	0.5 – 3	>50	
Dicyclomine	P	<0.1	~0.2	
Digoxin (in ng/mL)	S/P	(0.8-) 0.9 – 2.0 (2.2)	>4	AH, CGH, KTPH, NUH, SGH, TTSH
Diltiazem	S	0.05 – 0.4	0.8	
Diphenhydramine	P	0.1 – 1	>1	
Dothiepin	S	0.02 – 0.4	0.8	
Doxepin	P	0.02 – 0.15	>0.1	
Doxylamine	P	<0.2	>0.5	
Ephedrine	S/P	0.02 – 0.1	1	
Estazolam	P	<0.2	-	
Ethanol (in mg/dL)	B	-	>100	
Ethylene glycol (in mg/dL)	P	-	>20	
Etomidate	B	0.16 – 1.6	-	
Everolimus	B	3 – 8	-	SGH
Fenfluramine	P	0.05 – 0.15	>0.5	
Fentanyl	S/P	0.001 – 0.002	0.003	
Flecainide	P	0.2 – 1	2 – 3	
Fluconazole	S	5 – 15	>20	
Fluoxetine	P	<0.5	>1	
Flurazepam	B	0.0005 – 0.03	>0.2	
Fluvoxamine	P	0.05 – 0.25	-	
Frusemide	S	2 – 5(-10)	25 – 30	
Gabapentin	S/P	2 – 20	>50	

Compounds	Blood / Serum / Plasma	Normal / Therapeutic level (in µg/mL unless otherwise specified)	Critical / Reported Toxic level (µg/mL)	Service Provider*
Gentamicin	S	Trough: 0 – 2 Peak: 5 – 10 (-12)	Trough: > 2 Peak: >12	CGH, KKH, SGH, TTSH
Glibenclamide = Glyburide	P	<0.05 (diabetics)	>0.1	
Gliclazide	P	<4 (diabetics)	-	
Glipizide	P	<1	>2	
Griseofulvin	P	<2.5	-	
Guaifenesin	B	0.3 – 1.4	-	
Haloperidol	S	<0.05	>0.05 (B)	
Hydrochlorothiazide	S/P	0.074 – 0.45	-	
Hydroxychloroquine	P	<0.5	>2	
Hydroxyzine	S/P	0.03 – 0.09	0.1	
Ibuprofen	S	15 – 30	>100	
Imipramine	S	0.045 – 0.15	0.4 – 0.5	
Indomethacin	P	0.5 – 3	>5	
Isopropanol (in mg/dL)	B	-	20 – 40	
Ketamine	S	0.5 – 6.5	7 (abuse)	
Ketoprofen	P	<20	-	
Ketorolac	S	0.22 – 3.5	>5 (P)	
Lamotrigine	P	<10	>15	
Lead (in µmol/L)	B	<12 years: <0.48 ≥13 years: <0.97	-	SGH
Levetiracetam	S	10 – 37		
Lidocaine	P	2-5	>6	
Lithium (in mmol/L)	S	>12 years: 0.6 – 1.2	>10	CGH, SGH
Lorazepam	P	0.05 – 0.24	0.3 – 0.6	
MDA	P	-	>1	
MDMA	P	-	>0.35	
Mefenamic acid	P	<20	>25	
Melitracen	-	0.01 – 0.1	-	

Compounds	Blood / Serum / Plasma	Normal / Therapeutic level (in µg/mL unless otherwise specified)	Critical / Reported Toxic level (µg/mL)	Service Provider*
Meloxicam	-	0.4 – 2	-	
Metformin	P	<4 (diabetics)	>40	
Methadone	P	<0.1 (single dose); <1 (maintenance therapy)	>1	
Methaemoglobin	B	0 – 1.0%	-	TTSH
Methamphetamine	B	-	>0.1d	
Methanol (in mg/dL)	B	Endogenous, dietary < 0.15	>20	
Methotrexate	S	No reference available	-	SGH
Metoclopramide	P	<0.15	-	
Metoprolol	S/P	0.02 – 0.6	1	
Metronidazole	P	<20	-	
Midazolam	B	0.032 – 0.2	>1	
Mirtazapine	S	0.02 – 0.1 (-0.3)	-	
Moclobemide	P	<2	>20	
Morphine	B	0.01 – 0.07	-	
Mycophenolic acid	P	Trough: 2 – 4	-	HSA, SGH,
Naproxen	S	20 – 50	>200	
Nevirapine	P	Peak: 4 – 7	-	
Nifedipine	S	0.02 – 0.1	0.15 – 0.2	
Nitrazepam	P	0.03 – 0.07	>0.2	
Nordiazepam	B	0.01 – 1.05	-	
Nortriptyline	P	0.02 – 0.2 (0.05 – 0.15)	0.5	
Orphenadrine	S	0.1 – 0.2	>0.5	
Oxycodone	P	<0.05	>0.2	
Papaverine	P	<2	-	

