POISON MANAGEMENT GUIDELINES -2

POISON TREATMENT CENTER

NEW YANGON GENERAL HOSPITAL

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Preface

Poisoning is one of the leading causes of morbidity and mortality in Myanmar. Poison Management Guidelines for ten common poisonings admitted to Poison Treatment Center was published in June, 2020 and distributed to different levels of hospitals in Myanmar. I strongly believe that it was helpful to some extent in emergency management of acute poisoning cases in various regions of Myanmar.

After the COVID-19 pandemic, people all over the world including Myanmar have suffered a variety of financial and social problems and the number of suicidal poisoning cases admitted to Poison Treatment Center has been growing up. Among the admitted cases, it was found that some patients took drugs easily available at home: for example, a granddaughter took all the anti-hypertensive tablets of her grandmother. These drugs include commonly used cardiovascular drugs (e.g., calcium channel blockers, beta-blockers, salicylates and digoxin) and anti-psychotic drugs (e.g., olanzapine, quetiapine). Moreover, as Myanmar is an agricultural country, highly toxic pesticides used in rice storage areas such as aluminium phosphide was found to be the culprit of high morbidity and mortality in some patients. Because of global warming and air pollution, Myanmar was no exception to suffer from extremely hot weather during last summer and a number of fire outbreaks occurred despite precautions. Victims of fire outbreaks were admitted to hospitals with carbon monoxide poisoning, associated with cyanide poisoning in some cases. Besides, people living in small flats used to have carbon monoxide poisonings after using portable electrical generators in closed doors.

All the above mentioned poisonings seem to be less common than the poisonings described in the first book but all of them are deadly poisonous. Therefore, this book is a collection of management of less common but serious poisoning cases in Myanmar with locally available resources. For the completeness, the guidelines included standard investigations and treatment which are not currently available in our country. With all our dedicated efforts, I sincerely hope that this book will be a support for all the healthcare providers in different levels of medical care in Myanmar.

With best wishes,

Prof Thin Thin Nwe

Authors

Prof Thin Thin Nwe
MBBS, MMedSc (Int Med), MRCPI,
FRCPI, FRCP (Glasg), FRCP (Edin), FRCP (London),
DrMedSc (General Medicine), Dip.Med.Ed
Professor and Head
Department of Medicine
University of Medicine (1) Yangon
New Yangon General Hospital

Dr Thi Thi Tun
MBBS, MMedSc (Int Med),
DrMedSc (General Medicine),
MRCP (UK), FRCP (Glasg), FRCP (Edin),
Consultant Physician
Poison Treatment Center
New Yangon General Hospital

Carbon Monoxide Poisoning

Carbon monoxide is a colourless, odourless, flammable gas formed by incomplete combustion of carbon containing products such as diesel oils, petroleum products, domestic gas or solid fuels, including charcoal. Any source of combustion, where oxygen supply, and/or removal of waste combustion products are inadequate, may produce carbon monoxide.

Stoves, heaters, boilers, fires and portable fuel burners are all potential sources. Faulty flues from gas appliances are a common source of exposure. Poisoning may be more common during the winter months. Carbon monoxide poisoning has also been reported after prolonged smoking of shisha/hooka water pipes, from the use of barbecues in enclosed areas such as tents, indoor use of petroleum generators and from stored wood pellets used to fuel boilers. Carbon monoxide is also available in compressed gas cylinders for industrial use.

Mechanism of Toxicity

It is highly toxic. Carbon monoxide binds haemoglobin and reduces oxygen carrying capacity, causing severe tissue hypoxia. It also causes direct injury through inhibition of cytochrome oxidase. Poisoning usually occurs through inhalation of carbon monoxide, although carbon monoxide produced by catabolism of ingested or inhaled methylene chloride may also cause carbon monoxide poisoning.

Carbon monoxide also binds myoglobin in a manner similar to its binding of hemoglobin, causing direct cardiotoxicity. This may result in dysrhythmias, as well as exacerbation of underlying coronary artery disease.

Carbon monoxide is neurotoxic. Severe carbon monoxide poisoning damages the globus pallidus, hippocampus, cerebellum and white matter. Damage is caused by acute hypoxia, followed by an immune-mediated cascade of events that results in delayed lipid peroxidation. The result of this damage is delayed neurotoxicity, which is the most consequential problem affecting those who survive the initial insult. Dementia, psychosis, parkinsonism and paralysis may present up to forty days after exposure.

The half-life of carboxyhaemoglobin (COHb) while a patient is breathing room air is approximately 250 to 320 minutes, while breathing high flow oxygen via a non-

rebreathing facemask is about 90 minutes and with 100% hyperbaric oxygen is approximately 30 minutes.

Features of poisoning

Acute poisoning

- Headache, nausea and vomiting, irritability, weakness and tachypnoea followed by dizziness, confusion, ataxia, agitation, syncope, hypotension, seizures, impairment of consciousness and respiratory failure. Cerebral oedema and metabolic acidosis may develop in serious cases.
- Less common features include skin blisters, rhabdomyolysis, compartment syndrome, acute renal failure, pulmonary oedema, dysrhythmias, myocardial infarction, retinal haemorrhages, cortical blindness, choreoathetosis, mutism and hearing loss. Cherry red skin colour is rarely seen.
- An initial COHb concentration above 30% is likely to be associated with severe poisoning.

Commonly reported symptoms	**Frequency**
Headache	90%
Nausea and vomiting	50%
Vertigo	50%
Alteration in consciousness	30%
Subjective weakness	20%

Delayed features

- The majority of people exposed to carbon monoxide will recover uneventfully, but delayed neuropsychiatric features (DNS) may develop.
- Features include memory impairment, disorientation, apathy, mutism, irritability, inability to concentrate, personality change, emotional lability, neuropathy, incontinence, chorea, apraxia, psychosis, dementia and parkinsonism.
- Later features may be delayed by up to 40 days. Patients considered at higher risk are those who have experienced severe poisoning (e.g. unconsciousness etc).

Chronic poisoning

- Chronic carbon monoxide poisoning is frequently misdiagnosed or undiagnosed since the features are non specific. Features include headache, lethargy, nausea, memory problems and flu-like symptoms. The diagnosis should be considered particularly if there are other members of the same house experiencing similar symptoms.

Measurement of Carboxyhaemoglobin level

- Standard pulse oximetry (SpO_2) **CANNOT** screen for CO exposure, as it does not differentiate COHb from oxyhemoglobin.
- Blood PO_2 measurements also tend to be normal in CO poisoning because PO_2 reflects O_2 dissolved in blood, and this process is not affected by CO.
- Venous blood testing of COHb level can be done at Occupational Health Department, Yangon.
- A COHb measurement is essential for determining exposure, but levels correlate imprecisely with the degree of poisoning and are not predictive of delayed neurologic sequelae (DNS). If there is a significant delay between the exposure and obtaining blood, the COHb level may suggest a milder exposure than actually occurred. Therefore, symptoms and signs of the patient guide measurement, not COHb levels. Once the diagnosis of CO poisoning is established, repeat measurements are generally unnecessary.

Carboxyhaemoglobin level (%)	**Clinical findings**
0-5	Normal (Non-smoker)
5-10	Normal (Smoker)
15-20	Headache
> 20	Headache, Myocardial ischaemia, Syncope
> 50	Coma, Seizure

Management

All patients who have been exposed to this product as a result of self-harm should be referred for medical assessment. All patients who are symptomatic should be referred for medical assessment.

All patients who have remained asymptomatic after removal from exposure to carbon monoxide do not normally require medical assessment unless new symptoms develop.

Emergency management

- Maintain a clear airway and ensure adequate ventilation.
- Remove from exposure.
- Administer oxygen in as high concentrations as possible. Where available, consider the use of nasal high flow cannulae to deliver oxygen at up to 60 L/min.

Initial Assessment

- Monitor vital signs and check the capillary blood glucose.
- Check and record pupil size.
- Measure COHb concentration urgently, using either arterial or venous blood. A COHb concentration of 30% or more indicates severe exposure. However, concentrations less than this do not exclude significant poisoning.
- All patients who require assessment should be observed for at least **4 hours** after exposure. Asymptomatic patients can then be considered for discharge with advice to return if symptoms develop.
- In symptomatic patients, take blood for FBC, U&Es, CK, troponin and blood gas analysis.
- Perform a 12-lead ECG in all patients who require assessment.
- Consider repeating the ECG in **ANY OF** the following circumstances:
  - ✓ The initial ECG is abnormal.
  - ✓ The patient is symptomatic.
  - ✓ The recommended observation period (at least 12 hours) is not yet complete.
- Check cardiac rhythm, QT interval and QRS duration.

Management of Hypotension

- Ensure adequate fluid resuscitation.
- Consider early referral to critical care for patients with fluid-resistant hypotension, as these patients can deteriorate extremely rapidly; the management of children with fluid-resistant hypotension should be overseen by an experienced paediatrician.
- Invasive vascular monitoring and echocardiography may help determine the likely relative benefits of inotropes and vasopressors because reduced cardiac output and vasodilation often co-exist in severe or mixed poisoning.
- There have been very occasional reports of worsening of hypotension associated with adrenaline treatment, thought to be due to beta-receptor agonist effects.

- Vasopressors and inotropes can be initiated in an emergency through peripheral venous access but only under the direction of an experienced physician.

Management of Metabolic acidosis

- If metabolic acidosis persists despite correction of hypoxia and adequate fluid resuscitation, consider correction with intravenous sodium bicarbonate.

Adults: an initial dose of 50-100 mmol sodium bicarbonate (e.g. 50-100 mL 8.4% or 100-200 mL 4.2%) may be given and repeated as necessary, guided by arterial blood gas monitoring, aiming for a normal pH. The volumes for different concentrations of sodium bicarbonate to achieve a dose of 50-100 mmol in adults are shown here.

Concentration of $NaHCO_3$	Volume (ml) of $NaHCO_3$ providing		
	50 mmol	100 mmol	225 mmol
%	ml	ml	ml
8.4%	50	100	225
4.2%	100	200	450
1.4%	300	600	1350
1.26%	333	667	1500

Children: Give 1-2 mmol/kg sodium bicarbonate (1-2 mL/kg 8.4% or 2-4 mL/kg 4.2%) over 20 minutes. Repeat as necessary, aiming for a normal pH.

Adults and children: Recheck acid base status after administration of sodium bicarbonate. For severe acidosis, large amounts of bicarbonate with repeated pH checking may be required to correct the metabolic acidosis. Monitor electrolytes since there is a risk of hypokalaemia and possibly hypernatraemia.

Hyperbaric oxygen therapy (Not currently available in Myanmar)

- Hyperbaric oxygen therapy involves exposing patients to 100% O2 under supra-atmospheric conditions. This results in a decrease in the half-life of COHb, from approximately 90 mins on 100% normobaric oxygen to approximately 30 mins during hyperbaric oxygen therapy.
- Although hyperbaric oxygen does decrease the half-life of COHb, in practice, it is not instituted to improve oxygen delivery and never administered as a life-saving intervention.

- Rather, hyperbaric oxygen is administered in order to theoretically prevent or decrease the incidence of delayed neurological sequelae of carbon monoxide poisoning.
- In animal models, hyperbaric oxygen prevents lipid peroxidation and restores cytochrome oxidase function, effects which may be neuro-protective. Although older trials show no benefit, the most recent randomized controlled trial suggests that hyperbaric oxygen is effective in abating some of the delayed cognitive deficits from carbon monoxide poisoning.

Indications for hyperbaric oxygen therapy

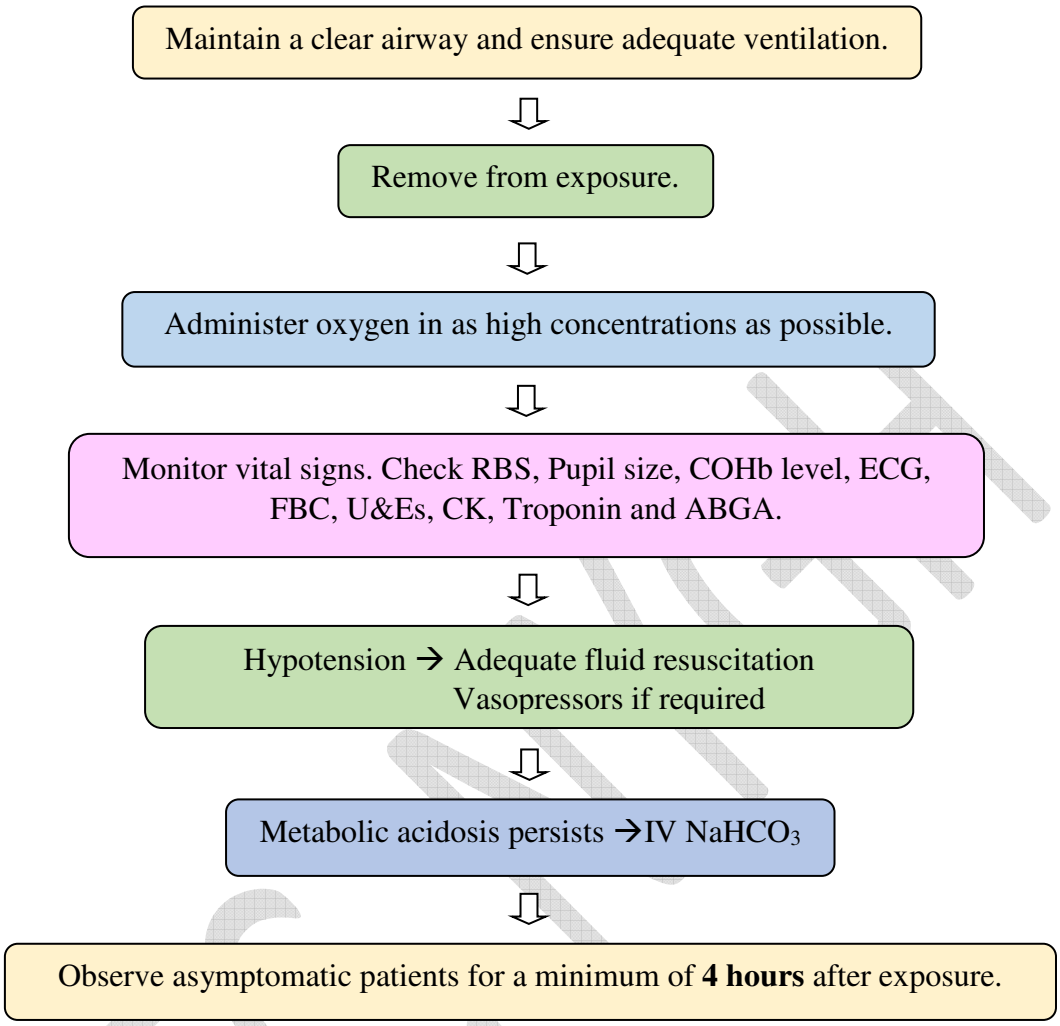
✓ COHb level > 25%
✓ COHb level > 20% in pregnancy
✓ Loss of consciousness
✓ Severe metabolic acidosis (pH < 7.1)
✓ Evidence of end-organ ischemia (e.g., ECG changes, chest pain or altered mental status)

If a patient has been exposed due to a house fire, consider also the possibility of cyanide poisoning.

Record a baseline neurological examination including tests of cognitive function in all patients. Look for extrapyramidal features and retinal haemorrhages in all patients who have been unconscious. Treat raised intra-cranial pressure conventionally.

Other measures as indicated by the patient's clinical condition. Patients should be advised on discharge to seek medical attention if symptoms subsequently develop.

Workflow for Acute Management of Carbon Monoxide Poisoning



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Cyanide Poisoning

Cyanide is among the most rapidly lethal poisons known to man. Acute cyanide poisoning may result from a broad range of exposure.

Sources of Cyanide

Industrial exposures
• Plastics production • Photography • Fumigation • Pesticides/Rodenticides • Synthetic rubber production • Fertilizer production • Metal polish • Hair removal from hides • Electroplating • Metallurgy
Plants and Fruits
• Bamboo sprout • Macadamia nuts • Hydrangea • Rosaceae family (plum, peach, pear, apple, bitter almond, cherry) • Cassava roots (Tapioca)
Miscellaneous
• Cigarette smoking • Phencyclidine synthesis • Artificial nail glue remover • Product tampering • Suicide/Terrorist attack
Drugs
• Sodium nitroprusside

• Laetrile
Combustion
• Wool • Silk • Polyurethanes • Polyacrylonitriles • Nylon • Melamine resins • Plastics

Mechanism of Toxicity

Cyanide has a high affinity for ferric ions in mitochondrial cytochrome oxidase, forming a relatively stable but reversible complex. Binding of cyanide to cytochrome a-a_3 complex inhibits electron transport and blocks ATP production causing reduced cellular oxygen utilization, anaerobic metabolism and lactic acidosis. The degree of lactic acidosis correlates with the severity of poisoning.

The cytochrome oxidase-cyanide complex dissociates through an enzymatic reaction using rhodanese as a catalyst. Rhodanese transfers sulphur (from endogenous thiosulphate) to cyanide with the formation of thiocyanate, which is subsequently excreted by the kidneys. Cytochrome oxidase is then released and normal cellular metabolism is able to resume. 80% of cyanide detoxification occurs by this route. Other endogenous methods of cyanide detoxification include binding to methaemoglobin, reaction with cysteine and incorporation into choline and methionine.

Features of poisoning

Ingestion/Inhalation

- Early features include headache, nausea, dizziness and anxiety followed by confusion, drowsiness, tachycardia, palpitations and tachypnoea.
- In cases of moderate toxicity, there may be brief episodes of loss of consciousness, convulsions, vomiting and hypotension.

- Cherry red skin and "bitter almond" odour on the patient's breath (due to excretion of hydrocyanic acid) are characteristic features but were only present in 11% and 15% of cases respectively.
- In severe poisoning, clinical features include deep coma, fixed unreactive pupils, cardiovascular collapse, respiratory depression, myocardial ischaemia, cardiac arrhythmias and pulmonary oedema. Profound sinus bradycardia or AV dissociation may occur in pre-terminal patients. Cyanosis is often a late sign and may not occur, even in patients with cardiovascular collapse.
- A profound lactic acidosis causing a high anion gap metabolic acidosis is the most consistent feature of moderate and severe cyanide poisoning.

Eye Exposure

- Pain, blepharospasm, lacrimation, conjunctivitis, palpebral oedema and photophobia. Acidic and alkaline solutions may cause corneal burns.
- Alkaline solutions in particular may penetrate all layers of the eye and find their way into the chambers causing iritis, anterior and posterior synechia, corneal opacification, cataracts, glaucoma and retinal atrophy. Alkali burns to the eyes should be considered an ophthalmic emergency.

Dermal Exposure

- Systemic toxicity from skin exposure requires a large surface area to be affected. Onset of toxicity may be delayed for several hours.

Chronic Exposure

- Most patients with acute poisoning either die or recover completely and do not generally develop prolonged features of toxicity.
- Long-term sequelae have been reported rarely following survival from substantial hydrogen cyanide exposure. Effects include intellectual deterioration, mental confusion and parkinsonism.
- Chronic low dose cyanide exposure may cause demyelinating lesions and encephalopathy. This usually presents with Parkinsonian-type features such as akinesia, dysarthria and rigidity. Spastic paraparesis, ataxia and deafness have been reported. Neuropsychiatric sequelae such as headaches, vertigo, convulsions, sleep disturbance and psychosis may develop. An MRI scan may show evidence of demyelinating lesions affecting the globus pallidus, posterior putamen and basal ganglia in particular.

- Respiratory tract irritation, breathlessness, hoarse voice, chronic rhinitis, deafness and acute liver injury have also been reported.
- Optic neuropathy has been reported as a result of cyanide toxicity. This presents as tobacco amblyopia in smokers. This condition is commonest in middle aged men, but is not related to the number of cigarettes smoked. Tropical amblyopia occurs as a result of cassava root ingestion, which contains a cyanogenic glycoside.
- Clinical features include progressive deterioration of vision, loss of red-green colour distinction, visual field changes with central scotoma, optic atrophy and afferent pupillary defect. The optical neuropathy in these cases responds to treatment with hydroxocobalamin, even if baseline vitamin B12 concentrations are normal.