Compounds	Blood / Serum / Plasma	Normal / Therapeutic level (in µg/mL unless otherwise specified)	Critical / Reported Toxic level (µg/mL)	Service Provider*
Paracetamol (= Acetaminophen)	S	10 – 20	4hr post ingestion: >200 16hr post ingestion: >30	AH, CGH, HSA, KTPH, KKH, NUH, SGH, TTSH
Paraquat	P	-	6hr post ingestion: >0.6 24hr post ingestion: >0.1	
Paroxetine	S	0.01 – 0.075	>0.4	
Pentazocine	B	0.03 – 0.15	>0.5	
Pentobarbitone	B	1.0 – 3.2	>8	
Pentoxifylline	S/P	0.5 – 2	-	
Pethidine = Meperidine	P	0.2 – 0.8	>2	
Phenobarbitone (=Phenobarbital)	S/P	(10-) 15 – 30 (-40)	-	AH, HSA, KTPH, SGH, TTSH
Phentermine	S	0.03 – 0.1	>0.9	
Phenylbutazone	P	50 – 100	>100	
Phenytion	S	10 – 20	>20	AH, CGH, HSA, KTPH, NUH, SGH, TTSH
Pholcodine	P	<0.2	-	
Piroxicam	P	5 – 10	-	
Prochlorperazine	P	<0.05	>0.3	

Compounds	Blood / Serum / Plasma	Normal / Therapeutic level (in µg/mL unless otherwise specified)	Critical / Reported Toxic level (µg/mL)	Service Provider*
Promethazine	P	<0.1	>1	
Propofol	B	0.23 – 1.07	-	
Propoxyphene	S	0.05 – 0.75	>1	
Propranolol	P	0.05 – 1.0	>2	
Propyphenazone	S	3 – 12	-	
Propylthiouracil	P	<5	-	
Pyrazinamide	S	30 – 75	-	
Pyrimethamine	P	<1	-	
Quetiapine	P	<0.6	-	
Quinine	P	3 – 7	>10	
Risperidone	P	0.02 – 0.06	-	
Ropivacaine	P	<5	-	
Salbutamol	P	<0.02 (inhaled dose); <0.2 (oral dose)	-	
Salicylic acid	S	Rheumatism: (child 150-) 200-300; Anticoagulant: 50-125	>300	
Salicylates (in µg/mL)	S	-	Toxic > 300, Lethal > 600	AH, CGH, KTPH, NUH
Salicylates (in mmol/L)	S	0 – 1.5	-	KKH, SGH, TTSH
Sertraline	S	0.05 – 0.25	-	
Sildenafil	P	<0.5	-	
Sirolimus	B	Trough: 0.005 – 0.015	-	SGH
Sulphamethoxazole	P	<60	>200	
Sulphasalazine	S/P	5 – 30	>50	
Sulpiride	S	0.04 – 0.6	-	
Tacrolimus (FK506)	B	0.005 – 0.02	-	SGH

Compounds	Blood / Serum / Plasma	Normal / Therapeutic level (in µg/mL unless otherwise specified)	Critical / Reported Toxic level (µg/mL)	Service Provider*
Theophylline	S	(8-) 10 – 20	25 – 30	AH, CGH, HSA, KTPH, SGH, TTSH
Thiopentone	B	1 – 42	-	
Thioridazine	S	0.2 – 1	>2 (B)	
Ticlopidine	P	<1	-	
Tolbutamide	S/P	40 – 100	100 – 500	
Toluene	B	-	>1	
Topiramate	P	<30	-	
Tramadol	B	0.1 – 0.8	>1	
Trazodone	B	0.5 – 2.5	>4	
Trifluoperazine	P	<0.05	>0.1	
Trimethoprim	P	1.5 – 2.5	>20 (P)	
Trimipramine	S	0.01 – 0.3	>0.5	
Tripolidine	P	<0.05	-	
Valproic acid	S	(40-) 50 – 100	>120	AH, CGH, HSA, KTPH, KKH, SGH, TTSH
Vancomycin	S	Trough: 5 – 10 Peak: (20-) 30 – 40	Trough: >15 Peak: >50	AH, CGH, KTPH, KKH, SGH, TTSH
Venlafaxine	P	0.25 – 0.75 (sum)	>1 (B)	
Verapamil	S	0.02 – 0.35	>0.9	
Warfarin	S/P	1 – 7	>10	
Zinc (in µmol/L)	S	13.8 – 22.3	-	SGH
Zolpidem	S	0.08 – 0.15	>0.5	
Zopiclone	S	0.01 – 0.05	>0.15	

Note:

B: Whole blood

P: Plasma

RBC: Red Blood Cell

S: Serum

U: Urine

sum: Refers to the sum of the concentrations of parent drug and active metabolites

^a Case report

^b Surgical anaesthesia

^c Measured parameters: RBC Cholinesterase and Packed Cell Volume

^d Blood methamphetamine levels $>0.1 \mu\text{g/mL}$ have been associated with driving impairment (typical driving behaviours noted include speeding, weaving, drifting out of lane of travel, and erratic driving).

* The test can be provided by the Analytical Toxicology Laboratory, Health Sciences Authority, unless otherwise indicated. Please note that the panel of tests offer by each laboratory may change with time.