Management

All patients exposed to this chemical should be referred to an Emergency Department. If this exposure has occurred at work or in a public space consider the implications for others exposed. Primary responders and secondary carers must consider wearing personal protective equipment (PPE).

Management of ingestion/inhalation

- Maintain a clear airway and ensure adequate ventilation.
- Administer oxygen to achieve adequate oxygenation.
- Remove from exposure.
- Monitor vital signs and check the capillary blood glucose.
- Check and record pupil size.
- Perform a 12-lead ECG in all patients who require assessment.
- Consider repeating the ECG in **ANY OF** the following circumstances:
  - ✓ The initial ECG is abnormal.
  - ✓ The patient is symptomatic.
  - ✓ The recommended observation period is not yet complete.
- Check cardiac rhythm, QT interval and QRS duration.
- In all patients, check U&Es (including chloride and bicarbonate) and blood lactate concentrations. Perform both venous and arterial blood gas analysis.
- Calculate the anion gap.

  ANION GAP = [SODIUM + POTASSIUM] - [BICARBONATE + CHLORIDE]

The usual anion gap is 12-16 mmol/L.

- Observe all patients for at least **6 hours** after ingestion/inhalation of **cyanide/cyanide salt** and at least **12 hours** after ingestion of **acetonitrile** or products containing **amygdalin**. Patients who are asymptomatic after this time with a **normal** ECG at this time can then be considered for discharge with advice to return if symptoms develop.
- **All patients with features of moderate or severe poisoning should be managed in a critical care environment**.
- Cyanide assays are only available in a small number of laboratories (not currently available in Myanmar) and cannot be performed rapidly, therefore treatment should not be withheld pending the result if clinical features suggest moderate or severe cyanide toxicity.
- Blood cyanide concentrations and toxicity:
  - ✓ mild toxicity: less than 1 mg/L (38 micromol/L);
  - ✓ moderate toxicity: 1-3 mg/L (38-114 micromol/L); and
  - ✓ severe toxicity: more than 3 mg/L (114 micromol/L).
- In the absence of a cyanide concentration, the following features suggest possible cyanide poisoning:
  - ✓ Lactate more than 7 mmol/L or
  - ✓ Elevated anion gap metabolic acidosis or
  - ✓ An increased venous oxygen concentration (relative to that expected given the inspired and arterial oxygen concentrations) is suggestive of cyanide toxicity.
- Assess the severity of the poisoning in symptomatic patients.

MILD POISONING

- Features: nausea, dizziness, drowsiness, hyperventilation, anxiety, lactate concentration less than 10 mmol/L.

MODERATE POISONING

- Features: reduced conscious level, vomiting, convulsions, hypotension, lactate concentration 10-15 mmol/L.

SEVERE POISONING

- Features: coma, fixed dilated pupils, cardiovascular collapse, respiratory failure, cyanosis, lactate concentration more than 15 mmol/L.
- Gut decontamination following ingestion: gastric decontamination is unnecessary in asymptomatic patients or those with features of mild toxicity only.

- Where the practical expertise exists, consider gastric lavage within 1 hour of ingestion in patients with features of moderate or severe toxicity, providing the airway can be protected. In a clinically symptomatic patient, other measures should be undertaken first (see below). Activated charcoal may be an alternative if gastric lavage is impractical or will be delayed.
- The use of antidotes in cyanide poisoning is dependent on the severity of poisoning. Assess the severity of poisoning in symptomatic patients:

MILD POISONING –

GIVE:

In an adult: 12.5 g of sodium thiosulphate (25 mL of 50% or 50 mL of 25% solution) intravenously over 10 minutes in an adult.

In a child: 400 mg/kg sodium thiosulphate (0.8 mL/kg of 50% or 1.6 mL/kg of 25% solution) intravenously. Note that the paediatric dose is higher than the equivalent adult dose.

MODERATE POISONING –

GIVE:

In an adult: 200 mL of 25 mg/mL hydroxocobalamin (5 g) intravenously over 15 minutes.

In a child: 70 mg/kg hydroxocobalamin (2.8 mL/kg of 25 mg/mL solution) intravenously over 15 minutes (maximum dose of 5 g).

- If hydroxocobalamin has been associated with acute kidney injury due to tubular necrosis OR **If hydroxocobalamin is not available:**

  GIVE IV Sodium thiosulphate (see the dose above).

SEVERE POISONING –

Treatment with antidote therapy is necessary in all cases. It is important to be aware if any antidote therapy has been given in the pre-hospital setting since repeat doses of some antidotes can cause unwanted side effects (see below).

- **GIVE:**

  In an adult: 200 mL of 25 mg/mL hydroxocobalamin (5 g) intravenously over 15 minutes. A second dose of 5 g can be given over 15 minutes to 2 hours depending on the severity of the poisoning and the patient's stability.

  In a child: 70 mg/kg hydroxocobalamin (2.8 mL/kg of 25 mg/mL solution) intravenously over 15 minutes (maximum dose of 5 g). A second dose of 70 mg/kg (maximum dose of 5 g) can be given over 15 minutes to 2 hours depending on the severity of the poisoning and the patient's stability.

  Hydroxocobalamin has been associated with acute kidney injury due to tubular necrosis.

- **Sodium thiosulphate may be used as an adjunct to hydroxocobalamin. (See the dose above)**

  A further dose of sodium thiosulphate may be given to both adults and children.

  OR

- **Although dicobalt edetate has been discontinued in October 2019 by the manufacturer, it is a very effective antidote for confirmed cyanide poisoning.**

  N.B. Dicobalt edetate is potentially toxic particularly in the absence of cyanide poisoning due to the presence in the formulation (Kelocyanor®) of free cobalt ions.

  If in-date stock is available,

  GIVE:

  In an adult: 20 mL of 1.5% dicobalt edetate solution (300 mg) IV over 1 minute followed immediately by 50 mL of 50% dextrose.

  In a child: 4 mg/kg dicobalt edetate intravenously over 1 minute followed by 2 mL/kg bolus of 10% glucose.

- If there is only a partial response to the first dose of dicobalt edetate, or the patient relapses after recovery, a further dose of dicobalt edetate should be given. If a second dose of dicobalt edetate is administered, there is a danger of inducing cobalt toxicity but only if the diagnosis is not cyanide poisoning.

- Response to treatment can be assessed by reduction in cyanide concentration, improved haemodynamic status and reduction in lactate concentration.

Management of Hypotension

- Ensure adequate fluid resuscitation.
- Consider early referral to critical care for patients with fluid-resistant hypotension, as these patients can deteriorate extremely rapidly; the management of children with fluid-resistant hypotension should be overseen by an experienced paediatrician.
- Invasive vascular monitoring and echocardiography may help determine the likely relative benefits of inotropes and vasopressors because reduced cardiac output and vasodilation often co-exist in severe or mixed poisoning.
- There have been very occasional reports of worsening of hypotension associated with adrenaline treatment, thought to be due to beta-receptor agonist effects.
- Vasopressors and inotropes can be initiated in an emergency through peripheral venous access but only under the direction of an experienced physician.

Management of Metabolic acidosis

- If metabolic acidosis persists despite correction of hypoxia and adequate fluid resuscitation, consider correction with intravenous sodium bicarbonate.

Adults: an initial dose of 50-100 mmol sodium bicarbonate (e.g. 50-100 mL 8.4% or 100-200 mL 4.2%) may be given and repeated as necessary, guided by arterial blood gas monitoring, aiming for a normal pH. The volumes for different concentrations of sodium bicarbonate to achieve a dose of 50-100 mmol in adults are shown here.

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8.4%	50	100	225
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1.4%	300	600	1350
1.26%	333	667	1500

Children: Give 1-2 mmol/kg sodium bicarbonate (1-2 mL/kg 8.4% or 2-4 mL/kg 4.2%) over 20 minutes. Repeat as necessary, aiming for a normal pH.

Adults and children: Recheck acid base status after administration of sodium bicarbonate. For severe acidosis, large amounts of bicarbonate with repeated pH checking may be required to correct the metabolic acidosis. Monitor electrolytes since there is a risk of hypokalaemia and possibly hypernatraemia.

Management of Convulsions

- Give oxygen; check blood glucose, U&Es, calcium, magnesium, phosphate and ABG.
- Correct acid base and metabolic disturbances as required.Single brief convulsions do not require treatment.
- Control convulsions that are frequent or prolonged with intravenous diazepam (10-20 mg in adults; 0.1-0.3 mg/kg body weight in children), lorazepam (4 mg in adults; 0.1 mg/kg in children), or midazolam (5-10 mg in adults; 0.05-0.15 mg/kg in children).
- If further doses of benzodiazepines may be needed in adults; refer to intensive care.

Other measures as indicated by the patient's clinical condition. Patients should be advised on discharge to seek medical attention if symptoms subsequently develop.

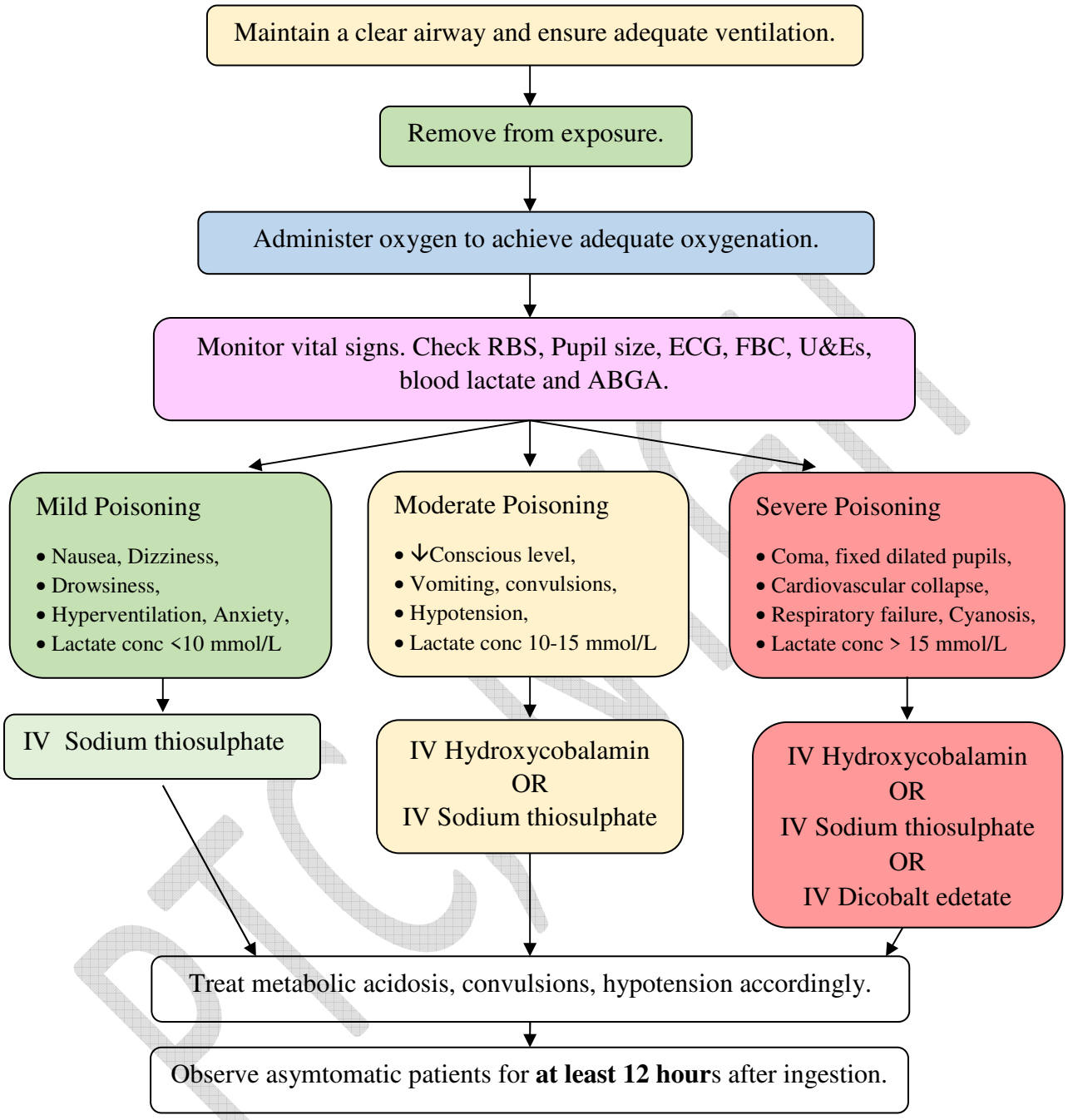
Management of Dermal Exposure

- Maintain a clear airway and ensure adequate ventilation.
- If appropriate, remove from exposure and give oxygen.
- If possible, the patient should remove contaminated clothing to prevent further absorption as per decontamination.
- If features of systemic toxicity are present manage as per ingestion/inhalation.

Management of Eye Exposure

- Decontaminate the eye and manage local effects.
- If features of systemic toxicity are present, manage as per ingestion/inhalation.

Workflow for Acute Management of Cyanide Poisoning



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Aluminium Phosphide Poisoning

Aluminium phosphide (ALP) is a dark grey/yellow crystalline solid which is formulated as discs, tablets or pellets. It is used as a fumigant for grain stored in ships' holds or silos. It is also used as an insecticide and rodenticide, especially in rice grain storage areas in Myanmar. It reacts with water or moisture in the air and with acids to liberate phosphine.

Toxic dose

Direct ingestion of ≥ **500 mg** of phosphides usually results in death.

Mechanism of Toxicity

It is highly toxic by ingestion (phosphine is released in the stomach), or by inhalation of liberated phosphine. Most cases in the developed world involve accidents in agricultural settings, while deliberate phosphide ingestion is a particular problem in the developing countries like Myanmar.

The onset of symptoms is usually very rapid and mortality is high. In a study of 195 aluminium phosphide ingestions, 115 died (Singh *et al*, 1996).

After ingestion of aluminium phosphide, phosphine is liberated on contact with gut fluids and absorbed through the gut mucosa. Experimentally, phosphine perturbs mitochondrial morphology, inhibits oxidative respiration by 70% and causes a severe drop in mitochondrial membrane potential. It also interacts with hydrogen peroxide to form highly reactive hydroxyl radicals such as H_3PO, which are capable of initiating lipid peroxidation. It also inhibits catalase and peroxidase activities thereby reducing the scavenging of radicals.

The short interval between ingestion of aluminium phosphide and the appearance of features of systemic phosphine toxicity indicates that aluminium phosphide is hydrolysed rapidly to phosphine, which is absorbed through the alimentary mucosa.

Features of poisoning

- The onset of symptoms is usually very rapid, typically within 30 minutes of exposure. One case series reported 55% of deaths within 12 hours and 91% of deaths within 24 hours.
- Early symptoms include nausea, vomiting, retrosternal and epigastric pain and dyspnoea. Haematemesis due to corrosive lesions of the oesophagus and stomach may occur and lead to the development of oesophageal stricture. There is often a smell of garlic on the breath due to the presence of impurities.

- Shock and cardiac failure are important early signs of severe poisoning and are frequent causes of death. ECG abnormalities include ST and T-wave changes; rarely, the ECG changes resemble those of myocardial infarction. Supraventricular and ventricular tachycardia are common in severe cases. Death typically results from cardiac arrhythmias or refractory shock and cardiac failure.
- Acute kidney injury is a frequent complication.
- Pulmonary oedema with tachypnoea, dyspnoea, crepitations and rhonchi occur frequently and usually 4-48 hours after ingestion.
- Hypokalaemia is common and is probably secondary to vomiting. Hypocalcaemia has also been reported. Metabolic acidosis, mixed metabolic acidosis and respiratory alkalosis are observed frequently. Arterial pH may be of prognostic significance. In one case series of aluminium phosphide poisoning, patients with pH < 7 or bicarbonate < 15 mmol/L died, whereas patients with pH > 7.35 survived.
- Hypoglycaemia, which may be persistent and severe, is due to impaired gluconeogenesis and glycogenolysis, possibly secondary to adrenal gland damage and low circulating cortisol concentrations. Hyperglycaemia also occurs and is secondary to adrenal damage and raised circulating cortisol and catecholamine concentrations, but other factors such as pancreatitis and hepatic impairment possibly also contribute.

Management

This agent is potentially very toxic. All patients exposed to this chemical should be referred to an Emergency Department. If this exposure has occurred at work or in a public space, consider the implications for others exposed. Primary responders and secondary carers must consider wearing personal protective equipment (PPE).

Emergency management

- **Resuscitate the patient according to standard guidelines.**
- **Phosphine may be released as a gas from emesis, faeces, or lavage materials and can cause respiratory distress in health care providers (HCPs) and other exposed persons although serious toxicity HCPs caring for patients poisoned with metallic phosphides has not been described. Thus, these patients should be managed in negative pressure rooms and emesis and faeces from the poisoned patient should be disposed of in closed containers.**

- Maintain a clear airway and ensure adequate ventilation.
- Administer oxygen to achieve adequate oxygenation.
- Gastric decontamination procedures are not recommended.

Initial Assessment

- Monitor vital signs and cardiac rhythm; check the capillary blood glucose.
- Check and record pupil size.
- Perform a 12-lead ECG in all patients who require assessment.
- Consider repeating the ECG in **ANY OF** the following circumstances:
  - ✓ The initial ECG is abnormal.
  - ✓ The patient is symptomatic.
  - ✓ The recommended observation period (at least 12 hours) is not yet complete.
- Check cardiac rhythm, QT interval and QRS duration.
- All patients who require assessment should be observed for at least **12 hours** after exposure. Asymptomatic patients can then be considered for discharge with advice to return if symptoms develop.
- In symptomatic patients, monitor FBC, U&Es, LFTs, cardiac enzymes, phosphate, blood glucose, calcium, magnesium and blood gases. Perform a chest X-ray and monitor cardiac rhythm.
- Supportive care is the mainstay of treatment.
- Consider the need for IV fluids and correct electrolyte abnormalities.
- In patients with hypomagnesemia, IV Magnesium Sulphate 1g followed one hour later by 1g given as a continuous infusion over three hours and then 1g every six hours until recovery or a maximum duration of five days can decrease mortality.
- Phosphine-induced hypotension is due to a reduced cardiac output.

Management of Hypotension

- Ensure adequate fluid resuscitation.
- Consider early referral to critical care for patients with fluid-resistant hypotension, as these patients can deteriorate extremely rapidly; the management of children with fluid-resistant hypotension should be overseen by an experienced paediatrician.

- Invasive vascular monitoring and echocardiography may help determine the likely relative benefits of inotropes and vasopressors because reduced cardiac output and vasodilation often co-exist in severe or mixed poisoning.
- There have been very occasional reports of worsening of hypotension associated with adrenaline treatment, thought to be due to beta-receptor agonist effects.
- Vasopressors and inotropes can be initiated in an emergency through peripheral venous access but only under the direction of an experienced physician.

Management of Cardiac Arrhythmias

- Manage atrial and ventricular arrhythmias according to Advanced Cardiac Life Support and Paediatric Life Support Guidelines.

Management of Pulmonary oedema and/or acute lung injury

- Treat pulmonary oedema and/or acute lung injury conventionally. Continuous positive airway pressure (CPAP) or in severe cases with IPPV and PEEP, and other standard therapies may be considered.

Management of Metabolic acidosis

- If metabolic acidosis persists despite correction of hypoxia and adequate fluid resuscitation, consider correction with intravenous sodium bicarbonate.

Adults: an initial dose of 50-100 mmol sodium bicarbonate (e.g. 50-100 mL 8.4% or 100-200 mL 4.2%) may be given and repeated as necessary, guided by arterial blood gas monitoring, aiming for a normal pH. The volumes for different concentrations of sodium bicarbonate to achieve a dose of 50-100 mmol in adults are shown here.