AH Alexandra Hospital, Department of Laboratory Medicine
Tel: 6379 3301

CGH Changi General Hospital, Department of Laboratory Medicine
Tel: 6850 4960

HSA Health Sciences Authority, Analytical Toxicology Laboratory
Tel: 6213 0740

KKH KK Women's and Children Hospital, Department of Pathology and
Laboratory Medicine
Tel: 6394 1352

KTPH Khoo Teck Puat Hospital, Department of Laboratory Medicine
Tel: 6602 2321/2

NUH National University Hospital, Department of Laboratory Medicine
Tel: 6772 4346

TTSH Tan Tock Seng Hospital, Department of Laboratory Medicine
Tel: 6357 8939

SGH Singapore General Hospital, Department of Pathology, Biochemistry
Section
Tel: 6321 4920

Annex C Socio-psychiatric aspects of poisons management

The psychosocial aspect of poisons management is usually complex and also depends on whether it is an act of attempted suicide or not. There is a difference between patients who have actually attempted suicide and failed in the attempt and those who have engaged in parasuicide or non-fatal deliberate self-harm.

While initial and immediate management of patients focuses on the medical problems caused by the attempt, precautions must be taken concurrently to ensure that the patient does not have the means to make a second attempt.

Besides a brief psychiatric history, a social history must be taken to identify social problems that triggered the attempt to self harm. However, it is not easy to assess such patients as they can remain uncommunicative and even hostile.

The Suicide Intervention Handbook[§] suggests guidelines that can help you to identify “Invitations to Help”. These signs and indications essentially help you to ways to activate follow up. Referrals could be made to the Medical Social Worker in the hospital or a Family Service Centre in the community.

“Invitations to Help” can be identified as you are attending to the patient’s immediate needs. You can look out for these invitations using this guide:

Learn about	Situations	Relationship problems, work problems / failing grades, trouble with the law, recent suicide and violence much publicized, almost anything else, depending on how the person feels about it.
Ask about	Physical changes	Lack of interest / pleasure in all things, lack of physical energy, disturbed sleep, change / loss of sexual interest, change / loss of appetite, weight, physical health complains.
Observe	Behaviours	Crying, emotional outbursts, alcohol / drug misuse, recklessness, fighting / law breaking, withdrawal, dropping out, prior suicidal behaviour, putting affairs in order.

[§] Ramsey RF. Suicide Intervention Handbook. LivingWorks Education Inc., 1999.

Listen for	Thoughts	Escape, no future, guilt, alone, damaged, helpless, preoccupied, talk of suicide or death, planning for suicide.
Sense	Feelings	Desperate, angry, sadness, shame, worthlessness, loneliness, disconnectedness, hopelessness.

When you observe behaviours that imply a cry for help, you can refer to these **“Ways to Explore Invitations”** for help:

Stress	<p>A person’s interest in talking about life events could be an invitation to help prevent suicide.</p> <ul style="list-style-type: none"> • Disruptive life events, particularly those experienced as an intolerable loss, may be accompanied by thoughts of suicides. • A loss that seems trivial to an adult can be a life-threatening crisis for an adolescent. 	<p>To determine the severity of a life event, ask about the person’s feelings about and view of the loss.</p> <p><i>“How are you feeling about the things that have happened to you?”</i></p>
Reactions	<p>Changes in behaviour, physical condition, thoughts or feelings can be invitations to help. The more those symptoms convey themes of hopelessness, helplessness and isolation, the greater the likelihood that thoughts of suicide may be involved.</p>	<p>To find out if this theme is present, ask the person.</p> <p><i>“Sounds like you might be feeling hopeless (helpless, alone) right now, is that correct?”</i></p>
Thoughts of Suicide	<p>Thoughts of suicide are the clearest invitations to help prevent suicide. These thoughts may not be directly or openly stated. When they are, they are often stated in a roundabout or indirect way.</p>	<p>To find out if a person is thinking about suicide, ask:</p> <p><i>“Are you thinking about suicide? Are you planning on killing yourself?”</i></p>

Once you identify a suicide risk, do a **“Risk Review”** by asking the following questions:

<p>Current Suicide Plan</p>	<p>A suicide plan includes choice of a method, preparation to carry out the plan, and a timeframe for completing the act. When asked directly, most people who are thinking about suicide will openly and honestly share the details of their plans. The more detailed the plan, the greater is the risk that the plan may be carried out. If the person will not tell you the details of this plan, assume that he has planned in great detail.</p>	<p><i>“Have you thought about how and when you would do it? What have you done about carrying out your plan?”</i></p>
<p>Pain</p>	<p>People with intolerable pain are desperate to end it. Desperation causes anything that might relieve the pain, including suicide, to happen more quickly. Persons who feel less pain or who believe that they have more ways to control their pain is less likely to act quickly. Ask about the person at risk’s view of their pain.</p>	<p><i>“Do you have pain that at times feels unbearable?”</i></p>
<p>Resources</p>	<p>Personal support systems can sustain an individual in times of great personal troubles. Resources might include a satisfactory job; adequate finances; a place to live; caring family or friends; access to psychological or medical help; or memberships in churches; clubs or other social institutions. Supportive resources can effectively lower the risk of suicidal behaviour. The absence of supportive resources can greatly increase the risk of suicide. The person most at risk is someone who is feeling alone and unconnected to others.</p>	<p><i>“Do you feel you have few, if any, resources?”</i></p>
<p>Prior Suicide Behaviour</p>	<p>People who have previously tried to kill themselves are 40 times more at risk of suicide than someone who has never tried before. A prior attempt means that suicide is familiar to the person. Familiar things are more likely to be done again.</p>	<p><i>“Have you ever attempted suicide before?”</i></p>