Concentration of $NaHCO_3$	Volume (ml) of $NaHCO_3$ providing		
	50 mmol	100 mmol	225 mmol
%	ml	ml	ml
8.4%	50	100	225
4.2%	100	200	450
1.4%	300	600	1350
1.26%	333	667	1500

Children: Give 1-2 mmol/kg sodium bicarbonate (1-2 mL/kg 8.4% or 2-4 mL/kg 4.2%) over 20 minutes. Repeat as necessary, aiming for a normal pH.

Adults and children: Recheck acid base status after administration of sodium bicarbonate. For severe acidosis, large amounts of bicarbonate with repeated pH checking may be required to correct the metabolic acidosis. Monitor electrolytes since there is a risk of hypokalaemia and possibly hypernatraemia.

Management of Acute Renal Failure

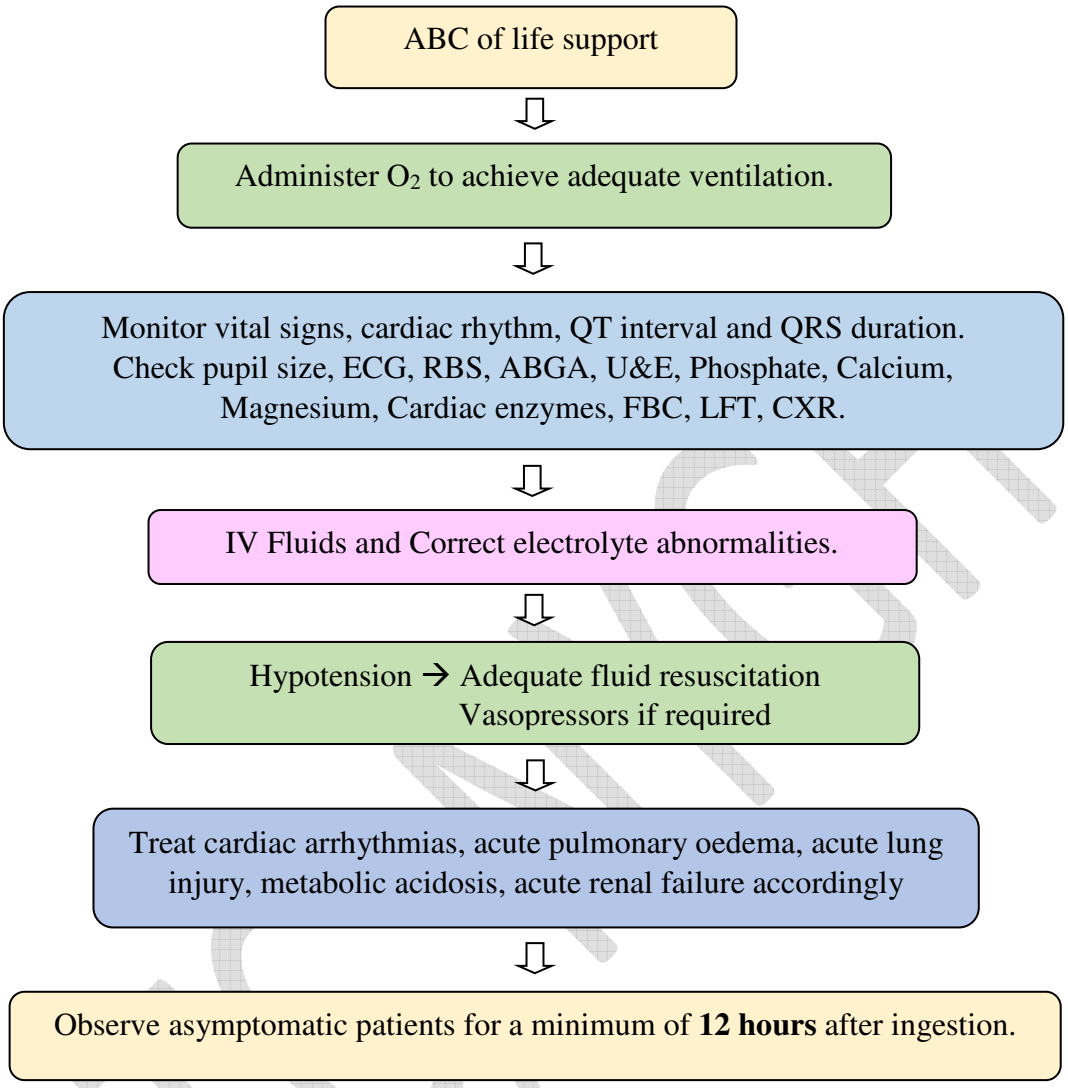
- Treat renal failure conventionally with haemodialysis, haemodiafiltration or haemofiltration.

Investigation of corrosive effects

- Features of severe tissue injury (severe abdominal pain, abdominal distension, circulatory collapse or lactic acidosis) may indicate the presence of bowel necrosis or perforation. Immediate surgical assessment is recommended because early resection of necrotic tissue and intraluminal stenting improves survival and reduces the risk of oesophageal stricture formation.
- **Drooling, dysphagia, vomiting, severe pain, haematemesis, stridor and extensive oropharyngeal burns are associated with more severe injuries and indicate the need for urgent imaging/endoscopy.**
- Both CT scan and fibreoptic endoscopy are useful in assessing the severity of injury, risk of mortality, and risk of subsequent stricture formation. These 2 imaging modalities are complementary and provide the best understanding of the injury and risk when combined. If there are severe clinical features, then endoscopy is best performed by a surgeon capable of undertaking definitive treatment.
- Asymptomatic patients do not require further imaging.

Other measures as indicated by the patient's clinical condition. Patients should be advised on discharge to seek medical attention if symptoms subsequently develop.

Workflow for Acute Management of Aluminium Phosphide Poisoning



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Beta-Blocker Overdose

Beta-blockers are mainly used for the management of hypertension, angina, arrhythmias and acute coronary syndrome. Propranolol is a non-selective beta-adrenergic blocker with sodium-channel blocking properties. It is also used as an adjunct to treatment of thyrotoxicosis and for migraine prophylaxis.

Some beta-blockers and their toxic doses

Drug	Toxic dose	Peak plasma concentration	Therapeutic elimination half life
Bisoprolol	0.7 mg/kg	2-4 hrs	10-12 hrs
Carvedilol	2.5 mg/kg	1 hr	6 hrs
Metoprolol	10 mg/kg	1.5-2 hrs	1-9 hrs
Propranolol	4.5 mg/kg	2 hrs	3-6 hrs
Atenolol	5 mg/kg	2-4 hrs	6-7 hrs (prolonged in renal impairment)

Mechanism of Toxicity

The predominant toxicity from beta-blockers is cardiac, mediated via beta-adrenergic blockade. Those with additional sodium channel-blocking effects (e.g., propranolol, acebutolol, carvedilol) may cause seizures, delirium and coma, while sotalol, which also blocks potassium channels, may cause QTc prolongation and torsade de pointes.

Features of poisoning

The key feature in severe poisoning is cardiovascular collapse.

Cardiac - the most important effects are on the heart. Bradycardia, hypotension, pulmonary oedema, syncope and cardiogenic shock may develop. Conduction abnormalities such as first or second degree AV block and intraventricular conduction delays may occur. Dysrhythmias have also been reported and can include asystole.

Some beta-blockers are associated with risk of VT associated with prolongation of QRS duration (e.g. propranolol) or prolongation of QT duration (e.g. sotalol).

Clinical features common to cardiac/cardiotoxic agents involved in mixed overdoses may be more severe or prolonged.

CNS – beta-blockers which are more lipid soluble (carvedilol, labetalol, metoprolol, oxprenolol, pindolol and propranolol) are more likely to cross the blood brain barrier causing drowsiness, confusion, convulsions, hallucinations, dilated pupils and in severe cases, coma. Neurological signs such as coma or absence of pupil reactivity are unreliable prognostic indicators during resuscitation or assessment of brain death.

Hydrophilic beta blockers (acebutolol, atenolol, bisoprolol, esmolol, nadolol, sotalol) have few CNS effects.

Other features - bronchospasm and occasionally CNS-mediated respiratory depression may occur. Hypoglycaemia and hypocalcaemia are rare.

Management

- All patients who have been exposed to beta-blockers as a result of self-harm should be referred for assessment.
- Medical assessment is recommended for ingestions in the following patients who are treatment naïve or who have taken more than their therapeutic dose:
  a. Patients with a significant cardiac history, e.g. heart failure, dysrhythmias
  b. Patients with asthma (particularly if unstable) or COPD
  c. Elderly patients (who are more at risk of complications).
- All patients who have exceeded their prescribed daily dose of ≥ 2 cardio-toxic agents should be referred for medical assessment irrespective of the dose ingested.

Emergency management

- Maintain a clear airway and adequate ventilation in patients who are unconscious. Early tracheal intubation may be of benefit in severe poisoning.
- In the event of cardiac arrest in hospital or witnessed out of hospital cardiac arrest with bystander CPR, resuscitation should be continued for at least 1 hour and only stopped after discussion with a senior clinician.
- If the patient may have been exposed to a sodium channel antagonist, or if QRS duration had been prolonged prior to cardiac arrest, administer a rapid bolus of 100 mL of 8.4% sodium bicarbonate urgently, preferably into a large vein. 8.4% sodium bicarbonate is irritant, and should be preceded and followed by a large fluid flush to confirm cannula position and reduce local contact. Monitor pH and administer further doses as necessary.
- Prolonged resuscitation for cardiac arrest is recommended following poisoning as recovery with good neurological outcome may occur.
- **The benefit of gastric decontamination is uncertain**. Consider activated charcoal (charcoal dose: 50 g for adults; 1 g/kg for children) if the patient presents within 1 hour of ingestion of more than a potentially toxic dose, providing it is safe to do so and the airway can be protected. Efficacy declines rapidly with time since ingestion but there may be

some potential benefit from later use, especially following ingestion of sustained release preparations or large ingestions.

Initial Assessment

- Monitor vital signs and cardiac rhythm.
- This agent is cardiotoxic and careful assessment of the ECG is required. Perform a 12-lead ECG in all patients who require assessment.
- In symptomatic patients, or patients with an abnormal ECG, consider early discussion with HDU/ITU.
- Consider repeating the ECG in **ANY OF** the following circumstances:
  - ✓ The initial ECG is abnormal.
  - ✓ The patient is symptomatic.
  - ✓ The recommended observation period is not yet complete.
- Check cardiac rhythm, QT interval and QRS duration.
- Check blood gases, U&Es and creatinine, calcium, FBC and monitor urine output. Check creatine kinase in patients who have been unconscious.
- Observe all patients who require assessment for **at least 6 hours after ingestion** and **12 hours after ingestion of modified release preparation.** Patients who are asymptomatic after this time with a **normal** ECG can then be considered for discharge with advice to return if symptoms develop.
- Following mixed overdoses involving cardiac/cardiotoxic agents, asymptomatic patients should be monitored for at least the longest period recommended in any of the individual TOXBASE® entries.

Management of Bradycardia

- For symptomatic bradycardia, give atropine intravenously, 0.5-1.2 mg for an adult or 0.02 mg/kg for a child. Repeat doses may be necessary.
- Dobutamine or isoprenaline may be considered if bradycardia is associated with hypotension.
- If bradycardia is associated with sino-atrial or atrioventricular block, temporary pacemaker insertion may be required, alternatively external pacing may be used.

Glucagon - severe hypotension (Not currently available in Myanmar)

- Glucagon is a treatment option for severe hypotension, heart failure or cardiogenic shock.

In adults:

- A bolus of 5-10 mg IV in adults should be administered over 1-2 minutes, followed by an infusion of 50-150 micrograms/kg/hour, titrated to clinical response. Infusion is an off-label method of glucagon administration. Limited evidence is available for the use of doses in excess of 10 mg/hour. If haemodynamic improvement is not achieved with this dose, consider the use of additional treatments for hypotension.

In children:

- A bolus of 50-150 micrograms/kg IV should be administered over 1-2 minutes, followed by an infusion of 50 micrograms/kg/hour, titrated to clinical response.

Note: Beware adverse effects of intravenous administration, in particular vomiting, hyperglycaemia, hypokalaemia and hypocalcaemia. Consider prophylactic treatment with an antiemetic.

Note: Glucagon must be used immediately following reconstitution, do not prepare well in advance. Calcium-containing solutions (e.g. Hartmann's) and sodium chloride are not suitable dilutents as precipitation may occur. The use of water as a diluent has been associated with thrombophlebitis. Cloudy solutions must not be used. There is no recommended final volume/concentration for dilution; for adults, it is usually convenient to dilute in 100 mL or 250 mL, but smaller or larger infusion volumes can be used.

High Dose Insulin Euglycaemic Therapy (For Adults)

- In patients with severe impairment of myocardial contractility, an insulin and dextrose infusion has been shown to improve systemic perfusion. It is particularly useful in the presence of acidosis.
- Give dextrose and insulin as per protocol. Monitor for hypoglycaemia and hypokalaemia.

Management of Hypotension

- Ensure adequate fluid resuscitation.
- Consider early referral to critical care for patients with fluid-resistant hypotension, as these patients can deteriorate extremely rapidly; the management of children with fluid-resistant hypotension should be overseen by an experienced paediatrician.

- Invasive vascular monitoring and echocardiography may help determine the likely relative benefits of inotropes and vasopressors because reduced cardiac output and vasodilation often co-exist in severe or mixed poisoning.
- There have been very occasional reports of worsening of hypotension associated with adrenaline treatment, thought to be due to beta-receptor agonist effects.
- Vasopressors and inotropes can be initiated in an emergency through peripheral venous access but only under the direction of an experienced physician.

Management of Metabolic acidosis

- If metabolic acidosis persists despite correction of hypoxia and adequate fluid resuscitation, consider correction with intravenous sodium bicarbonate.

Adults: an initial dose of 50-100 mmol sodium bicarbonate (e.g. 50-100 mL 8.4% or 100-200 mL 4.2%) may be given and repeated as necessary, guided by arterial blood gas monitoring, aiming for a normal pH. The volumes for different concentrations of sodium bicarbonate to achieve a dose of 50-100 mmol in adults are shown here.

Concentration of $NaHCO_3$	Volume (ml) of $NaHCO_3$ providing		
	50 mmol	100 mmol	225 mmol
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8.4%	50	100	225
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1.4%	300	600	1350
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Children: Give 1-2 mmol/kg sodium bicarbonate (1-2 mL/kg 8.4% or 2-4 mL/kg 4.2%) over 20 minutes. Repeat as necessary, aiming for a normal pH.

Adults and children: Recheck acid base status after administration of sodium bicarbonate. For severe acidosis, large amounts of bicarbonate with repeated pH checking may be required to correct the metabolic acidosis. Monitor electrolytes since there is a risk of hypokalaemia and possibly hypernatraemia.

Mechanical Cardiac Support (Not currently available in Myanmar)

- Mechanical adjuncts which may be a bridge to recovery in patients with life-threatening haemodynamic instability where other measures have failed -

- ✓ vaECMO (veno-arterial extracorporeal membrane oxygenation) or cardiac bypass.
- ✓ intra-aortic balloon pump (for those patients without severe rhythm disturbance).

Management of Pulmonary oedema and/or acute lung injury

- Treat pulmonary oedema and/or acute lung injury conventionally. Continuous positive airway pressure (CPAP) or in severe cases with IPPV and PEEP, and other standard therapies may be considered.

Management of Bronchospasm

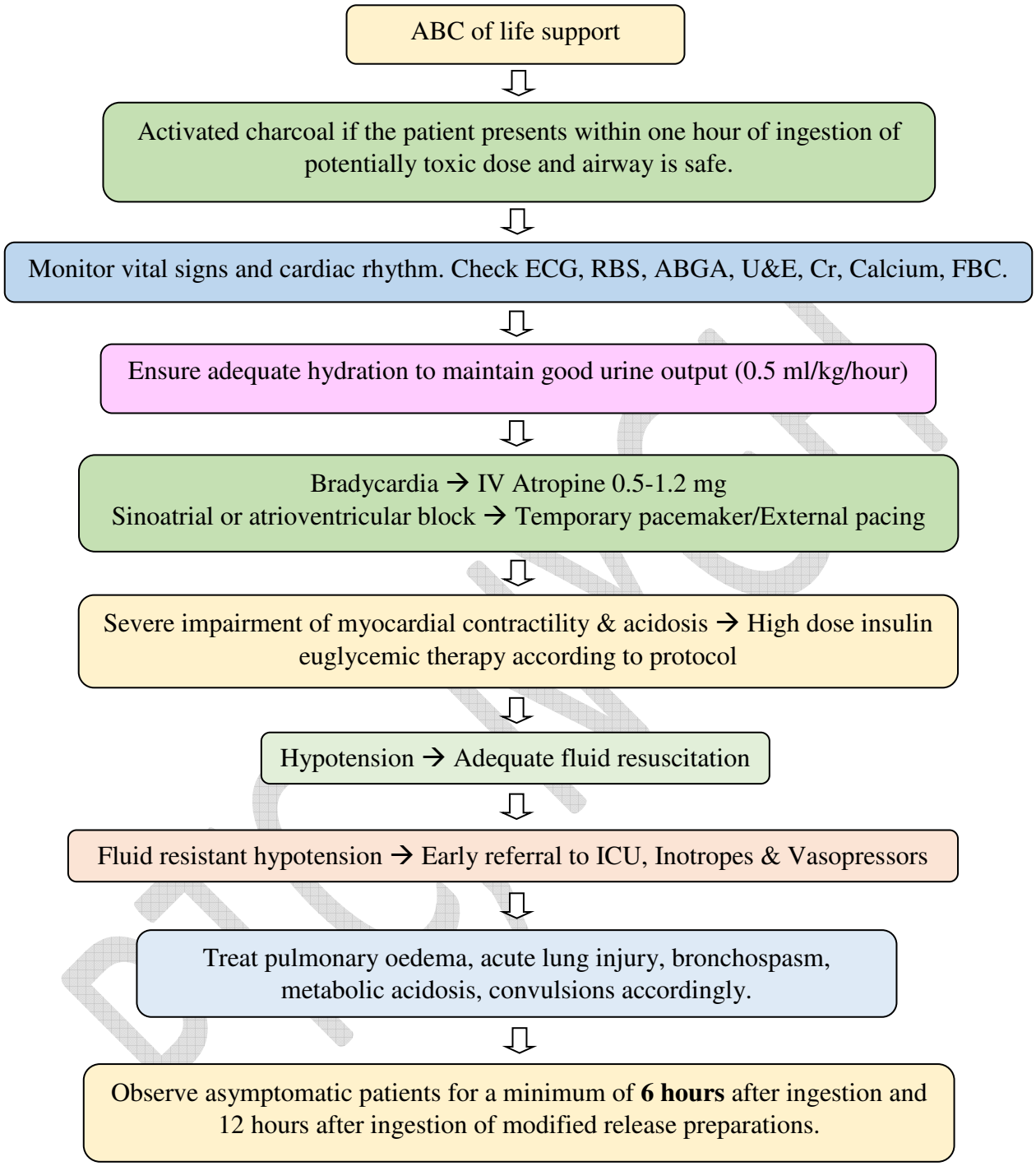
- If the patient has clinical features of bronchospasm, treat conventionally with nebulised bronchodilators and steroids.

Management of Convulsions

- Give oxygen; check blood glucose, U&Es, calcium, magnesium, phosphate and ABG. Correct acid base and metabolic disturbances as required.
- Single brief convulsions do not require treatment.
- Control convulsions that are frequent or prolonged with intravenous diazepam (10-20 mg in adults; 0.1-0.3 mg/kg body weight in children), lorazepam (4 mg in adults; 0.1 mg/kg in children), or midazolam (5-10 mg in adults; 0.05-0.15 mg/kg in children).
- Further doses of benzodiazepines may be needed in adults; refer to intensive care. In children seek consultant paediatric input.
- If unresponsive to the above measures, the patient should be referred urgently to critical care. Barbiturates are recommended as second line therapy and avoid phenytoin.

Other measures as indicated by the patient's clinical condition. Patients should be advised on discharge to seek medical attention if symptoms subsequently develop.