Mental Health	Persons with a history of mental health problems or those suffering currently with a mental health problem are far more likely to die by suicide or to harm themselves than those who do not have these problems. If the person answers “yes” to the following question, assume that they are more vulnerable to suicide.	<i>“Are you receiving or have you received mental healthcare?”</i>
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Resources / Helplines you can recommend for Crisis Situations

Age Group	Organization	Contact	Available Hours
Elderly	Care Corner	1800 353 5800 www.carecorner.org.sg	10am – 10pm
	Singapore Action Group for Elders	SENIORS Helpline 1800 555 5555	Mon – Fri: 9am – 7pm Sat: 9am – 1pm
All	Samaritans of Singapore	1800 221 4444 www.samaritans.org.sg	24 hours
Mental Health	IMH Helpline	6389 2222	24 hours
	Singapore Association for Mental Health	1800 283 7019 www.samhealth.org.sg	Mon – Fri: 9am – 6pm
For Youths	Youthline	6336 3434	Mon – Fri: 9am – 6pm
	Teen Challenge	6346 9332	Mon – Fri: 10am - 5pm
	Touchline	1800 377 2752	Mon – Fri: 9am – 6pm
	Audible Hearts (by Health Promotion Board)	www.audiblehearts.sg	N.A.
	Pregnancy Crisis Line	6339 9770	24 hours
For Children	Tinkle Friend (12 years old & below)	1800 274 4788	Mon – Fri: 9.30am – 11.30am 2.30pm – 5pm

Annex D Resources for industrial chemical exposure

(I) Useful sources of information to assist diagnosis and management

Useful websites:

- Medical management guidelines for acute chemical exposures:
<http://www.atsdr.cdc.gov/MMG/index.asp>
- General industrial health information on chemicals for workers, employers and occupational health professionals:
<http://www.cdc.gov/niosh/npg/>
- Recognising toxic effects of chemicals from pictograms in Safety Data Sheets (SDS) and labels:
<http://www.unece.org/trans/danger/publi/ghs/pictograms.html>

Common Globally Harmonized System (GHS) pictograms for identification of chemical hazards

GHS pictograms	Hazard Class	Example
	<ul style="list-style-type: none"> • Flammable gas / solid / liquid • Pyrophoric • Self-reactive 	<ul style="list-style-type: none"> • Hydrogen • Acetylene • Toluene • Xylene • Ethanol
	Oxidizers: <ul style="list-style-type: none"> • Oxidising gas / solid / liquid 	<ul style="list-style-type: none"> • Hydrogen Peroxide • Nitric acid • Sulfuric acid
	Health Hazard <ul style="list-style-type: none"> • Acute Toxicity (Severe) 	<ul style="list-style-type: none"> • Hydrogen Cyanide • Hydrogen sulfide • Hydrochloric acid • Toluene
	Corrosives: <ul style="list-style-type: none"> • Skin corrosion • Eye irritation • Corrosive to metals 	<ul style="list-style-type: none"> • Hydrochloric acid • Nitric acid • Sulfuric acid • Sodium Hydroxide • Hydrogen Peroxide

	<p>Warning:</p> <ul style="list-style-type: none"> • Irritant • Skin sensitizer • Acute Toxicity (Harmful) • Narcotic effects 	<ul style="list-style-type: none"> • Acetylene • Xylene • Benzene • Trichloroethylene • Perchloroethylene
	<p>Health Hazard:</p> <ul style="list-style-type: none"> • Carcinogen • Respiratory sensitizer • Reproductive toxicity • Mutagenicity • Target organ toxicity 	<ul style="list-style-type: none"> • Benzene • Trichloroethylene • Perchloroethylene • Asbestos

(II) Relevant legislation

- Workplace Safety and Health Act 2006 and subsidiary regulations
 - Protection of safety, health and welfare of persons at work in workplaces.
- Work Injury Compensation Act
 - Provides a low-cost expedient compensation system that is an alternative to claiming for damages under the common law.

Website: <http://www.mom.gov.sg/legislation/occupational-safety-health/Pages/default.aspx>

Notification of workplace accidents, incidents and occupational diseases to Ministry of Manpower under the Workplace Safety and Health Act (WSHA) and Work Injury Compensation Act (WICA).

A registered medical practitioner who fails to notify the Commissioner for Workplace Safety and Health within 10 days of diagnosing an occupational disease is guilty of an offence and is liable on conviction:

- a) For 1st offence, to a fine not exceeding \$5000
- b) For 2nd or subsequent offence, to a fine not exceeding \$10,000 or imprisonment for a term not exceeding 6 months or to both.

FOR OCCUPATIONAL DISEASES:	FOR FATAL ACCIDENTS AND DANGEROUS OCCURRENCES WHICH REQUIRE IMMEDIATE NOTIFICATION:
<p>Doctor and employer to submit the notification report electronically within 10 days of diagnosis at http://www.mom.gov.sg/iReport for following diseases:</p> <ul style="list-style-type: none"> a) Poisoning from any of the following chemicals: <ul style="list-style-type: none"> • Aniline • Arsenic • Benzene • Beryllium • Cadmium • Carbamate • Carbon bisulphide • Cyanide • Halogen derivatives of hydrocarbon compound • Hydrogen sulphide • Lead • Manganese • Mercury • Organophosphate • Phosphorus 	<p>Employer to notify the Commissioner immediately, by phone or fax: Tel No: 6317 1111 Fax No: 6317 1261</p> <p>Notification should include the following information:</p> <ul style="list-style-type: none"> • Date and time of the accident/ incident; • Place of the accident/ incident; • Name and identification number of the injured/ deceased, if any; • Name of the employer and occupier; • Brief description of the accident/ incident; and • Your name and contact details.