Workflow for Acute Management of Beta-Blocker Overdose



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Calcium Channel Blocker Overdose

Calcium channel blockers (CCBs) are mainly used for the treatment and prophylaxis of angina, and the treatment of hypertension where an ACE inhibitor/angiotensin 2 receptor antagonist is unsuitable. Additionally, nifedipine is used to treat Raynaud's phenomenon and as a tocolytic to delay or prevent premature labour; verapamil is used to treat supraventricular arrhythmias and for the prophylaxis of cluster headaches. Topical diltiazem (2%) is also used off-license to treat anal fissure.

Calcium channel blockers and toxic doses

Drug	Suggested oral referral dose	Peak plasma concentration	Therapeutic elimination half life
Dihydropyridines			
Amlodipine	0.2 mg/kg	6-12 hours	35-50 hours
Nifedipine	1.2 mg/kg	30-60 min (normal release); 1.5-4.2 hrs (sustained-release)	1.7-3.4 hrs (normal release); 6-11 hrs (sustained release)
Non-dihydropyridines			
Verapamil	5 mg/kg	1-2 hrs (normal release); 4-8 hrs (sustained release)	2-8 hrs (normal release); 3-8 hrs (sustained release)
Diltiazem	5 mg/kg	1-4 hrs (normal release); 5-11 hrs (sustained release)	3-8 hrs (normal release); 48 hrs (sustained release)
Note:	The elimination half-life may be prolonged in overdose.		

Mechanism of Toxicity

Toxicity is mainly due to antagonism of calcium channels in smooth muscles, peripheral vasodilation and severe hypotension. High doses can cause blockade of calcium channels in the heart, leading to bradyarrhythmias including junctional escape rhythms, atrio-ventricular conduction block and asystole. Blockade of calcium channels in the pancreas causes hyperglycaemia.

Features of poisoning

Verapamil and diltiazem have a profound cardiac depressant effect causing hypotension, bradyarrhythmias including junctional escape rhythms, atrio-ventricular conduction block and asystole. They may also cause hypotension secondary to profound peripheral vasodilation.

Dihydropyridine calcium antagonists (e.g., Amlodipine, Nifedipine) cause severe hypotension secondary to profound peripheral vasodilation. Hypotension may be delayed and/or prolonged. This may be associated with reflex tachycardia. Bradycardia, AV block and cardiac depression may be present in severe poisoning.

Clinical features common to cardiac/cardiotoxic agents involved in mixed overdoses may be more severe or prolonged.

Hyperglycaemia is common and may be a marker of severe poisoning.

Other non-cardiovascular features include GI upset, dizziness, flushing, headache, fatigue, visual disturbances, agitation, confusion, CNS depression and occasionally coma. Metabolic acidosis, hyperkalaemia and hypocalcaemia may be present. Convulsions, pulmonary oedema, paralytic ileus, acute pancreatitis, hepatotoxicity, acute renal failure, rhabdomyolysis and mesenteric infarction have been reported.

Management

Calcium channel blockers are highly toxic in large overdoses. All patients who have been exposed to this product as a result of self-harm should be referred for assessment. All patients who have exceeded their prescribed daily dose of 2 or more cardio-toxic agents should be referred for medical assessment irrespective of the dose ingested. All children should be referred for medical assessment. Adults who have ingested a toxic dose or more (see the above table), or those who are symptomatic, should be referred for medical assessment.

Emergency management

- Maintain a clear airway and ensure adequate ventilation.
- In the event of cardiac arrest in hospital or witnessed out of hospital cardiac arrest with bystander CPR, resuscitation should be continued for at least 1 hour and only stopped after discussion with a senior clinician. Prolonged resuscitation for cardiac arrest is recommended following poisoning as recovery with good neurological outcome may occur.
- **The benefit of gastric decontamination is uncertain**. Consider activated charcoal (charcoal dose: 50 g for adults; 1 g/kg for children) if the patient presents within 1 hour of ingestion of a toxic dose or more, providing it is safe to do so and the airway can be protected. Efficacy declines rapidly with time since ingestion but there may be some

potential benefit from later use, especially following ingestion of sustained release preparations or large ingestions.

- Where the practical expertise exists, consider gastric aspiration/lavage in adults within 1 hour of a potentially life-threatening overdose, providing the airway can be protected.
- Consider whole bowel irrigation in patients who have taken a potentially large overdose of sustained or modified release preparations. This will reduce absorption. Ensure that the airway can be protected, and the patient is haemodynamically stable and free of bowel obstruction, perforation or ileus.

Initial Assessment

- Monitor vital signs and cardiac rhythm.
- Check and record pupil size.
- Monitor fluid balance. Check U&Es, LFTs, FBC, calcium and glucose. Monitor arterial blood gases and monitor capillary blood sugar in all hypotensive and symptomatic patients.
- Perform a 12-lead ECG in all patients who require assessment.
- Consider repeating the ECG in **ANY OF** the following circumstances:
  - ✓ The initial ECG is abnormal.
  - ✓ The patient is symptomatic.
  - ✓ The recommended observation period is not yet complete.
- Check cardiac rhythm, QT interval and QRS duration. If patients are symptomatic or have an abnormal ECG, consider early discussion with HDU/ITU.
- Patients are at high risk of sudden deterioration if they have any one of the following features:
  - ✓ Hypotension
  - ✓ New hyperglycaemia
  - ✓ Rising blood lactate concentration
- Such patients should be referred urgently to critical care and considered for specific treatments (e.g. calcium, high dose insulin, inotropes).
- Ensure adequate hydration to maintain a good urine output (0.5 mL/kg/hour) and perfusion.

- All patients should be observed for at least **12 hours after ingestion of normal release preparations**, and for at least **24 hours after ingestion of modified-release preparations**.
- Asymptomatic patients with a normal ECG at this time can then be considered for discharge with advice to return if symptoms develop.
- Following mixed overdoses involving cardiac/cardiotoxic agents, asymptomatic patients should be monitored for at least the longest period recommended in any of the individual TOXBASE® entries.

Management of Bradycardia

- For symptomatic bradycardia, give atropine intravenously, 0.5-1.2 mg for an adult or 0.02 mg/kg for a child. Repeat doses may be necessary.
- Dobutamine or isoprenaline may be considered if bradycardia is associated with hypotension.
- If bradycardia is associated with sino-atrial or atrioventricular block, temporary pacemaker insertion may be required, alternatively external pacing may be used.

Management of Hypotension – Calcium Treatment

- For mild to moderate reductions in blood pressure, give 10% calcium chloride 0.2 mL/kg, up to 10 mL over 5 minutes. Give 2-3 times this dose if calcium gluconate is used (0.6 mL/kg, up to 30 mL of 10% calcium gluconate over 5 minutes).
- If required, repeat the dose of calcium every 10-20 minutes until a maximum of 4 doses given, or consider an infusion of calcium chloride at 0.2 mL/kg/hour (maximum 10 mL/hour); calcium gluconate at 0.6 mL/kg/hour (maximum 30 mL/hour). Monitor the calcium level if repeat doses or infusion given, aim for high normal concentration; ionised calcium concentration may be a more accurate measure.

High Dose Insulin Euglycaemic Therapy (For Adults)

- Calcium channel blockers block pancreatic calcium channels, reducing insulin release. In toxicity, myocardial cells require glucose for metabolism. Insulin is provided in very large quantities to support this process.

- In patients with severe impairment of myocardial contractility, an insulin and dextrose infusion has been shown to improve systemic perfusion. It is particularly useful in the presence of acidosis.
- Give dextrose and insulin as per protocol. Monitor for hypoglycaemia and hypokalaemia.

Glucagon - severe hypotension (Not currently available in Myanmar)

- Glucagon is a treatment option for severe hypotension, heart failure or cardiogenic shock.

In adults:

- A bolus of 5-10 mg IV in adults should be administered over 1-2 minutes, followed by an infusion of 50-150 micrograms/kg/hour, titrated to clinical response. Infusion is an off-label method of glucagon administration. Limited evidence is available for the use of doses in excess of 10 mg/hour. If haemodynamic improvement is not achieved with this dose consider the use of additional treatments for hypotension.

In children:

- A bolus of 50-150 micrograms/kg IV should be administered over 1-2 minutes, followed by an infusion of 50 micrograms/kg/hour, titrated to clinical response.

Note: Beware adverse effects of intravenous administration, in particular vomiting, hyperglycaemia, hypokalaemia and hypocalcaemia. Consider prophylactic treatment with an antiemetic.

Note: Glucagon must be used immediately following reconstitution, do not prepare well in advance. Calcium-containing solutions (e.g. Hartmann's) and sodium chloride are not suitable dilutents as precipitation may occur. The use of water as a diluent has been associated with thrombophlebitis. Cloudy solutions must not be used. There is no recommended final volume/concentration for dilution; for adults, it is usually convenient to dilute in 100 mL or 250 mL, but smaller or larger infusion volumes can be used.

Vasopressors

- An adrenoceptor agonist should be instituted if hypotension fails to respond to the above measures. Adrenaline [epinephrine] has both alpha and beta adrenergic effects and may improve both cardiac dysfunction and decreased systemic vascular resistance. Alternatively, a combination of alpha and beta adrenergic agonists (such as dobutamine and noradrenaline [norepinephrine]) may be used.

- If hypotension is mainly due to decreased systemic vascular resistance, drugs with mainly alpha adrenergic activity such as noradrenaline or high dose dopamine (10-30 micrograms/kg/min) are more beneficial.
- If hypotension is secondary to the negative chronotropic and inotropic effects of the calcium channel blockers with little evidence of systemic vasodilation, beta adrenergic agonists such as dobutamine, isoprenaline or low dose dopamine (2-10 micrograms/kg/min) may be of benefit.

Mechanical Cardiac Support (Not currently available in Myanmar)

- Mechanical adjuncts which may be a bridge to recovery in patients with life-threatening haemodynamic instability where other measures have failed -
  - ✓ vaECMO (veno-arterial extracorporeal membrane oxygenation) or cardiac bypass.
  - ✓ intra-aortic balloon pump (for those patients without severe rhythm disturbance).

Management of Pulmonary oedema and/or acute lung injury

- Treat pulmonary oedema and/or acute lung injury conventionally. Continuous positive airway pressure (CPAP) or in severe cases with IPPV and PEEP, and other standard therapies may be considered.

Management of Metabolic acidosis

- If metabolic acidosis persists despite correction of hypoxia and adequate fluid resuscitation, consider correction with intravenous sodium bicarbonate.

Adults: an initial dose of 50-100 mmol sodium bicarbonate (e.g. 50-100 mL 8.4% or 100-200 mL 4.2%) may be given and repeated as necessary, guided by arterial blood gas monitoring, aiming for a normal pH. The volumes for different concentrations of sodium bicarbonate to achieve a dose of 50-100 mmol in adults are shown here.

Concentration of $NaHCO_3$	Volume (ml) of $NaHCO_3$ providing		
	50 mmol	100 mmol	225 mmol
%	ml	ml	ml
8.4%	50	100	225
4.2%	100	200	450
1.4%	300	600	1350
1.26%	333	667	1500

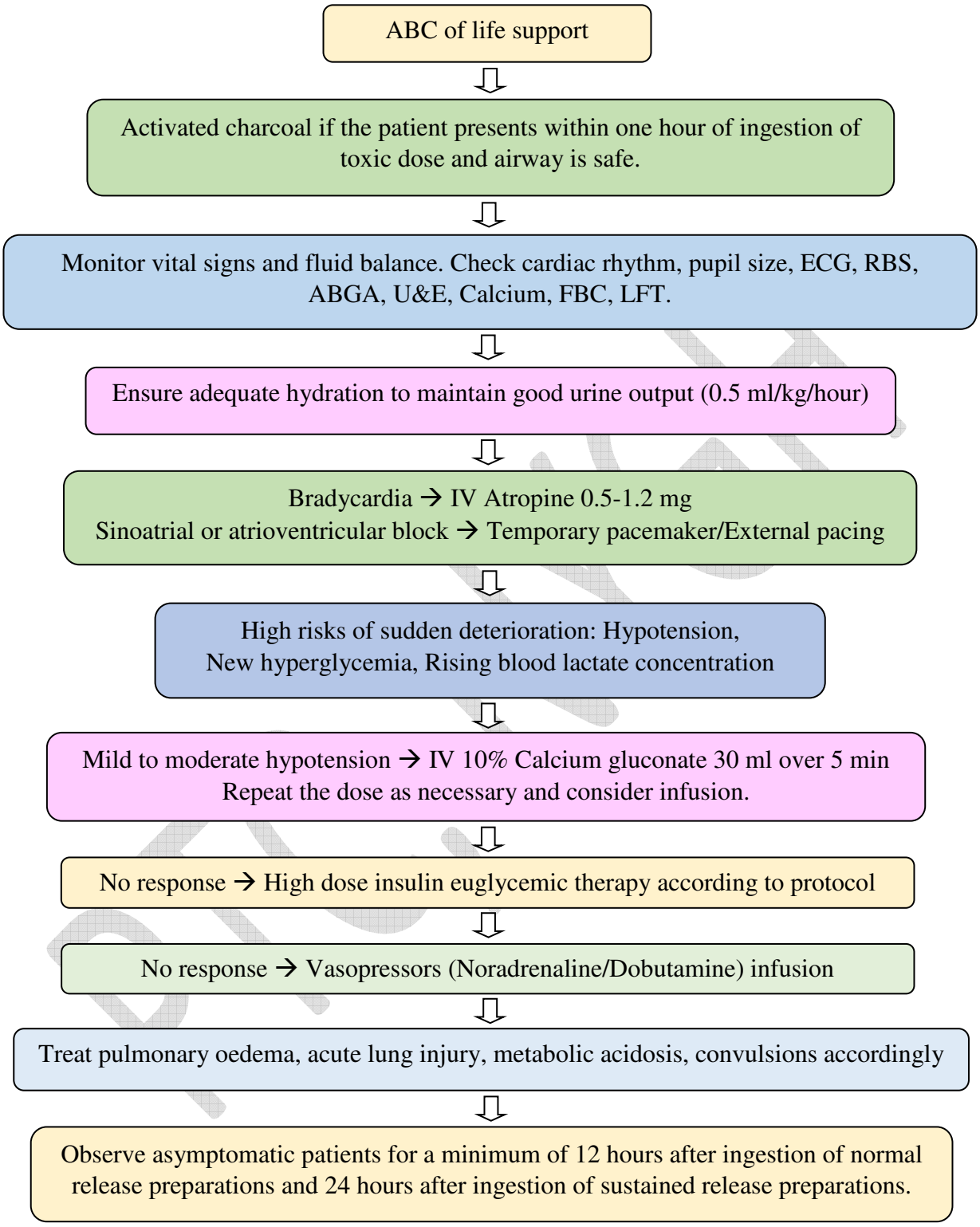
Children: Give 1-2 mmol/kg sodium bicarbonate (1-2 mL/kg 8.4% or 2-4 mL/kg 4.2%) over 20 minutes. Repeat as necessary, aiming for a normal pH.

Adults and children: Recheck acid base status after administration of sodium bicarbonate. For severe acidosis, large amounts of bicarbonate with repeated pH checking may be required to correct the metabolic acidosis. Monitor electrolytes since there is a risk of hypokalaemia and possibly hypernatraemia.

Management of Convulsions

- Give oxygen; check blood glucose, U&Es, calcium, magnesium, phosphate and ABG. Correct acid base and metabolic disturbances as required.
- Single brief convulsions do not require treatment.
- Control convulsions that are frequent or prolonged with intravenous diazepam (10-20 mg in adults; 0.1-0.3 mg/kg body weight in children), lorazepam (4 mg in adults; 0.1 mg/kg in children), or midazolam (5-10 mg in adults; 0.05-0.15 mg/kg in children).
- Further doses of benzodiazepines may be needed in adults; refer to intensive care. In children seek consultant paediatric input.
- If unresponsive to the above measures, the patient should be referred urgently to critical care. Barbiturates are recommended as second line therapy and avoid phenytoin.

Workflow for Acute Management of Calcium Channel Blocker Overdose



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Digoxin Overdose

Digoxin is a cardiac glycoside used in the treatment of chronic heart failure and controlling the ventricular rate in persistent atrial fibrillation. Poisoning with digoxin is usually accidental, arising from prescription of an excessive dose, impairment of renal function or drug interactions. In South Asia, deliberate self-poisoning with yellow oleander (*Thevetia peruviana*), containing cardiac glycosides, is common.

Toxic dose

Digoxin has a narrow therapeutic index and toxicity is common. The fatal dose is variable depending on whether patients are already taking digoxin therapeutically or are digoxin-naive. Death usually occurs from ventricular arrhythmias, conduction impairment or pump failure. Cardiovascular toxicity from digoxin is likely to be more severe in patients exposed to other cardiotoxic substances e.g. beta blockers and rate limiting calcium channel blockers.

Asymptomatic adults who are **not** on digoxin therapeutically and who have accidentally ingested **≥ 20 µg/kg** should be referred for medical assessment.

Asymptomatic adults who **are** on digoxin therapeutically and who have accidentally ingested 3 or more times their normal daily dose should be referred for medical assessment.

Mechanism of Toxicity

Cardiac glycosides are used primarily to increase inotrophy in cardiac myocytes but also affect cells in the vascular smooth muscle and sympathetic nervous system.

Normal depolarization of the cardiac myocyte begins with the opening of the fast sodium channels. The resulting increase in intracellular sodium, and subsequent change in the resting membrane potential, opens voltage-gated calcium channels. The initial influx of calcium induces further release of calcium from the sarcoplasmic reticulum, which results in muscle contraction. Sodium is then removed from the cell by, among several mechanisms, the sodium-potassium-ATPase. Some calcium is removed from the cell by the sodium-calcium antiporter.

Cardiac glycosides reversibly inhibit the sodium-potassium-ATPase, causing an increase in intracellular sodium and a decrease in intracellular potassium. The increase in intracellular sodium prevents the sodium-calcium antiporter from expelling calcium from the myocyte, which increases intracellular calcium. The net increase in intracellular calcium augments inotropy. Cardiac glycosides also increase vagal tone, which results in decreased conduction through the sinoatrial and atrioventricular nodes.

Excessive intracellular calcium may cause delayed after-depolarizations, which may in turn lead to premature contractions and trigger arrhythmias. Cardiac glycosides shorten repolarization of atria and ventricles, decreasing the refractory period of the myocardium, thereby increasing automaticity and the risk for arrhythmias.

Features of poisoning

Acute overdose in patients on regular therapy is expected to be more toxic than in naïve patients dose-for-dose. Plasma digoxin concentrations do not correlate well with features of toxicity in poisoning. Cardiac effects may take more than 12 hours to fully develop. Severe toxic effects may be seen with digoxin concentrations greater than 4 µg/L (4.0 nanogram/mL; 5.2 nanomol/L). Young children tend to tolerate a higher peak plasma digoxin concentration than adolescents and adults.

Poor prognostic factors include: age over 55 years, male, underlying heart disease, high degree atrioventricular block and hyperkalaemia. Patients with renal impairment are also at greater risk of toxicity.

General features:

- Nausea, vomiting, diarrhoea and general malaise may develop within 1-2 hours of acute overdose, but cardiac features may take 6 hours or more to develop.
- Onset of features in toxicity from chronic therapy can be very variable, but is often preceded by dehydration from other causes or drug interactions.
- CNS features such as anorexia, headache, weakness and rarely blurred vision or alteration in colour perception (classically xanthopsia) may also occur.

Cardiac effects:

- Acute overdose usually causes a marked bradycardia with PR and QRS prolongation.
- Sinus arrest, varying degrees of AV block with dissociation or escape rhythms may occur, including paroxysmal atrial tachycardia with AV block, junctional tachycardia, frequent ventricular ectopics and bigeminy.

- Hypotension may occur. In cases of severe toxicity, ventricular tachycardia and ventricular fibrillation may occur.
- Arrhythmias are most common if there is pre-existing heart disease or there are electrolyte disturbances such as hypokalaemia.
- Clinical features common to cardiac/cardiotoxic agents involved in mixed overdoses may be more severe or prolonged.