<p>b) Other occupational diseases:</p> <ul style="list-style-type: none"> • Chrome ulceration • Epitheliomatous ulceration • Occupational asthma • Occupational skin disease • Toxic anemia • Toxic hepatitis • Mesothelioma 	
<p>For all suspected cases:</p> <ul style="list-style-type: none"> • If urgent, call 6317 1111. • If non-urgent, refer to <ol style="list-style-type: none"> (1) Toxicology Consultation Clinic, Changi General Hospital Tel No: 6850 3333 (2) Occupational Health Clinic at: <ul style="list-style-type: none"> – Geylang Polyclinic Tel No: 6547 6922; – Hougang Polyclinic Tel No: 6496 6600; or – Jurong Polyclinic Tel No: 6355 3000 	

(III) In the event of spills in the clinic

Check Safety Data Sheet (SDS) for type of personal protective equipment needed and correct method to contain spills

Evacuate if necessary



Activate in-house emergency response team



Contact SCDF/Police (if necessary)



Engage toxic industrial waste collectors licensed by NEA (if necessary)

(IV) Useful local contact numbers

	Tel No.	Webpage address
In-house emergency response no.		
SCDF	995	
Police	999	
Ministry of Manpower – Occupational Safety and Health Division	6317 1111	http://www.mom.gov.sg/iReport
Health Science Authority – Analytical Toxicology Laboratory	6213 0740	http://www.hsa.gov.sg/publish/hsaportal/en/applied_sciences/Illicit_Drugs_Toxicology/Analytical_Toxicology_Laboratory.html
Geylang Polyclinic	6547 6922	
Hougang Polyclinic	6496 6600	
Jurong Polyclinic	6355 3000	
Changi General Hospital – Toxicology Consultation Clinic	6850 3333	http://www.cgh.com.sg/Medical_Specialities/Medical_Services/Pages/AccidentEmergency_toxicology.aspx
List of Toxic Industrial Waste Collectors licensed by NEA		http://app2.nea.gov.sg/data/cmsresource/20090316562565217318.pdf

(V) List of Toxicology Laboratories

<http://www.mom.gov.sg/workplace-safety-health/worker-workplace-surveillance/workers-health-surveillance/Pages/default.aspx>

Annex E Alternative medicine

Introduction

Alternative Medicine (AM) has an important role in the general healthcare of underserved communities, and continues to infuse new ideas and treatment into modern Western medicine for the benefit of our patients. It can play an important complementary role to Western medicine.

Despite the prevalent use of AM products, adverse outcome and death only arise occasionally.⁵³⁸ It is safe to conclude that in most instances dietary supplements and herbal medicines are safe when used appropriately. Nevertheless inappropriate use and use of some formulation can lead to toxicities.

Problem areas

Problems commonly reported regarding AM products include allergic reaction, inappropriate indication, inappropriate dose and duration, intentional adulteration, contamination, inherent toxicities of herbs, variation in the content of active ingredient in these products, and drug-herb or herb-herb interaction (see Tables E.1 and E.2).

In most instances, problems arise due to inappropriate usage of AM. AM products can be toxic when used for inappropriate indications; prepared inappropriately; used in large excessive dosage; or for a prolonged duration of time. Using traditional AM herbs for non-traditional indications like weight-loss, athletic performance and recreation can also lead to toxicities. When patients provide such a history of use, physicians should be on the look-out for possible toxicities.⁵³⁹⁻⁵⁴²

AM products generally do not produce immediate relief of symptoms as most of them are concerned with homeostasis. When products claim to provide immediate relief of symptoms, physicians should watch out for possible intentional adulteration with pharmaceuticals. These products are usually in the form of finished products meant for ingestion or occasionally, for topical applications. Another form of adulteration is the substitution of one herb for another that may be cheaper or more readily available, but has a less desirable safety profile. The most common adulterants are pharmaceuticals that are used to relieve uncomfortable symptoms like non-steroidal anti-inflammatory drugs (NSAIDs) and antihistamines.⁵⁴³⁻⁵⁴⁵ Adulteration with steroids and sexual enhancing drugs like Sildenafil are also commonly reported.⁵⁴⁶⁻⁵⁴⁸

In patients taking multiple medications and AM products, physicians should look out for drug-herb interactions. Patients most at risk of harmful drug-herb interactions are those at extremes of age, on multiple prescriptions, those with chronic illnesses or impaired organ functions, and those on prescription medications with a narrow therapeutic margin (e.g. warfarin).⁵⁴⁹⁻⁵⁵²

AM products that possess pronounced pharmacological effects or toxic constituents can be inherently poisonous. Physicians should anticipate problems with such toxicities if they encounter patients using these products (see Table E.3). The problem of the inherent toxicity can be compounded by variation in content of the active ingredients found in these products. Even in finished products like pills and liquids, there can be large batch-to-batch variation in content, and this can result in toxicity.

Management of patients with toxicities

The approach to patients with toxicities from AM products is similar to the approach to patients with other forms of toxicities. Patients who present with unstable medical conditions require immediate stabilization. Once they are stable, an extended history-taking, physical examination and laboratory investigation can be performed. Once root-cause of the problem is identified as being due to the AM product, then use of the AM product can be stopped and appropriate therapy can be initiated.

Good resuscitative, symptomatic and supportive care is paramount. Patients who present early with toxic ingestion of AM products that can cause life-threatening effects (e.g. *Aconitium* species) should undergo gastric lavage with adequate airway protection. Similarly activated charcoal may be given in acute overdose if there is adequate airway protection.

When obtaining history from patients suspected of suffering from AM toxicities, it is important to remember that patients often do not volunteer important information to their physicians. When AM product-taking behaviour is suspected, physicians need to ask patients specifically if they were or currently are consuming such products. These products could include raw herbs, finished dosage forms, and even specialty teas use for weight loss or calming effects.

Delayed effect or long-term effects, such as hepatotoxicity or nephrotoxicity, may be prevented if the products are identified and stopped early, however immediate identification or analysis is often not possible. Adverse reaction to AM products should be reported to Vigilance Branch of Health Sciences

Authority (Tel 6866 3538), whereupon the Branch may secure samples of the suspect products for testing.

Basic diagnostic studies, such as blood count, electrolytes and renal function, liver function and electrocardiogram should be performed, as well as other tests based on patient's clinical presentation. If symptoms are non-specific or suggestive of heavy metal toxicity, a heavy metal screen may be useful.

Discussing dietary supplements and herbal medicines with patients

Opportunities arise at times to discuss use of AM with patients or patient's family members/caregivers. Physicians trained in Western medicine may find themselves inadequately prepared for this task, or simply denounce all such products. However, such an act may alienate patients and their family members, and may also cause patients to avoid approaching their physicians for help should adverse effects arise.

Ko outlines useful advice for patient education or discussion about AM in general.⁵⁵³ Some points which can be easily committed to memory and applied in discussions are listed:

- (1) AM products should be considered as medicines. Hence a specific dosage recommendation should be followed and long-term unmonitored therapy should be avoided. If unsure whether a product is safe or useful, or if it will interact with one's prescription, always consult a physician or pharmacist first.
- (2) Obtain AM products from reputable sources and licensed practitioners.
- (3) If new symptoms developed during the use of these products, stop using the product and consult a physician.
- (4) Vulnerable patients (e.g. women who are pregnant or nursing, elderly patients, and young children) should use AM products with caution.

Table E.1 – Predisposing Factors and Warning Signals*

Factors Predisposing to Toxicities	Warning signals
Inappropriate usage and inherent toxicity of herbs	Inappropriate indications (non-traditional indications) – weight loss, athletic performance, recreational use.
	Inappropriate duration – use for prolonged periods of time (several weeks to months).
	Inappropriate dosage – excessive dose in order to achieve a desired result.
	Inadequate processing – herbs usually consumed in a certain way were processed in other non-recommended ways.
	Herbs with pronounced pharmacological effects or toxic components.
Adulteration with modern pharmaceuticals (NSAIDs, steroids, antihistamines, sildenafil, sulfonylureas)	Finished AM products claiming fast relief of symptoms or sexual enhancement.
Drug-AM interaction	Patients taking AM together with multiple modern pharmaceuticals (especially drugs with narrow therapeutic index e.g. warfarin). <i>(See Table E-2)</i>
	Patients taking multiple AM and other herbal products.
Heavy metal toxicities	Finished products from questionable/contaminated sources.

**Note that the above table is not exhaustive*

Table E.2 – Some Commonly Reported Drug-AM Interactions in the Literature*

Drug	AM Products and Effects
Warfarin	<p>Increase coagulation: Ginger, ginkgo, garlic, <i>Angelica</i>, willows, coumarin-containing product, St. John's wort.</p> <p>Decrease coagulation: Vitamin C, A, K.</p>
Digoxin	Risk of digoxin toxicities: <i>Digitalis</i> , <i>Thevetia</i> .
Hypnotics / Sedative	Increase sedation: Kava extract, valerian herbs.
Calcium-Channel Blockers (CCB)	Grapefruit juice (large quantities) increases serum level of CCB, which resulted in severe toxicities.
Cyclosporine	<p>Increase serum level: Grapefruit juice (large quantities).</p> <p>Decrease serum level: St. John's Wort.</p>

**Note that the above table is not exhaustive*

Table E.3 – Common products and their adverse effects*

Herbs	Effects
Cardiac	
<i>Aconitum</i> species	Sodium channel effects (widen QRS, shock).
<i>Digitalis</i> species, bufo toads	Digoxin-like effects.
Central Nervous System	
Strychnine, thujone, essential oils (camphor, eucalyptus)	Seizures.
<i>Valeriana</i> species, kava kava	Sedation.
Dermatological	
Cantharidin (Chinese blister beetle)	Burns and blistering .
Hematological	
G-herbs (ginger, garlic, ginkgo)	Coagulopathies.
Colchicine, podophyllotoxin	Agranulocytosis.
Hepatotoxic	
Multiple agents, germander commonly reported	Hepatitis.
Pyrrrolizidine alkaloids (comfrey, <i>Senecio</i> species, <i>Heliotropium</i> species)	Veno-occlusive disease.
Nephrotoxic	
<i>Aristolochia</i> species	Renal failure.
Licorice (a.k.a. liquorice)	Hypertension, hyperkalemia.
Anticholinergic	
<i>Datura metel</i> commonly used in Chinese medicine; <i>Datura stramonium</i> used recreationally in the west; Hexing herbs (<i>Atropa</i> species, <i>Hyoscyamus</i> species, <i>Mandragora officinarum</i>) commonly used in Western alternative medicine.	Dry skin and mucosa, miosis, flushed, tachycardia, urinary retention, delirium, seizures.
Sympathomimetic	
<i>Ephedra</i> species, <i>Citrus aurantium</i> (bitter orange)	Raised BP, tachycardia, AMI, ICH.
Salicylate	
Willow bark, checkerberry	Salicylate toxicity.