Metabolic effects:

- Hyperkalaemia is common in severe poisoning, and is associated with poorer prognosis. It may be due to the effect of kidney injury, toxicity of other drugs, or a result of blockade of the sodium-potassium-ATPase pump causing potassium shift from the intracellular to the extracellular space.
- While hyperkalaemia is a useful marker of toxicity in acute overdose, it is less useful in chronic poisoning, as its absence does not indicate lack of toxicity.
- A metabolic acidosis may also be present.

Management

All patients who have been exposed to this product as a result of self-harm should be referred for assessment. All patients who have exceeded their prescribed daily dose of 2 or more of their cardiac medicines should be referred for medical assessment irrespective of the dose ingested. All children and symptomatic adults who have ingested digoxin should be referred for medical assessment.

Asymptomatic adults who are **not** on digoxin therapeutically and who have accidentally ingested ≥ 20 µg/kg should be referred for medical assessment. Asymptomatic adults who **are** on digoxin therapeutically and who have accidentally ingested ≥ 3 times their normal daily dose should be referred for medical assessment.

Emergency Management

- Maintain a clear airway and ensure adequate ventilation.
- **Cardiac arrest:**

In hospital or witnessed out of hospital cardiac arrest with bystander CPR, resuscitation should be continued for at least 1 hour and only stopped after discussion with a senior clinician. Recovery without sequelae after continuous CPR for 3 hours has been reported.

- Treat hyperkalaemia conventionally.

- Collect a sample for digoxin concentration (if possible).

  Note: Currently, digoxin level cannot be assessed in Myanmar.

Digoxin specific antibodies (FAB fragments)) (Not currently available in Myanmar)

- **Indications:**
  - ✓ Severe bradyarrythmia or life-threatening ventricular arrhythmia.
  - ✓ Severe hyperkalaemia (e.g. $K^+ > 6.5$ mmol/L) resistant to conventional treatments.
- Urgently administer digoxin-specific antibody FAB fragments as an IV bolus; each vial should be reconstituted with 4 mL of sterile water by gentle mixing. Repeat as necessary after 15 minutes.
- **For digoxin and digitoxin:**
  - ✓ >40 kg: 5 vials (200 mg)
  - ✓ 20-40 kg: 2 vials (80 mg)
  - ✓ Child ≤ 20 kg: 1 vial (40 mg)
- The antidote effect is usually seen within 15-30 minutes of administration. Repeated doses may be necessary depending on the clinical features.

GI decontamination

- **To reduce absorption** consider giving activated charcoal (charcoal dose: 50 g for adults; 1 g/kg for children) if the patient is symptomatic, or has ingested of 20 micrograms/kg or more digoxin, or ingested any amount of a toxic plant, provided the airway can be protected and gut motility is normal. Even late administration of activated charcoal may be beneficial when this substance is ingested in overdose.

Initial assessment

- Monitor vital signs and check the capillary blood glucose.
- Check and record pupil size.
- Perform a 12-lead ECG in all patients who require assessment.
- Repeat 12-lead ECGs are recommended, especially in symptomatic patients or in those who have ingested other cardiotoxic medications.
- Digoxin specific antibodies are the treatment of choice for severe bradyarrhythmias and for life-threatening ventricular arrhythmias. The antidote effect is usually seen within 15-30 minutes of administration.

- Check U&Es and magnesium in all patients. Serum potassium correlates with cardiotoxicity.
- Observe all patients who require assessment for at least **6 hours** after ingestion.
- Following mixed overdoses involving cardiac/cardiotoxic agents, asymptomatic patients should be monitored for at least the longest period recommended in any of the individual TOXBASE® entries.
- Patients who are asymptomatic after this time with a normal ECG can then be considered for discharge with advice to return if symptoms develop.
- In symptomatic patients, or patients with an abnormal ECG, consider early discussion with HDU/ITU.
- Ensure rapid fluid resuscitation in patients with hypovolaemia; this may require invasive monitoring in patients with a history of left ventricular dysfunction. This will reduce plasma digoxin concentration rapidly in patients with hypovolaemia.

Management of Hyperkalaemia

Treat severe hyperkalaemia conventionally.

Adults:

- Give 10 mL of 10% calcium chloride (6.8 mmol) by slow intravenous injection with continuous cardiac monitoring. Alternatively, give 10 mL of 10% calcium gluconate (2.3 mmol) by slow intravenous injection. This dose can be repeated in 5-10 minutes if there is no improvement in the ECG up to a maximum of 30 mL (6.8 mmol).
- Give 5 mg nebulised salbutamol.
- Insulin and dextrose: Give 10 units of short acting insulin (e.g. Actrapid) with 100 mL of 20% dextrose IV over 5 minutes. If hyperkalaemia is not improving these doses may need to be repeated.
- In the presence of metabolic acidosis consider correction with intravenous sodium bicarbonate. An initial dose of 50 mmol sodium bicarbonate may be given and repeated as necessary, guided by arterial blood gas monitoring (aim for a pH of 7.44 [Hydrogen ion concentration 36]).

Children (less than 12 years):

- Early discussion with local paediatric teams is recommended.
- If evidence of ECG changes, with continuous cardiac monitoring, give 0.1 mL/kg bodyweight (max 10 mL) 10% calcium chloride by SLOW intravenous injection.

- Give nebulized salbutamol (2.5 mg under 5 years; 5 mg over 5 years) and remeasure serum potassium and blood pH.
- In the presence of metabolic acidosis give sodium bicarbonate 1-2 mmol/kg over 10 minutes and repeat until pH is 7.35 or above.
- If serum potassium is high in the absence of metabolic acidosis, give 5 mL/kg 10% glucose and commence intravenous 10% glucose with 0.9% NaCl at maintenance rate. Monitor blood glucose concentrations. Once glucose concentrations are above 10 mmol/L, if serum potassium is still not falling, commence an insulin infusion 0.05 units/kg/hour and titrate glucose rate to maintain blood glucose concentration above 5 mmol/L, which must be measured frequently.
- Hyperkalaemia secondary to digoxin overdose also responds to treatment with digoxin-specific antibody fragments.
- Administration of calcium gluconate has been shown to be safe in digoxin overdose.

Management of Hypokalaemia

- If there is hypokalaemia, give oral or intravenous potassium supplementation to keep serum potassium level at the high end of normal.

Measurement of Digoxin Concentration (Currently not available in Myanmar)

- Digoxin poisoning can be confirmed by elevated plasma concentration (usual therapeutic range: 1.3–2.5 mmol/L). After chronic exposure, concentrations > 5 mmol/L suggest serious poisoning.
- Digoxin concentration should be measured at least 6 hours post-ingestion. Samples for digoxin do not need to be measured urgently unless features of severe toxicity are present and treatment with digoxin specific antibodies is being considered.
- Following treatment with digoxin specific antibodies, current immunoassays will give falsely elevated digoxin concentrations as they measure both free digoxin and Fab-digoxin complexes.
- Digoxin elimination is slow (half-life 30-40 hours with normal renal function and up to 100 hours in patients with impaired renal function) and frequent analysis of digoxin is unhelpful.

Management of arrhythmias

- In severe bradyarrythmia or life-threatening ventricular arrhythmia, administer digoxin specific antibodies (Fab fragments) (See above).
- If digoxin specific antibodies are not immediately available for managing severe bradycardia and AV block, give atropine intravenously, 1.2 mg for an adult or 0.02 mg/kg for a child. Repeat doses may be necessary. Then, consider use of digoxin specific antibodies.
- Consider insertion of a temporary pacing wire if digoxin specific antibody fragments are not readily available and there is evidence of significant bradycardia or AV block with haemodynamic compromise.

Haemodialysis

- Haemodialysis or haemoperfusion are unlikely to enhance the elimination of digoxin as this drug has a large volume of distribution and is highly protein bound.
- However, in the presence of renal failure, haemodialysis may be of benefit for severe hyperkalaemia or acidosis, but potassium must be monitored repeatedly if digoxin specific antibody fragments are administered since the potassium concentration may fall rapidly.

Management of Hypotension

- Ensure adequate fluid resuscitation.
- Consider early referral to critical care for patients with fluid-resistant hypotension, as these patients can deteriorate extremely rapidly; the management of children with fluid-resistant hypotension should be overseen by an experienced paediatrician.
- Invasive vascular monitoring and echocardiography may help determine the likely relative benefits of inotropes and vasopressors because reduced cardiac output and vasodilation often co-exist in severe or mixed poisoning.
- There have been very occasional reports of worsening of hypotension associated with adrenaline treatment, thought to be due to beta-receptor agonist effects.
- Vasopressors and inotropes can be initiated in an emergency through peripheral venous access but only under the direction of an experienced physician.

Management of Metabolic acidosis

- If metabolic acidosis persists despite correction of hypoxia and adequate fluid resuscitation, consider correction with intravenous sodium bicarbonate.

Adults: an initial dose of 50-100 mmol sodium bicarbonate (e.g. 50-100 mL 8.4% or 100-200 mL 4.2%) may be given and repeated as necessary, guided by arterial blood gas monitoring, aiming for a normal pH. The volumes for different concentrations of sodium bicarbonate to achieve a dose of 50-100 mmol in adults are shown here.

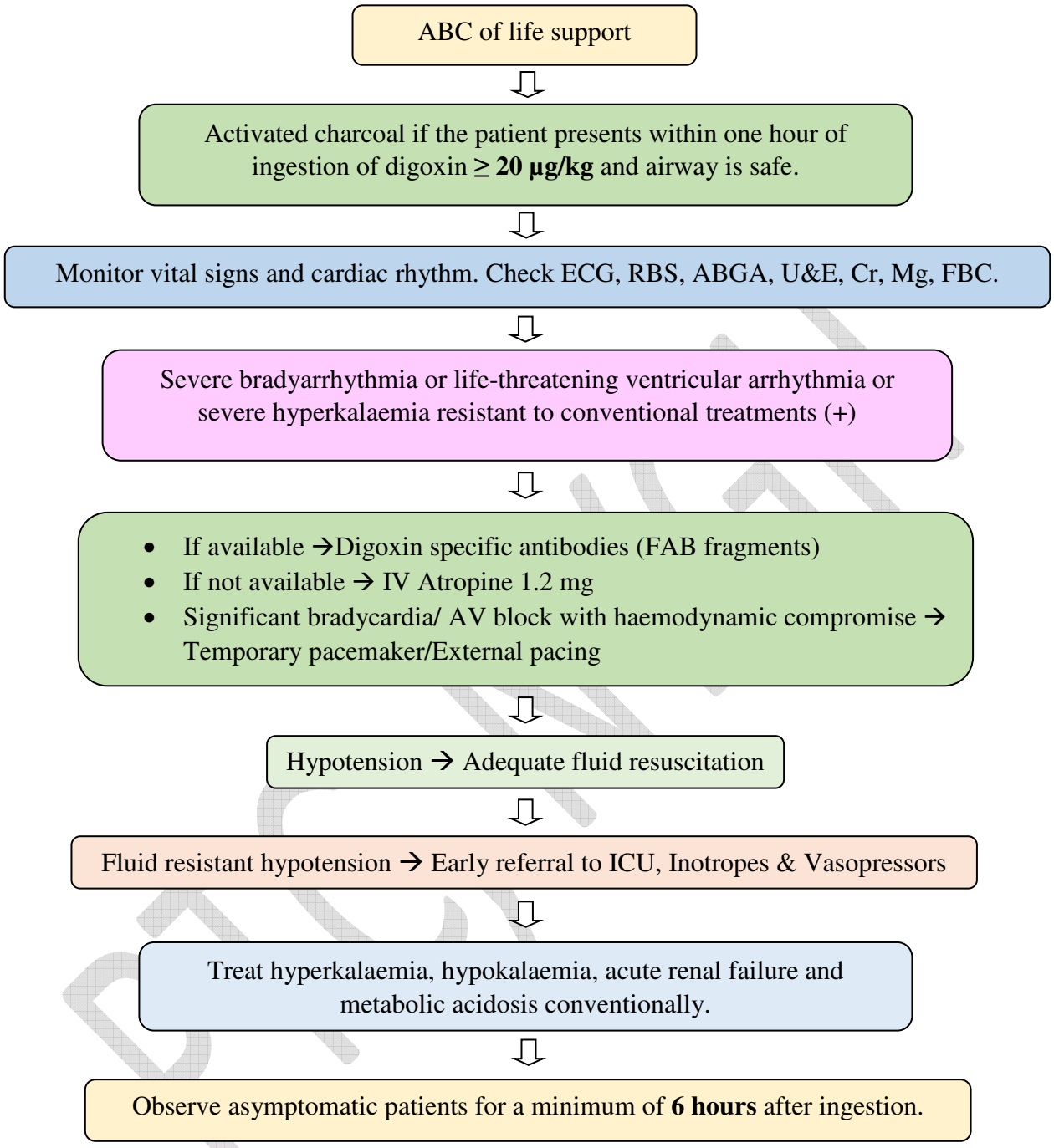
Concentration of $NaHCO_3$	Volume (ml) of $NaHCO_3$ providing		
	50 mmol	100 mmol	225 mmol
%	ml	ml	ml
8.4%	50	100	225
4.2%	100	200	450
1.4%	300	600	1350
1.26%	333	667	1500

Children: Give 1-2 mmol/kg sodium bicarbonate (1-2 mL/kg 8.4% or 2-4 mL/kg 4.2%) over 20 minutes. Repeat as necessary, aiming for a normal pH.

Adults and children: Recheck acid base status after administration of sodium bicarbonate. For severe acidosis, large amounts of bicarbonate with repeated pH checking may be required to correct the metabolic acidosis. Monitor electrolytes since there is a risk of hypokalaemia and possibly hypernatraemia.

Other measures as indicated by the patient's clinical condition. Patients should be advised on discharge to seek medical attention if symptoms subsequently develop.

Workflow for Acute Management of Digoxin Overdose



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Acute Salicylate (Aspirin) Overdose

Aspirin is non-steroidal anti-inflammatory analgesic and antiplatelet medication used for prevention of thrombotic events. It is a weak acid with poor water solubility. It is present in many over-the-counter preparations.

Mechanism of Toxicity

Low doses of salicylates have a direct irritant effect on the gastrointestinal tract. In higher doses, salicylates directly stimulate the respiratory centre in the medulla triggering hyperventilation and the development of respiratory alkalosis. Uncoupling of oxidative phosphorylation leads to anaerobic metabolism and the production of lactate and heat. The net result of these changes is a high anion gap metabolic acidosis. Rhabdomyolysis may occur.

At normal physiological pH, most salicylate is present in the ionized form; at lower blood pH, more is present in the non–ionized form which has a higher volume of distribution and crosses the blood brain barrier into the CNS more readily.

Maintaining blood pH above normal increases the proportion of ionized salicylate and therefore reduces the penetration to the CNS and resulting toxicity. Increasing urinary pH to greater than 7.5 increases the elimination of salicylate.

Uncoupling of oxidative phosphorylation increases tissue demand for glucose oxidation. The brain seems especially sensitive to this effect, and CNS glucose depletion (neuroglycopenia) can occur in the presence of normal blood sugar concentrations. If hepatic glycogen stores are adequate, catecholamine production stimulates glycogenolysis, leading to hyperglycaemia, which may persist for several days.

The mechanism for ototoxicity is thought to be multifactoral: vasoconstriction causes reduced cochlear blood flow; membrane permeability changes cause loss of outer hair cell turgor in the organ of Corti (Nelson et al, 2011).

Although rarely a clinical problem, salicylate intoxication is often accompanied by hypoprothrombinaemia due to warfarin-like action of salicylates on the physiologically important Vitamin K-epoxide cycle.

Features of poisoning

Mild poisoning (Ingested dose ≥ 150 mg/kg)

Usually associated with a peak salicylate concentration of less than 300 mg/L (2.2 mmol/L): nausea, vomiting, tinnitus, deafness, lethargy or dizziness.

Moderate poisoning (Ingested dose ≥ 250 mg/kg)

Usually associated with a salicylate concentration of 300 - 700 mg/L (2.2 - 5.1 mmol/L): dehydration, restlessness, sweating, warm extremities with bounding pulses, increased respiratory rate and hyperventilation. Respiratory alkalosis is often present at lower concentrations; metabolic acidosis may co-exist.

Severe poisoning (Ingested dose ≥ 500 mg/kg)

Usually associated with a peak salicylate concentration of more than 700 mg/L (5.1 mmol/L): cardiac dysrhythmias, acute non-cardiogenic pulmonary oedema, cerebral oedema, convulsions, confusion, coma, hyperpyrexia, heart failure, renal failure and worsening metabolic and lactic acidosis. Central nervous system features including confusion, disorientation, coma and convulsions are more common in children.

Most adult deaths occur in patients whose concentrations exceed 700 mg/L (5.1 mmol/L). Patients are more likely to die if they are aged over 70 years, or if they develop coma, convulsions, confusion, agitation, hyperpyrexia, pulmonary oedema or metabolic acidosis.

Common acid-base changes:

A mixed respiratory alkalosis and metabolic acidosis with normal or high arterial pH (normal or reduced hydrogen ion concentration) is often seen in adults and children over the age of 4 years. Anion gap is usually increased in severe cases. However very high salicylate concentrations can cause a falsely high chloride concentration on some analyzers and cause the anion gap to appear normal.

Children aged 4 years or less may not develop respiratory alkalosis.

Uncommon features

Haematemesis, hyperpyrexia, hypokalaemia, thrombocytopenia, ketonemia, increased INR/PTR, DIC. Hypoglycaemia or hyperglycaemia has been reported and is more common in younger children.

Patient with **chronic salicylate intoxication** may present with only non-specific features such as confusion, malaise and dyspnoea.

Management

Children and adults who might have ingested **≥ 125 mg/kg** salicylate, or those who are **symptomatic**, should be referred for medical assessment. Children or adults for whom the amount accidentally ingested is known to be < 125 mg/kg salicylate and who have no new symptoms since the time of ingestion do not need to be referred for medical assessment (provided the preparation does not contain other agents). Patients should be advised to seek medical attention if symptoms develop.

Emergency Management

- Maintain a clear airway and ensure adequate ventilation.
- Avoid intubation unless there is evidence of respiratory failure (worsening respiratory acidosis, severe hypoxemia). Loss of hyperventilatory drive can result in sudden decompensation and death.
- Ensure hypokalaemia is corrected and urinary alkalinisation is instigated prior to intubation where possible. Frequent arterial blood gas monitoring is required to maintain pH of 7.5 to 7.6.
- **The benefit of gastric decontamination is uncertain.** Consider activated charcoal (charcoal dose: 50 g for adults; 1 g/kg for children) if the patient presents within 1 hour of ingestion of 125 mg/kg or more salicylate, or any amount of methyl salicylate, providing it is safe to do so and the airway can be protected. Efficacy declines rapidly with time since ingestion but there may be some potential benefit from later use, especially following large ingestions.
- A second dose of charcoal may be warranted in patients whose plasma salicylate concentration continues to rise, suggesting delayed gastric emptying, or who have taken enteric coated preparations where absorption may be slower.
- Where the practical expertise exists, consider gastric lavage in adults within 1 hour of a potentially life-threatening overdose (suggested dose ≥ 500 mg/kg salicylate), providing the airway can be protected.

Measurement of Plasma salicylate concentration

- Ideally, an urgent plasma salicylate concentration should be taken at least 2 hours (symptomatic patients) or 4 hours (asymptomatic patients) after ingestion, since it may take several hours for peak plasma concentrations to occur with enteric-coated preparations.
- Repeat salicylate concentrations every 2 hours in all patients who are symptomatic, or those with initial plasma salicylate concentrations of 200 mg/L or more until concentrations are falling and any clinical features have improved. However, **plasma salicylate concentration cannot be assessed in Myanmar currently**.
- There is no need to measure salicylate concentrations in conscious overdose patients who deny taking salicylate-containing preparations and who have no features suggesting salicylate toxicity.

Initial Assessment

- Monitor vital signs and cardiac rhythm; check the capillary blood glucose.
- Check and record pupil size.
- Check acid-base status, U&Es, INR and FBC.
- Perform a 12-lead ECG in all patients who require assessment.
- Consider repeating the ECG in **ANY OF** the following circumstances:
  - ✓ The initial ECG is abnormal
  - ✓ The patient is symptomatic
  - ✓ The recommended observation period (6 hours after overdose) is not yet complete.
- Check cardiac rhythm, QT interval and QRS duration.
- Asymptomatic patients with normal acid-base status can be considered for discharge after observation for **6 hours following the overdose**, provided their plasma salicylate concentration is below 300 mg/L (2.2 mmol/L). As plasma salicylate level cannot be assessed currently, it is advisable to keep the asymptomatic patient under observation for 24 hours after overdose.
- Treat hypokalaemia urgently; this will reduce the risk of severe hypokalaemia with bicarbonate therapy if this becomes necessary later.
- Once the serum potassium concentration is within the normal range, start to correct metabolic acidosis in an adult with intravenous sodium bicarbonate 50-100 mmoL given

over 30 minutes. Administration of sodium bicarbonate will reduce transfer of salicylate into the central nervous system and hence reduce toxicity. Child: 1 mL/kg 8.4% bicarbonate diluted in 0.5 L 5% dextrose or normal saline at 2-3 mL/kg/hour.

Urinary alkalinisation

- The elimination of salicylate may be increased by alkalinisation of the urine, using the regimen given below. The optimum urine pH is 7.5-8.5.
  - ✓ Adults:
    Give 225 mmol sodium bicarbonate i.e.1.5 L of 1.26% over two hours Or
    225 mL of 8.4% over one hour
    Aim to increase the urine pH to greater than 7.5.
  - ✓ Children:
    Give 4-10 mL/kg of 4.2% sodium bicarbonate diluted in an equal volume of 5% glucose over one hour.
  - ✓ In both adults and children:
    Further doses of sodium bicarbonate may be required to obtain and subsequently maintain a urine pH greater than 7.5.
- Since 4.2% and 8.4% bicarbonate are irritant to veins, and can rarely cause local necrosis in cases of extravasation, administer into a large vein (or via a central line where possible). A bolus should be preceded and followed by a large flush to confirm cannula position and to reduce local contact.
- The urinary pH should be checked hourly. Plasma sodium and potassium should also be checked 1-2 hourly, and potassium replaced IV, if necessary, to maintain plasma potassium around 4-4.5 mmol/L.
- **Indications for urine alkalinisation:**
  - ✓ Plasma salicylate concentration is above 500 mg/L (3.6 mmol/L) in adults and 350 mg/L (2.5 mmol/L) in children
  - ✓ S/S of severe salicylate poisoning such as altered mental status, pH < 7.2, hypoxaemia, impaired renal function
- Forced diuresis should not be used since it does not enhance salicylate excretion and may cause pulmonary oedema.

Haemodialysis

- Haemodialysis (or haemodiafiltration) is the treatment of choice for severe poisoning.
- **Indications for haemodialysis:**
  - ✓ salicylate concentration of 900 mg/L (6.4 mmol/L) or more
  - ✓ salicylate concentrations greater than 700 mg/L (5.1 mmol/L) with a metabolic acidosis
  - ✓ coma due to salicylate poisoning
- It should also be considered for patients with a plasma salicylate concentration greater than 700 mg/L (5.1 mmol/L).
- Dialysis may also benefit those with severe acidosis, renal failure, congestive cardiac failure, or non-cardiogenic pulmonary oedema.
- Patients aged less than 10 years, or over 70 years old, have increased risk of salicylate toxicity and may require dialysis at lower plasma salicylate concentrations.
- Haemodialysis/diafiltration is the modality of choice because it removes salicylate and corrects acidosis more rapidly than haemofiltration. In hospitals without dialysis facilities, haemofiltration may be an alternative, particularly if transfer is likely to be delayed.
- Urine akalinisation should not be withheld whilst awaiting haemodialysis, although caution is needed to avoid volume overload if the patient is oliguric.

Management of Hyperthermia

- Mild to moderate hyperthermia may respond to conventional cooling measures such as:
  - ● Mist and fan techniques
  - ● Ice packs to groin and axillae
  - ● External cooling devices.
- When rising body temperature exceeds 38.5°C, urgent cooling measures with regular monitoring of core temperature, at least every 30 minutes, should be employed according to local protocols.
- Dantrolene may be considered where there is muscular hyperactivity (initially 2-3 mg/kg by intravenous injection, to a maximum of 10 mg/kg.).
- In patients with pyrexia, monitor renal function and CK activity. Ensure adequate

hydration and monitor urine output carefully.

- Consider other causes (e.g., serotonin toxicity, neuroleptic malignant syndrome) as hyperthermia may be caused by conditions other than poisoning.

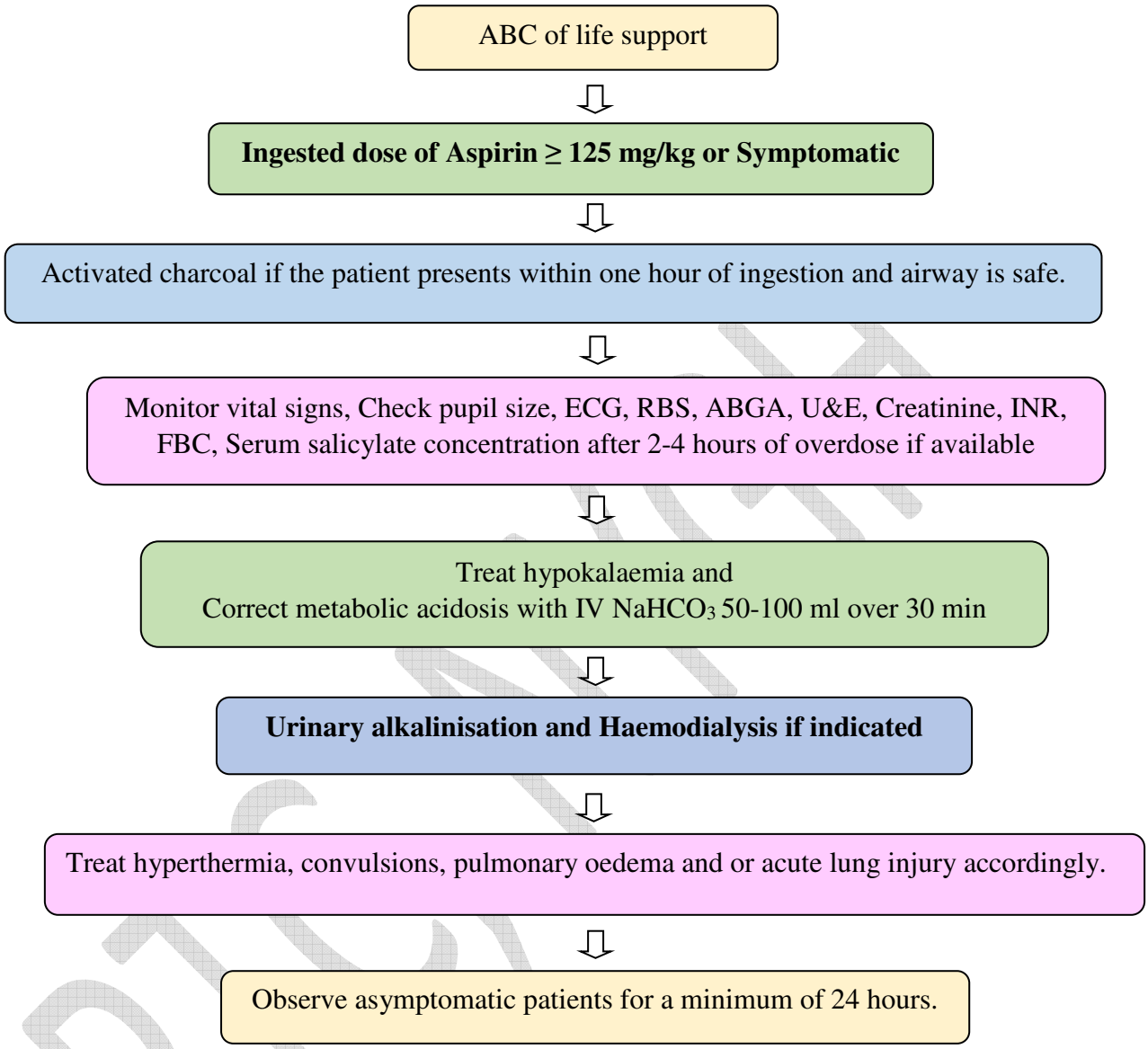
Management of Convulsions

- Give oxygen; check blood glucose, U&Es, calcium, magnesium, phosphate and ABG.
- Correct acid base and metabolic disturbances as required. Single brief convulsions do not require treatment.
- Control convulsions that are frequent or prolonged with intravenous diazepam (10-20 mg in adults; 0.1-0.3 mg/kg body weight in children), lorazepam (4 mg in adults; 0.1 mg/kg in children), or midazolam (5-10 mg in adults; 0.05-0.15 mg/kg in children).
- If further doses of benzodiazepines may be needed in adults; refer to intensive care.

Management of Pulmonary oedema and/or acute lung injury

- Treat pulmonary oedema and/or acute lung injury conventionally. Continuous positive airway pressure (CPAP) or in severe cases with IPPV and PEEP, and other standard therapies may be considered.

Workflow for Management of Acute Salicylate Overdose



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Tricyclic Antidepressant Overdose

Tricyclic antidepressants (TCAs) block the re-uptake of both serotonin and noradrenaline and are used in the management of depression, anxiety disorders and neuropathic pain. Currently available TCAs include amitriptyline, clomipramine, dosulepin, doxepin, imipramine, lofepramine, nortriptyline and trimipramine.

Some TCAs and their toxic doses

Drug	Toxic dose	Peak plasma concentration	Therapeutic elimination half life
Amitriptyline	3 mg/kg	6 hrs	9-25 hrs
Clomipramine	4 mg/kg	-	12-36 hrs
Desipramine	3 mg/kg	2-6 hrs	17-27 hrs
Dosulepin	3 mg/kg	3.5 hrs	14-24 hrs
Doxepin	4 mg/kg	2-4 hrs	8-24 hrs
Imipramine	4 mg/kg	2-8 hrs	19 hrs
Nortriptyline	2.5 mg/kg	2-8 hrs	26 hrs
Trimipramine	5 mg/kg	2 hrs	23 hrs
Lofepramine	4.5 mg/kg	1 hr	5 hrs

Mechanism of Toxicity

Tricyclic antidepressants are **highly toxic** by ingestion; fatal cardiac arrhythmias may occur soon after ingestion. Toxicity is due to a combination of anticholinergic (antimuscarinic, atropine-like) effects at autonomic nerve endings and in the brain, cardiac sodium channel blockade and alpha 1 adrenergic receptor blockade. In addition, tricyclic antidepressants block pre-synaptic uptake of amines and the cardiac delayed rectifier potassium channel (Ikr).

Features of poisoning

- Severe toxicity occurs from sodium channel blockade and may cause arrhythmias, cardiovascular collapse, convulsions and coma.
- Features include those of anti-cholinergic toxicity: sinus tachycardia, confusion, drowsiness, hot dry skin, dry mouth and tongue, dilated pupils, urinary retention and ileus. Ataxia, nystagmus, divergent squint, and myoclonus may occur.
- **In severe cases**, central nervous system depression may progress rapidly to deep coma, with convulsions, respiratory depression and respiratory arrest. Adult respiratory distress syndrome may develop. Convulsions may herald cardiovascular shock.

- ECG features include prolongation of the PR, QRS and QT intervals, non-specific ST segment and T wave changes, and atrioventricular block. Brugada electrocardiographic pattern has been reported. Prolonged QRS is a predictor of convulsions and ventricular arrhythmias.
- Hypotension, hypokalaemia and metabolic acidosis may occur. Hypothermia and rhabdomyolysis, and occasionally skin blisters, may occur in patients who have been unconscious.
- Increased tone and hyper-reflexia may be present with extensor plantar reflexes. In deep coma, all reflexes (including brain-stem reflexes) may be abolished.
- **During recovery**, confusion, agitation and visual hallucinations may occur.
- **Serotonin syndrome** is a possibility. It is characterized by the triad of altered mental status, neuromuscular hyperactivity and autonomic instability. Mental status changes occur in 40% of patients. Features may include agitation, confusion, delirium, and hallucinations. Drowsiness and coma may occur in severe cases. Neuromuscular features occur in around 50% of patients and include profound shivering, tremor, teeth grinding, myoclonus and hyperreflexia. Autonomic instability occurs in around 50% of patients. Features include tachycardia, fever and hypertension or hypotension. Flushing, diarrhoea and vomiting are also common. In severe cases, convulsions, hyperthermia, rhabdomyolysis, acute kidney injury, coagulopathies and multi-organ failure may develop.
- The cardiovascular and CNS effects in overdose will be potentiated by simultaneous ingestion of alcohol, cardiovascular agents and other psychotropic drugs.
- Clinical features common to cardiac/cardiotoxic agents involved in mixed overdoses may be more severe or prolonged.

Management

- All patients who have been exposed to this product as a result of self-harm should be referred for assessment.
- All patients who have exceeded their prescribed daily dose of ≥ 2 cardio-toxic agents should be referred for medical assessment irrespective of the dose ingested.
- All children who have ingested any amount of a tricyclic antidepressant should be referred for medical assessment.

- Adults who have ingested a toxic dose or more (see the above table), or those who are symptomatic, should be referred for medical assessment.

Emergency management

Do not give flumazenil to reverse benzodiazepine toxicity in mixed overdoses.

- Maintain a clear airway and adequate ventilation.
- In the event of cardiac arrest in hospital or witnessed out of hospital cardiac arrest with bystander CPR, resuscitation should be continued for at least 1 hour and only stopped after discussion with a senior clinician.
- If the patient may have been exposed to a sodium channel antagonist, or if QRS duration had been prolonged prior to cardiac arrest, administer a rapid bolus of 100 mL of 8.4% sodium bicarbonate urgently, preferably into a large vein. 8.4% sodium bicarbonate is irritant, and should be preceded and followed by a large fluid flush to confirm cannula position and reduce local contact. Monitor pH and administer further doses as necessary.
- Prolonged resuscitation for cardiac arrest is recommended following poisoning as recovery with good neurological outcome may occur.
- **The benefit of gastric decontamination is uncertain**. Consider activated charcoal (charcoal dose: 50 g for adults; 1 g/kg for children) if the patient presents within 1 hour of ingestion of more than a potentially toxic dose, providing it is safe to do so and the airway can be protected. A second dose of charcoal (charcoal dose: 50 g for adults; 1 g/kg body weight for children) should be considered after 1-2 hours in patients with features of toxicity who are able to swallow, or who have been intubated. Although it may seem reasonable to assume that late administration of activated charcoal may be beneficial for modified release preparations, there is no clinical trial evidence to support this.

Initial Assessment

- Monitor vital signs and cardiac rhythm.
- This agent is cardiotoxic and careful assessment of the ECG is required. Perform a 12-lead ECG in all patients who require assessment.
- Consider repeating the ECG in **ANY OF** the following circumstances:
  - ✓ The initial ECG is abnormal.
  - ✓ The patient is symptomatic.
  - ✓ The recommended observation period is not yet complete.

- Check cardiac rhythm, QT interval and QRS duration. Prolongation of the QRS interval (especially if >160 msec) indicates severe sodium channel blockade and a high risk of arrhythmia.
- **If the QRS is prolonged, these patients need treatment with sodium bicarbonate (see below for doses).**
    - Concentrated bicarbonate is irritant; administer into a large vein (or via a central line where possible). A bolus should be preceded and followed by a large fluid flush to confirm cannula position and reduce local contact.
    - Monitor electrolytes; hypokalaemia, hypocalcaemia or hypernatraemia may occur after large doses of sodium bicarbonate.
    - Correct hypoxia, hypercapnia and acidosis.
    - **Monitor QRS duration and aim for a serum pH of 7.5-7.55 (H^+ 28-32).**

Cardiac arrest, VT or QRS ≥ 160 msec	Administer a rapid bolus of 100 mmol (i.e.100 mL 8.4%) sodium bicarbonate **urgently**. A repeat bolus may be administered if there is persistent QRS prolongation or arrhythmias and the pH is < 7.5.
QRS 120-160 msec	Administer 50 mmol (i.e. 50 mL 8.4%) sodium bicarbonate. A repeat bolus may be administered if there is persistent QRS prolongation
Children with QRS prolongation	Administer 1-2 mL/kg 8.4% (centrally) or 2-4 mL/kg 4.2% (peripherally): If cardiac arrest or VT – as a bolus If prolonged QRS alone – over 20 minutes

Patients may additionally need treatment with magnesium if the QT is prolonged.

- Check U&Es and monitor urine output. Check serum CK in patients who have been unconscious.
- Consider arterial/venous blood gas analysis in patients who have a reduced level of consciousness, reduced oxygen saturation on pulse oximetry or metabolic disturbance.
- All patients who require assessment should be observed for at least **6 hours** after exposure.

- Following mixed overdoses involving cardiac/cardiotoxic agents, asymptomatic patients should be monitored for at least the longest period recommended in any of the individual TOXBASE® entries.
- Check pulse and blood pressure. Monitor cardiac rhythm. Repeat ECGs should be performed. In symptomatic patients, or patients with an abnormal ECG, consider early discussion with HDU/ITU.
- Asymptomatic patients with a normal ECG after 6 hours can be considered for discharge with advice to return if symptoms develop.

Management of Metabolic acidosis

- If metabolic acidosis persists despite correction of hypoxia and adequate fluid resuscitation, consider correction with intravenous sodium bicarbonate.

Adults: an initial dose of 50-100 mmol sodium bicarbonate (e.g. 50-100 mL 8.4% or 100-200 mL 4.2%) may be given and repeated as necessary, guided by arterial blood gas monitoring, aiming for a normal pH. The volumes for different concentrations of sodium bicarbonate to achieve a dose of 50-100 mmol in adults are shown here.

Concentration of $NaHCO_3$	Volume (ml) of $NaHCO_3$ providing		
	50 mmol	100 mmol	225 mmol
%	ml	ml	ml
8.4%	50	100	225
4.2%	100	200	450
1.4%	300	600	1350
1.26%	333	667	1500

Children: Give 1-2 mmol/kg sodium bicarbonate (1-2 mL/kg 8.4% or 2-4 mL/kg 4.2%) over 20 minutes. Repeat as necessary, aiming for a normal pH.

Adults and children: Recheck acid base status after administration of sodium bicarbonate. For severe acidosis, large amounts of bicarbonate with repeated pH checking may be required to correct the metabolic acidosis. Monitor electrolytes since there is a risk of hypokalaemia and possibly hypernatraemia.

Management of Convulsions

- Give oxygen; check blood glucose, U&Es, calcium, magnesium, phosphate and ABG. Correct acid base and metabolic disturbances as required.
- Single brief convulsions do not require treatment.
- Control convulsions that are frequent or prolonged with intravenous diazepam (10-20 mg in adults; 0.1-0.3 mg/kg body weight in children), lorazepam (4 mg in adults; 0.1 mg/kg in children), or midazolam (5-10 mg in adults; 0.05-0.15 mg/kg in children).
- Further doses of benzodiazepines may be needed in adults; refer to intensive care. In children seek consultant paediatric input.
- If unresponsive to the above measures, the patient should be referred urgently to critical care. Barbiturates are recommended as second line therapy and avoid phenytoin.

Management of Hypotension

- Ensure adequate fluid resuscitation. Treat brady and tachyarrhythmias appropriately.
- Consider early referral to critical care for patients with fluid-resistant hypotension, as these patients can deteriorate extremely rapidly.
- Sodium bicarbonate administration may be of benefit in fluid resistant hypotension in the context of sodium channel blocker toxicity, especially if there is QRS prolongation. Consider administration of 50 mmol (i.e. 50 mL 8.4%) sodium bicarbonate. Repeat doses may be required. Aim for **a serum pH of 7.5 - 7.55 (H^+ 28-32).**
- Invasive vascular monitoring and echocardiography may help determine the likely relative benefits of inotropes and vasopressors because reduced cardiac output and vasodilation often co-exist in severe or mixed poisoning.
- There have been very occasional reports of worsening of hypotension associated with adrenaline treatment, thought to be due to beta-receptor agonist effects.
- Vasopressors and inotropes can be initiated in an emergency through peripheral venous access but only under the direction of an experienced physician.