*Note that the above table is not exhaustive

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Self-assessment (MCQs)

After reading the Clinical Practice Guidelines, you can claim one CME point under Category 3A (Self-Study) of the SMC Online CME System.

Instruction: Indicate whether each statement is true or false.

- | | True | False |
|---|--------------------------|--------------------------|
| 1. The following antidotes can be used for the following overdose: | | |
| A) Glucagon for beta-blocker overdose | <input type="checkbox"/> | <input type="checkbox"/> |
| B) High dose insulin euglycemia (HIE) treatment for sulphonylurea overdose | <input type="checkbox"/> | <input type="checkbox"/> |
| C) Calcium gluconate for calcium channel blocker overdose | <input type="checkbox"/> | <input type="checkbox"/> |
| D) Sodium bicarbonate for sodium channel blocker medications overdose | <input type="checkbox"/> | <input type="checkbox"/> |
| E) Flumazenil for sympathomimetic agents like amphetamine overdose | <input type="checkbox"/> | <input type="checkbox"/> |
| 2. The following statements about single dose activated charcoal are true: | | |
| A) Single dose activated charcoal is effective for iron poisoning. | <input type="checkbox"/> | <input type="checkbox"/> |
| B) The recommended dose of single dose activated charcoal is 50g for adults or 1g/kg for children. | <input type="checkbox"/> | <input type="checkbox"/> |
| C) Studies have shown that single dose activated charcoal is useful as a gastric decontaminant within 1 hour following ingestion of a potentially toxic amount of a poison. | <input type="checkbox"/> | <input type="checkbox"/> |
| D) In patients with GCS < 8, the airway must be secured BEFORE commencing administration of activated charcoal. | <input type="checkbox"/> | <input type="checkbox"/> |
| E) Combined use of ipecac and activated charcoal is more effective than use of either one of these agents by themselves. | <input type="checkbox"/> | <input type="checkbox"/> |
| 3. The following is/are true of analgesia poisoning: | | |
| A) Serum NSAID levels should be done in patient in patients with seizures with suspected mefenamic acid overdose. | <input type="checkbox"/> | <input type="checkbox"/> |

	True	False
B) Pulse oxymetry is sensitive in detecting early respiratory compromise in a patient on facemask oxygen 10L/min with suspected opioid poisoning.	<input type="checkbox"/>	<input type="checkbox"/>
C) Patients with respiratory insufficiency should be supported with bag mask ventilation and 100 percent oxygen to correct respiratory acidosis before or while naloxone is administered in a patient with suspected opioid poisoning.	<input type="checkbox"/>	<input type="checkbox"/>
D) A 3 year old child can be observed at home if accidentally ingested only 1 mL of medicated ointment with methylsalicylate.	<input type="checkbox"/>	<input type="checkbox"/>
E) Intubation should be done to prevent respiratory fatigue in an alert 50 year old female with witnessed salicylate poisoning presenting with severe shortness of breath and respiratory rate of 46/min.	<input type="checkbox"/>	<input type="checkbox"/>
4. The following is/are true of paracetamol poisoning:		
A) A single acute ingestion of 200mg/kg/day or more for both children and adults is considered toxic ingestion.	<input type="checkbox"/>	<input type="checkbox"/>
B) Repeated oral ingestion totaling 150mg/kg/day for children more than 6 years old or adults with no risk factors is considered toxic ingestion.	<input type="checkbox"/>	<input type="checkbox"/>
C) Activated charcoal via nasogastric tube should be given to a drowsy 40kg adolescent female who took 20 tablets of 500g of paracetamol 2 hours ago.	<input type="checkbox"/>	<input type="checkbox"/>
D) There is no urgent need to start intravenous N-acetylcysteine in a combative patient with severe right abdominal pain with witnessed massive paracetamol ingestion 3 hours ago till serum levels are done with confirmed paracetamol toxicity after 4 hours post ingestion.	<input type="checkbox"/>	<input type="checkbox"/>
E) Once the 3-stage infusion of intravenous N-Acetylcysteine totaling 300mg/kg has been completed in patients with established paracetamol-induced hepatitis, there is no further use in continuing N-acetylcysteine.	<input type="checkbox"/>	<input type="checkbox"/>

	True	False
5. The following is/are true of antihistamine and anticholinergic poisoning:		
A) An asymptomatic 2 year old child who had accidentally ingested a single lomotil tablet should be observed in the hospital for at least 24 hours.	<input type="checkbox"/>	<input type="checkbox"/>
B) ECG, serum creatinine kinase and urine analysis should be done in a patient with diphenhydramine poisoning with tachycardia and myalgia.	<input type="checkbox"/>	<input type="checkbox"/>
C) Orphenadrine toxicity usually cause delirium, sedation, excitation and peripheral anticholinergic effects but no life threatening toxicity.	<input type="checkbox"/>	<input type="checkbox"/>
D) Unlike amphetamine overdose, a delirious patient with anticholinergic toxicity will have tachycardia, hyperthermia delirium and anhidrosis.	<input type="checkbox"/>	<input type="checkbox"/>
E) Sepsis can be easily differentiated from the symptoms of anticholinergic toxicity.	<input type="checkbox"/>	<input type="checkbox"/>
6. The following is/are true of the management of antihistamine and anticholinergic poisoning:		
A) Gastric lavage can be considered in massive anticholinergic overdose.	<input type="checkbox"/>	<input type="checkbox"/>
B) Activated charcoal should be used in an agitated patient with distended abdomen if the anticholinergic overdose occurred 45 minutes ago.	<input type="checkbox"/>	<input type="checkbox"/>
C) The cornerstone in managing moderate to severe anticholinergic poisoning is treatment with cholinergic agents.	<input type="checkbox"/>	<input type="checkbox"/>
D) Physostigmine can be considered in stable but agitated and delirious patients with no known cardiac, reactive respiratory airway disease or underlying cardiac disease with cardiac monitoring in the intensive care.	<input type="checkbox"/>	<input type="checkbox"/>
E) Physostigmine should be used in patients with seizures secondary to anticholinergic overdose.	<input type="checkbox"/>	<input type="checkbox"/>

	True	False
7. The following statements is/are true on acute organophosphate OP poisoning:		
A) Mechanism of toxicity of OP involves inhibition of acetylcholinesterase enzyme activity.	<input type="checkbox"/>	<input type="checkbox"/>
B) Following acute OP exposure, a spot serum acetyl cholinesterase level in the low normal range is indicative of severity of poisoning.	<input type="checkbox"/>	<input type="checkbox"/>
C) In managing OP poisoned patients, personal protection of emergency care providers & decontamination of casualties are key to preventing secondary casualties amongst rescue and healthcare providers.	<input type="checkbox"/>	<input type="checkbox"/>
D) Atropine as an antidote reverses the nicotinic effects of OP poisoning.	<input type="checkbox"/>	<input type="checkbox"/>
E) Carbamates have a similar mechanism of action to OP's but are spontaneously reversible hence do not need atropine.	<input type="checkbox"/>	<input type="checkbox"/>
8. The following statements is/are true about oxime therapy in acute organophosphate (OP) poisoning:		
A) Oximes are theoretically only effective when give early before aging of the OP-enzyme complex.	<input type="checkbox"/>	<input type="checkbox"/>
B) There are several types of oximes including pralidoxime, HI 6, obidoxime with variable effectiveness to different OP types.	<input type="checkbox"/>	<input type="checkbox"/>
C) Current evidence is insufficient to indicate whether oximes are beneficial or harmful in the management of acute organophosphate poisoning in humans.	<input type="checkbox"/>	<input type="checkbox"/>
E) Pralidoxime is contraindicated for poisoning with carbamates.	<input type="checkbox"/>	<input type="checkbox"/>
D) Inadequate dosing and short duration of therapy with oximes are an unlikely cause for development of intermediate syndrome after successful initial therapy of acute OP poisoning.	<input type="checkbox"/>	<input type="checkbox"/>

	True	False
9. The following medication can be used for treating hydrofluoric acid (HF) burn:		
A) Intravenous regional calcium gluconate via Bier's block for fingertip HF burns.	<input type="checkbox"/>	<input type="checkbox"/>
B) Calcium gluconate nebulization for respiratory symptoms from inhalational exposure to HF.	<input type="checkbox"/>	<input type="checkbox"/>
C) Calcium chloride infusion for systemic toxicity caused by HF.	<input type="checkbox"/>	<input type="checkbox"/>
D) Calcium gluconate gel for dermal HF burns.	<input type="checkbox"/>	<input type="checkbox"/>
E) Subcutaneous injection of calcium gluconate for dermal HF burns.	<input type="checkbox"/>	<input type="checkbox"/>
10. Clinical features that suggest serious caustic ingestion include:		
A) Stridor	<input type="checkbox"/>	<input type="checkbox"/>
B) Dysphagia	<input type="checkbox"/>	<input type="checkbox"/>
C) Hematemesis	<input type="checkbox"/>	<input type="checkbox"/>
D) Airway burns	<input type="checkbox"/>	<input type="checkbox"/>
E) Accidental ingestion	<input type="checkbox"/>	<input type="checkbox"/>

Answers:

- 1 A) T
B) F
C) T
D) T
E) F

- 2 A) F
B) T
C) T
D) T
E) F

- 3 A) F
B) F
C) T
D) F
E) F

- 4 A) T
B) T
C) F
D) F
E) F

- 5 A) T
B) T
C) F
D) T
E) F

- 6 A) T
B) F
C) F
D) T
E) F

- 7 A) T
B) F
C) T
D) F
E) F

- 8 A) T
B) T
C) T
D) F
E) F

- 9 All T

- 10 A) T
B) T
C) T
D) F
E) F

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