Glucagon - severe hypotension (Not currently available in Myanmar)

- Glucagon is a treatment option for severe hypotension, heart failure or cardiogenic shock.

In adults:

- A bolus of 5-10 mg IV in adults should be administered over 1-2 minutes, followed by an infusion of 50-150 micrograms/kg/hour, titrated to clinical response. Infusion is an off-

label method of glucagon administration. Limited evidence is available for the use of doses in excess of 10 mg/hour. If haemodynamic improvement is not achieved with this dose, consider the use of additional treatments for hypotension.

In children:

- A bolus of 50-150 micrograms/kg IV should be administered over 1-2 minutes, followed by an infusion of 50 micrograms/kg/hour, titrated to clinical response.

Note: Beware adverse effects of intravenous administration, in particular vomiting, hyperglycaemia, hypokalaemia and hypocalcaemia. Consider prophylactic treatment with an antiemetic.

Note: Glucagon must be used immediately following reconstitution, do not prepare well in advance. Calcium-containing solutions (e.g. Hartmann's) and sodium chloride are not suitable dilutents as precipitation may occur. The use of water as a diluent has been associated with thrombophlebitis. Cloudy solutions must not be used. There is no recommended final volume/concentration for dilution; for adults, it is usually convenient to dilute in 100 mL or 250 mL, but smaller or larger infusion volumes can be used.

High Dose Insulin Euglycaemic Therapy (For Adults)

- In patients with severe impairment of myocardial contractility, an insulin and dextrose infusion has been shown to improve systemic perfusion. It is particularly useful in the presence of acidosis.
- Give dextrose and insulin as per protocol. Monitor for hypoglycaemia and hypokalaemia.

Mechanical Cardiac Support (Not currently available in Myanmar)

- Mechanical adjuncts which may be a bridge to recovery in patients with life-threatening haemodynamic instability where other measures have failed -
    - ✓ vaECMO (veno-arterial extracorporeal membrane oxygenation) or cardiac bypass.
    - ✓ intra-aortic balloon pump (for those patients without severe rhythm disturbance).

Management of Agitation and Delirium/Psychosis

- Where available, follow local guidelines for treatment of agitation and delirium.
- The primary goal of management is to keep patient and staff safe while allowing continued evaluation. Ensure other causes are excluded (e.g. hypoxia, infection,

hypoglycaemia and raised ICP). Attempt de-escalation by reducing environmental stimuli (e.g. quiet room) and providing basic needs (e.g. a close relative, a warm blanket and food (if appropriate)).

For pharmacotherapy in adults:

- Give an initial dose of oral or IV diazepam (10-20 mg) or lorazepam (1-2 mg). Further boluses, given IV, may be administered if the patient remains agitated, provided there is no impairment of respiratory function.
- If oral and IV routes are not available, give lorazepam IM (1-2 mg) or midazolam IM (5-10 mg) repeated as necessary.
- Patients with severe agitation may need high doses of intravenous diazepam (total dose in excess of 100 mg given incrementally). These patients need urgent referral to critical care.
- **Haloperidol** (5-10 mg IM) may be an adjunct when agitation remains resistant to two or more benzodiazepine doses as described above. Antipsychotics should be avoided in patients with Parkinson's disease.
- **Ketamine** has also been used for uncontrolled agitation but must be used by a practitioner experienced in its use in an appropriate clinical environment with equipment for intubation if necessary.

Management of Hypothermia

- Rewarm slowly using conventional methods.

Management of Hyperthermia

- Mild to moderate hyperthermia may respond to conventional cooling measures such as:
  - ✓ Mist and fan techniques
  - ✓ Ice packs to groin and axillae
  - ✓ External cooling devices.
- When rising body temperature exceeds 38.5°C, urgent cooling measures with regular monitoring of core temperature, at least every 30 minutes, should be employed according to local protocols.
- Such measures include:
  - ✓ Ice-baths (may achieve rapid cooling but caution in elderly/comorbidities)

- ✓ Internal/invasive measures - cold fluid lavage (gastric, bladder, peritoneal), intravascular cooling techniques.

- Sedation should be employed where it can be safely performed (diazepam 10-20 mg in adults; 0.25 mg/kg body weight in children).
- Patients with severe hyperthermia may need high doses of intravenous diazepam (total dose in excess of 100 mg given incrementally). These patients need urgent referral to critical care.
- Dantrolene may be considered where there is muscular hyperactivity (initially 2-3 mg/kg by intravenous injection, to a maximum of 10 mg/kg.
- In patients with pyrexia, monitor renal function and CK activity. Ensure adequate hydration and monitor urine output carefully.

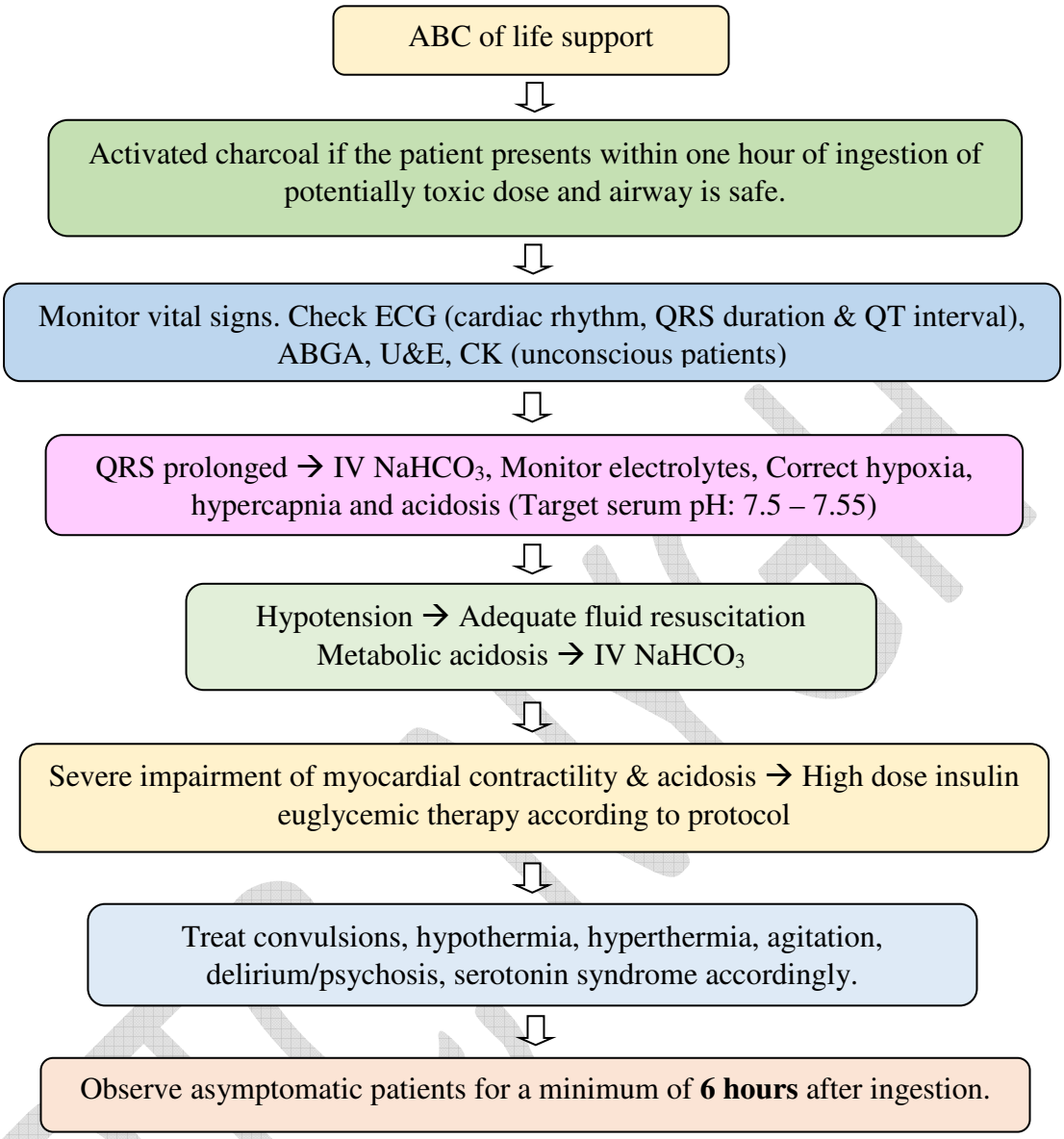
Management of Serotonin Syndrome

- Standard treatment of serotonin toxicity is benzodiazepines. Most mild cases will resolve spontaneously within 24 hours.
- Avoid all serotonergic agents including:
  - ✓ fentanyl patches (remove if already in place)
  - ✓ sedation using fentanils
- In serious cases, consider cyproheptadine and chlorpromazine. These are 5HT2A antagonists and have successfully been used to treat serotonin toxicity following overdose but there are no controlled trials to support the use of either agent.
- Give cyproheptadine (12 mg orally or via NG tube, followed by 4-8 mg every 6 hours in adults and children aged 13 years and older (32 mg max in 24 hours); 0.25 mg/kg/day (max 12 mg) in 4 divided doses in children aged 12 years or younger).
- In severe cases, give chlorpromazine 12.5-25 mg IV (fluid load first to avoid hypotension) followed by 25 mg orally every 6 hours.

Forced diuresis, haemodialysis and haemoperfusion are of no value due to the large volume of distribution of tricyclic antidepressants. Dialysis and haemoperfusion are not recommended for tricyclic overdoses (EXTRIP).

Other measures as indicated by the patient's clinical condition. Patients should be advised on discharge to seek medical attention if symptoms subsequently develop.

Workflow for Acute Management of TCA Overdose



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2. TOXBASE®. Serotonin toxicity - features and management updated 1/2021; Available from: http://www.toxbase.org.
3. Thomas SHL(2018) Tricyclic antidepressants in Poisoning by specific pharmaceutical agents: Davidson's Principles and Practice of Medicine 23rd Ed: 138-139.

Quetiapine Overdose

It is atypical antipsychotic used for management of schizophrenia and mania associated with bipolar disorder.

Toxic dose

Doses of around 20 mg/kg have been associated with sedation, agitation and hypotension. The lowest fatal dose reported is 10.8 g for an adult. The elimination half-life is approximately 7 hours in therapeutic use, but may be up to 22 hours in overdose.

Mechanism of Toxicity

It is an antagonist at D2 and 5HT2 receptors. It also produces alpha-adrenergic and histamine receptor blockade and anticholinergic effects.

Features of poisoning

- Toxicity is predominantly cardiovascular and neurological. Major clinical manifestations include coma, convulsions, tachycardia, hypotension and respiratory depression.
- Delayed onset convulsions have been reported 24-28 hours after ingestion.
- Sinus tachycardia, first degree AV block, QT and QRS prolongation and torsade de pointes may occur. Tachycardia and QT interval prolongation may persist for more than 48 hours after ingestion. Clinical features common to cardiac/cardiotoxic agents involved in mixed overdoses may be more severe or prolonged.
- Anticholinergic clinical features may occur including drowsiness, dizziness, lethargy, delirium, agitation, dry mouth, urinary retention, slurred speech and confusion.
- Hypokalaemia has been reported. There are isolated case reports of priapism and rhabdomyolysis.
- There is also a risk of neuroleptic malignant syndrome and dystonias.

Management

This agent is potentially very toxic. All patients who have been exposed to this product as a result of self-harm should be referred for assessment. All children who have taken any amount should be referred to hospital for medical assessment. All patients who have exceeded their prescribed daily dose of 2 or more cardio-toxic agents should be referred for medical assessment irrespective of the dose ingested. Adults who have accidentally ingested **≥ 15 mg/kg** quetiapine, or who have symptoms, should be referred for medical assessment.

Emergency management

- Maintain a clear airway and ensure adequate ventilation.
- In the event of cardiac arrest in hospital or witnessed out of hospital cardiac arrest with bystander CPR, resuscitation should be continued for at least 1 hour and only stopped after discussion with a senior clinician. Prolonged resuscitation for cardiac arrest is recommended following poisoning as recovery with good neurological outcome may occur.
- **The benefit of gastric decontamination is uncertain**. Consider activated charcoal (charcoal dose: 50 g for adults; 1 g/kg for children) if the patient presents within 1 hour of ingestion of 15 mg/kg or more quetiapine, providing it is safe to do so and the airway can be protected. Efficacy declines rapidly with time since ingestion but there may be some potential benefit from later use, especially following ingestion of sustained release preparations or large ingestions.

Initial Assessment

- Monitor vital signs and cardiac rhythm.
- Check and record pupil size.
- In symptomatic patients, check U&Es, LFTs, FBC, blood glucose and CK.
- Perform a 12-lead ECG in all patients who require assessment.
- Consider repeating the ECG in **ANY OF** the following circumstances:
  - ✓ The initial ECG is abnormal.
  - ✓ The patient is symptomatic.
  - ✓ The recommended observation period (at least 6 hours)is not yet complete.
- Check cardiac rhythm, QT interval and QRS duration.
- If the QT is prolonged (QT 'at risk' on nomogram):
  - Check serum potassium, magnesium and calcium concentrations and replace as necessary to keep within the high normal range.
  - Correct hypoxia and acidosis.
  - Administer magnesium sulphate IV over 10-15 minutes: adults 2 g (8 mmol Mg^{2+}), children 25-50 mg/kg (max 2 g). Note that while magnesium sulphate may terminate torsade de pointes, it does not shorten the QT interval.

  Note: Drugs that prolong the QT interval (e.g. amiodarone, quinidine) should be avoided and only considered on specialist advice.

- Observe all patients for at least **6 hours** after ingestion or **12 hours if a sustained release preparation** has been ingested.
- At the end of this period, patients who are alert and asymptomatic and have normal repeat 12 lead ECG can be considered for discharge with advice to return if symptoms develop. Symptomatic patients should be observed until symptoms are resolved.
- Following mixed overdoses involving cardiac/cardiotoxic agents, asymptomatic patients should be monitored for at least the longest period recommended in any of the individual TOXBASE® entries.

Management of Agitation and Delirium/Psychosis

- Where available, follow local guidelines for treatment of agitation and delirium.
- The primary goal of management is to keep patient and staff safe while allowing continued evaluation. Ensure other causes are excluded (e.g. hypoxia, infection, hypoglycaemia and raised ICP). Attempt de-escalation by reducing environmental stimuli (e.g. quiet room) and providing basic needs (e.g. a close relative, a warm blanket and food (if appropriate)).

For pharmacotherapy in adults:

- Give an initial dose of oral or IV diazepam (10-20 mg) or lorazepam (1-2 mg). Further boluses, given IV, may be administered if the patient remains agitated, provided there is no impairment of respiratory function.
- If oral and IV routes are not available, give lorazepam IM (1-2 mg) or midazolam IM (5-10 mg) repeated as necessary.
- Patients with severe agitation may need high doses of intravenous diazepam (total dose in excess of 100 mg given incrementally). These patients need urgent referral to critical care.
- **Haloperidol** (5-10 mg IM) may be an adjunct when agitation remains resistant to two or more benzodiazepine doses as described above. Antipsychotics should be avoided in patients with Parkinson's disease.
- **Ketamine** has also been used for uncontrolled agitation but must be used by a practitioner experienced in its use in an appropriate clinical environment with equipment for intubation if necessary.

For pharmacotherapy in children:

- **Pharmacological management of agitation in children must be supervised by staff experienced in paediatric airway management and sedation.**
- If required, **midazolam** is an appropriate drug for managing agitation in children and young people.
- This may be delivered -
  - ✓ buccally (dose 0.2 mg/kg to a maximum of 10 mg),
  - ✓ IM (dose 0.2 mg/kg to a maximum dose of 10 mg) or
  - ✓ IV (dose 0.025-0.05 mg/kg to a maximum dose of 6 mg in 6 months to 5 years old or 0.05-0.1 mg/kg to a maximum dose of 10 mg in 5-12 year olds)
- **Lorazepam** (0.01 mg/kg IV; max 2 mg) is an alternative.
- Repeat doses can be given if necessary up to the maximum cumulative dose. There is a particular risk of paradoxical increased agitation in young children.
- **Ketamine** has been used for severe agitation but should only be administered by a practitioner experienced in its use in an appropriate clinical environment with equipment for intubation if necessary.

Management of Convulsions

- Give oxygen; check blood glucose, U&Es, calcium, magnesium, phosphate and ABG. Correct acid base and metabolic disturbances as required.
- Single brief convulsions do not require treatment.
- Control convulsions that are frequent or prolonged with intravenous diazepam (10-20 mg in adults; 0.1-0.3 mg/kg body weight in children), lorazepam (4 mg in adults; 0.1 mg/kg in children), or midazolam (5-10 mg in adults; 0.05-0.15 mg/kg in children).
- Further doses of benzodiazepines may be needed in adults; refer to intensive care. In children, seek consultant paediatric input.
- If unresponsive to the above measures, the patient should be referred urgently to critical care.
- The barbiturates are recommended as second line therapy and phenytoin should be avoided.

Management of Hypotension

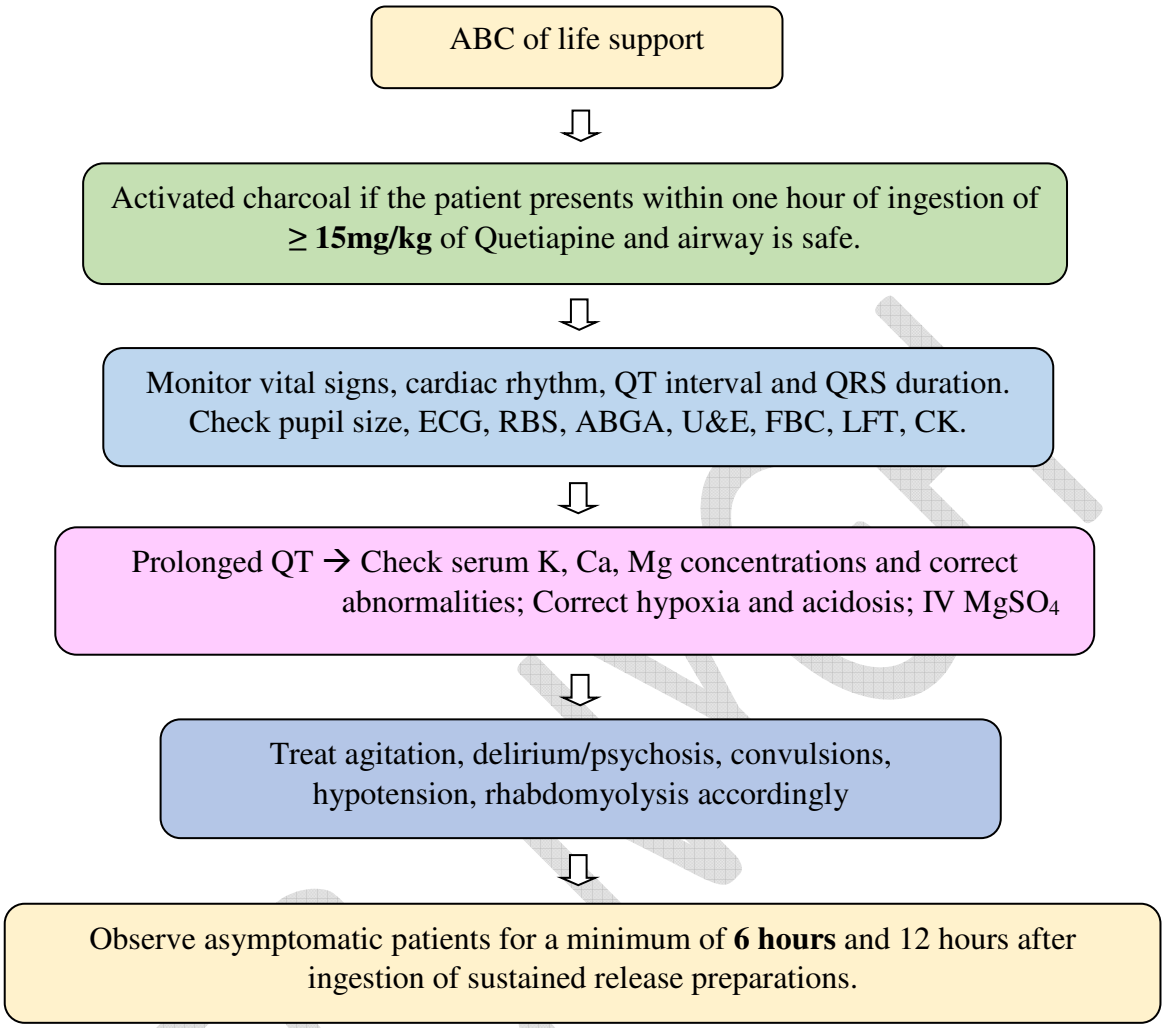
- Ensure adequate fluid resuscitation.
- Consider early referral to critical care for patients with fluid-resistant hypotension, as these patients can deteriorate extremely rapidly; the management of children with fluid-resistant hypotension should be overseen by an experienced paediatrician.
- Invasive vascular monitoring and echocardiography may help determine the likely relative benefits of inotropes and vasopressors because reduced cardiac output and vasodilation often co-exist in severe or mixed poisoning.
- There have been very occasional reports of worsening of hypotension associated with adrenaline treatment, thought to be due to beta-receptor agonist effects.
- Vasopressors and inotropes can be initiated in an emergency through peripheral venous access but only under the direction of an experienced physician.

Management of Rhabdomyolysis

- If rhabdomyolysis is present (CK activity greater than 5 x the upper limit of the normal range), renal failure can develop, particularly if the CK activity is greater than 5000 iu/L.
- **Give intravenous volume replacement as soon as possible and continue in order to maintain an adequate urine output (≥ 1mL/kg/h).**
- Monitor closely for development of metabolic acidosis and manage appropriately.
- Monitor fluid balance, plasma sodium and potassium and urine pH. Beware severe hyperkalaemia.
- Haemodialysis / haemodiafiltration / haemofiltration may be required if acute renal failure develops or severe hyperkalaemia is present.
- If initial CK is normal but there is concern about muscle damage, consider repeat measurement.

Other measures as indicated by the patient's clinical condition. Patients should be advised on discharge to seek medical attention if symptoms subsequently develop.

Workflow for Acute Management of Quetiapine Overdose



References

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Olanzapine Overdose

It is a thienobenzodiazepine atypical antipsychotic used in the treatment of schizophrenia and moderate to severe manic episodes.

Toxic dose

Anyone who is symptomatic, or who has ingested **≥ 1 mg/kg** olanzapine should be referred for medical assessment.

Dose (Adult)	Effect
< 40 mg	Therapeutic sedation and anti-psychotic effects
40-100 mg	Mild to moderate sedation with potential for anti-cholinergic effects
100-300 mg	Sedation with intermittent marked agitation
> 300 mg	Increasing sedation progressing to coma requiring intubation, Hypotension

Dose related risk assessment in Olanzapine Toxicity (Long, 2020)

Mechanism of Toxicity

Effects in overdose are mainly due to antagonist effects at histamine (sedative), dopamine and muscarinic receptors, and blockade of cardiac potassium channel.

Peak plasma levels occur 5-8 hours after oral administration and 15-45 minutes after intramuscular injection. In children, the onset of features has been reported to occur 1 to 2 hours post-ingestion. The therapeutic half-life is between 30-38 hours, however this may be prolonged in overdose. Following intramuscular injection, the half-life is reported to be 30 days. If taken with other serotonergic agents, there is a greater risk of serotonin toxicity (serotonin syndrome).

Features of poisoning

- Features include tachycardia, hypotension or hypertension, slurred speech, dry mouth or hypersalivation, ataxia, miosis (or rarely dilated pupils) and blurred vision. The most common symptoms reported in children are lethargy, tachycardia and agitation.
- Extrapyramidal symptoms have been reported. Children may be at greater risk than adults of developing extrapyramidal symptoms. Extrapyramidal symptoms may also be delayed, occurring up to 36-54 hours post ingestion, and potentially prolonged.

- Common features in severe overdose are tachycardia, agitation, hypertension, miosis, and coma, which may be prolonged. Mental status may fluctuate from somnolence to agitation. Convulsions may occur.
- Neuroleptic malignant syndrome (NMS) has been reported following acute overdose of olanzapine following abstinence of therapy for several weeks. There is usually a combination of hyperthermia, altered mental status, autonomic instability and muscle rigidity. Akinesia and dystonia may also be present.
- **Serotonin Toxicity**

  Serotonin toxicity may occur, especially in those exposed to multiple drugs affecting the serotonin system. Features include CNS effects (including agitation or coma), autonomic instability (including hyperpyrexia), and neuromuscular excitability (including clonus and raised CK).
- Death of patients with serotonin toxicity may be due to hyperpyrexia with associated multi-organ failure.

Management

All patients who have been exposed to this product as a result of self-harm should be referred for assessment. Children and adults who are symptomatic, or those who have ingested **≥ 1 mg/kg** olanzapine should be referred for medical assessment.

Children or adults who have accidentally ingested less than 1 mg/kg olanzapine and who have no new symptoms since the time of ingestion, or injection, do not need to be referred for medical assessment. Patients should be advised to seek medical attention if symptoms develop.

Emergency management

- Maintain a clear airway and ensure adequate ventilation.
- In the event of cardiac arrest in hospital or witnessed out of hospital cardiac arrest with bystander CPR, resuscitation should be continued for at least 1 hour and only stopped after discussion with a senior clinician.
- If the patient may have been exposed to a sodium channel antagonist, or if QRS duration had been prolonged prior to cardiac arrest, administer a rapid bolus of 100 mL of 8.4% sodium bicarbonate urgently, preferably into a large vein. 8.4% sodium bicarbonate is irritant, and should be preceded and followed by a large fluid flush to confirm cannula position and reduce local contact. Monitor pH and administer further doses as necessary.

- Prolonged resuscitation for cardiac arrest is recommended following poisoning as recovery with good neurological outcome may occur.
- **Following ingestion:** Consider oral activated charcoal (charcoal dose: 50 g for adults; 1 g/kg for children) in adults and children who have ingested 1 mg/kg olanzapine or more within 1 hour, providing it is safe to do so and the airway can be protected. Efficacy declines rapidly with time since ingestion but there may be some potential benefit from later use, especially following large ingestions.

Initial Assessment

- Monitor vital signs and cardiac rhythm. Check the capillary blood glucose.
- Check and record pupil size and assess the ankle clonus.
- Perform a 12-lead ECG in all patients who require assessment.
- Consider repeating the ECG in **ANY OF** the following circumstances:
  - ✓ The initial ECG is abnormal.
  - ✓ The patient is symptomatic.
  - ✓ The recommended observation period (at least 6 hours) is not yet complete.
- Check cardiac rhythm, QT interval and QRS duration.
- If the QT is prolonged (QT 'at risk' on nomogram):
  - Check serum potassium, magnesium and calcium concentrations and replace as necessary to keep within the high normal range.
  - Correct hypoxia and acidosis.
  - Administer magnesium sulphate IV over 10-15 minutes: adults 2 g (8 mmol Mg^{2+}), children 25-50 mg/kg (max 2 g). Note that while magnesium sulphate may terminate torsade de pointes, it does not shorten the QT interval.

  Note: Drugs that prolong the QT interval (e.g. amiodarone, quinidine) should be avoided and only considered on specialist advice.
- If torsade de pointes and VT/VF preceded by prolonged QT (QT 'at risk' on nomogram) –
  - ✓ Urgently administer 2 g $MgSO_4$ IV over 2 minutes; dose (8 mmol, or 4 ml of 2 mmol/ml solution) in adults and 25-50 mg/kg (max 2 g) in children.
  - ✓ If underlying rhythm remains unchanged, two further boluses of magnesium may be administered at intervals of 5-15 minutes.
  - ✓ Torsade de pointes may respond to increasing the underlying heart rate through atrial or ventricular pacing or by isoprenaline (isoproterenol) infusion to achieve an initial

heart rate of 90-110 beats per minute. Magnesium concentration should be measured after administration.

- Patients may additionally need treatment with sodium bicarbonate if the QRS is prolonged.
- All patients who require assessment should be observed for at least **6 hours** after exposure. Asymptomatic patients can then be considered for discharge with advice to return if symptoms develop.
- In symptomatic patients, check U&Es, LFTs, FBC, blood glucose and CK.
- Consider arterial/venous blood gas analysis in patients who have a reduced level of consciousness, reduced oxygen saturation on pulse oximetry or metabolic disturbance.

Management of Hypotension

- Ensure adequate fluid resuscitation.
- Consider early referral to critical care for patients with fluid-resistant hypotension, as these patients can deteriorate extremely rapidly; the management of children with fluid-resistant hypotension should be overseen by an experienced paediatrician.
- Invasive vascular monitoring and echocardiography may help determine the likely relative benefits of inotropes and vasopressors because reduced cardiac output and vasodilation often co-exist in severe or mixed poisoning.
- There have been very occasional reports of worsening of hypotension associated with adrenaline treatment, thought to be due to beta-receptor agonist effects.
- Vasopressors and inotropes can be initiated in an emergency through peripheral venous access but only under the direction of an experienced physician.

Management of Agitation and Delirium/Psychosis

- Where available, follow local guidelines for treatment of agitation and delirium.
- The primary goal of management is to keep patient and staff safe while allowing continued evaluation. Ensure other causes are excluded (e.g. hypoxia, infection, hypoglycaemia and raised ICP). Attempt de-escalation by reducing environmental stimuli (e.g. quiet room) and providing basic needs (e.g. a close relative, a warm blanket and food (if appropriate)).

For pharmacotherapy in adults:

- Give an initial dose of oral or IV diazepam (10-20 mg) or lorazepam (1-2 mg). Further boluses, given IV, may be administered if the patient remains agitated, provided there is no impairment of respiratory function.
- If oral and IV routes are not available, give lorazepam IM (1-2 mg) or midazolam IM (5-10 mg) repeated as necessary.
- Patients with severe agitation may need high doses of intravenous diazepam (total dose in excess of 100 mg given incrementally). These patients need urgent referral to critical care.
- **Haloperidol** (5-10 mg IM) may be an adjunct when agitation remains resistant to two or more benzodiazepine doses as described above. Antipsychotics should be avoided in patients with Parkinson's disease.
- **Ketamine** has also been used for uncontrolled agitation but must be used by a practitioner experienced in its use in an appropriate clinical environment with equipment for intubation if necessary.

For pharmacotherapy in children:

- **Pharmacological management of agitation in children must be supervised by staff experienced in paediatric airway management and sedation.**
- If required, **midazolam** is an appropriate drug for managing agitation in children and young people.
- This may be delivered -
  - ✓ buccally (dose 0.2 mg/kg to a maximum of 10 mg),
  - ✓ IM (dose 0.2 mg/kg to a maximum dose of 10 mg) or
  - ✓ IV (dose 0.025-0.05 mg/kg to a maximum dose of 6 mg in 6 months to 5 years old or 0.05-0.1 mg/kg to a maximum dose of 10 mg in 5-12 year olds)
- **Lorazepam** (0.01 mg/kg IV; max 2 mg) is an alternative.
- Repeat doses can be given if necessary up to the maximum cumulative dose. There is a particular risk of paradoxical increased agitation in young children.
- **Ketamine** has been used for severe agitation but should only be administered by a practitioner experienced in its use in an appropriate clinical environment with equipment for intubation if necessary.

Management of Serotonin Syndrome

- Standard treatment of serotonin toxicity is benzodiazepines. Most mild cases will resolve spontaneously within 24 hours.
- Avoid all serotonergic agents including:
  - ✓ fentanyl patches (remove if already in place)
  - ✓ sedation using fentanils
- In serious cases, consider cyproheptadine and chlorpromazine. These are 5HT2A antagonists and have successfully been used to treat serotonin toxicity following overdose but there are no controlled trials to support the use of either agent.
- Give cyproheptadine (12 mg orally or via NG tube, followed by 4-8 mg every 6 hours in adults and children aged 13 years and older (32 mg max in 24 hours); 0.25 mg/kg/day (max 12 mg) in 4 divided doses in children aged 12 years or younger).
- In severe cases, give chlorpromazine 12.5-25 mg IV (fluid load first to avoid hypotension) followed by 25 mg orally every 6 hours.

Management of Hyperthermia

- Mild to moderate hyperthermia may respond to conventional cooling measures such as:
  - ✓ Mist and fan techniques
  - ✓ Ice packs to groin and axillae
  - ✓ External cooling devices.
- When rising body temperature exceeds 38.5°C, urgent cooling measures with regular monitoring of core temperature, at least every 30 minutes, should be employed according to local protocols.
- Such measures include:
  - ✓ Ice-baths (may achieve rapid cooling but caution in elderly/comorbidities)
  - ✓ Internal/invasive measures - cold fluid lavage (gastric, bladder, peritoneal), intravascular cooling techniques.
- Sedation should be employed where it can be safely performed (diazepam 10-20 mg in adults; 0.25 mg/kg body weight in children).
- Patients with severe hyperthermia may need high doses of intravenous diazepam (total dose in excess of 100 mg given incrementally). These patients need urgent referral to critical care.

- Dantrolene may be considered where there is muscular hyperactivity (initially 2-3 mg/kg by intravenous injection, to a maximum of 10 mg/kg.
- In patients with pyrexia, monitor renal function and CK activity. Ensure adequate hydration and monitor urine output carefully.

Management of Acute Dystonic Reactions

- Reassure patients with acute dystonic reactions.
- Acute dystonic reactions usually respond to antimuscarinic agents, e.g., procyclidine (5-10 mg IV/IM). Repeat doses may be required for prolonged reactions.
- An alternative to procyclidine is benztropine mesilate (1-2 mg IM).
- Diazepam (10-20 mg in adults; 0.25 mg/kg body weight in children) may be used as an alternative if antimuscarinics are unavailable.

Management of Convulsions

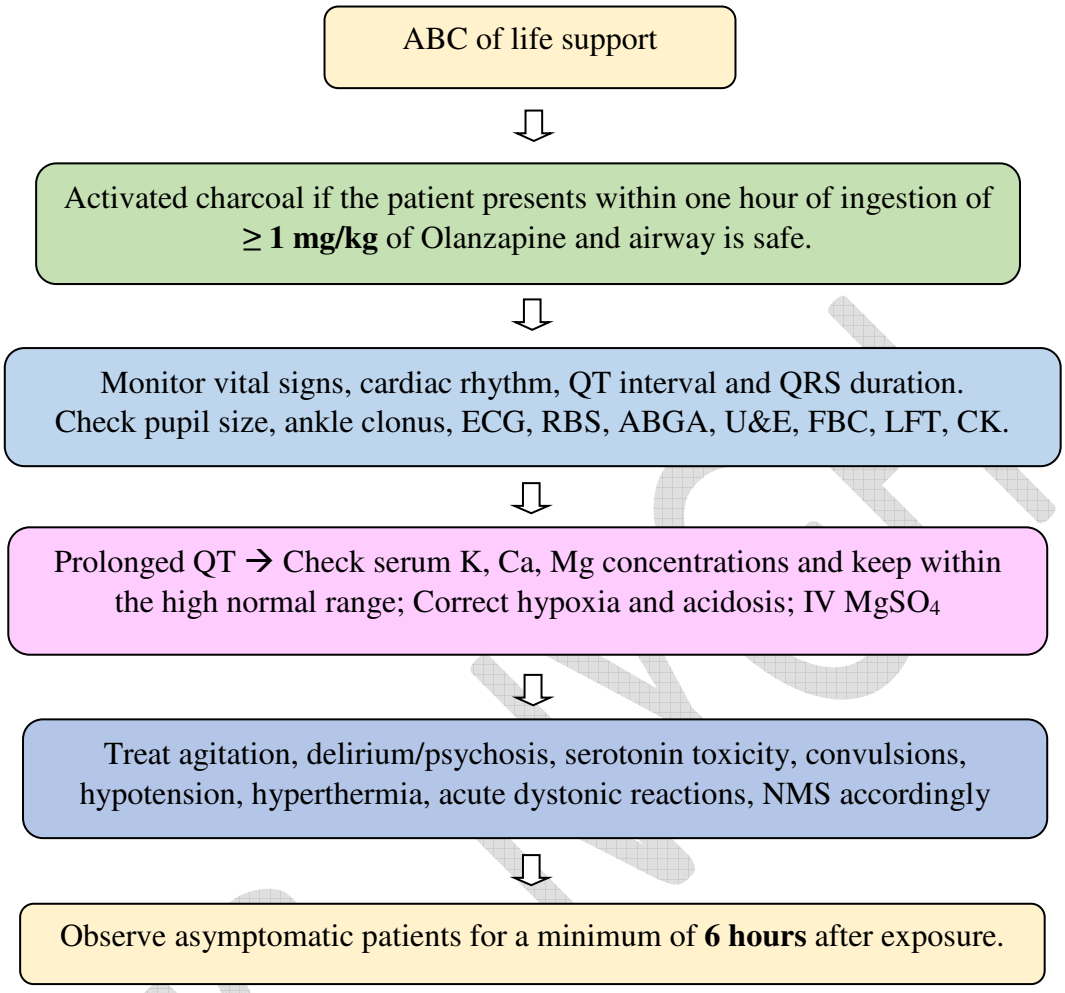
- Give oxygen; check blood glucose, U&Es, calcium, magnesium, phosphate and ABG. Correct acid base and metabolic disturbances as required.
- Single brief convulsions do not require treatment.
- Control convulsions that are frequent or prolonged with intravenous diazepam (10-20 mg in adults; 0.1-0.3 mg/kg body weight in children), lorazepam (4 mg in adults; 0.1 mg/kg in children), or midazolam (5-10 mg in adults; 0.05-0.15 mg/kg in children).
- Further doses of benzodiazepines may be needed in adults; refer to intensive care. In children, seek consultant paediatric input.
- If unresponsive to the above measures, the patient should be referred urgently to critical care.
- The barbiturates are recommended as second line therapy and phenytoin should be avoided.

Management of Neuroleptic Malignant Syndrome (NMS)

- Supportive care is the mainstay of therapy in mild to moderate NMS with attention to temperature, fluid status and appropriate sedation with agents such as benzodiazepines. Patients with moderate or severe NMS should be assessed for admission to a high dependency or intensive care setting.

Other measures as indicated by the patient's clinical condition. Patients should be advised on discharge to seek medical attention if symptoms subsequently develop.

Workflow for Acute Management of Olanzapine Overdose



References

1. TOXBASE®. Olanzapine overdose - features and management updated 1/2020; Available from: http://www.toxbase.org.
2. Long N (2020) Olanzapine toxicity, Drugs and Toxicants, Toxicology Library. Available from https://litfl.com/olanzapine-toxicity/

High Dose Insulin Euglycaemic Therapy

High-dose insulin euglycaemic therapy is administered as a bolus of short-acting insulin followed by continuous insulin infusion, together with a dextrose infusion. Instructions for making up the insulin infusion are provided below. The protocol for dilution and administration is different from conventional insulin infusions used for other indications in medicine.

Before commencing high dose insulin euglycaemic therapy:

1. Ensure plasma glucose is greater than 10 mmol/L.
2. Correct hypokalaemia.

Administration of high dose insulin euglycaemic therapy:

3. Commence therapy with a bolus of intravenous insulin: A bolus of short acting insulin (e.g. Actrapid) at 1.0 unit/kg intravenously over 2-3 minutes

Example: A 70 kg patient should be administered a bolus of 70 units of Actrapid intravenously over 2-3 minutes.

4. Continue therapy with a continuous infusion of insulin:
    - Start at 1.0 unit/kg/hour.
    - Titrate up the infusion dose by 2.0 units/kg/hour every 15 minutes to clinical response (aim systolic BP > 90mmHg).
    - Doses up to 10 units/kg/hour, and in rare circumstances even higher, have been safely administered.

Example of how to make up insulin infusion:

Take 5 mL from a vial of Actrapid (100 IU/mL) and dilute with 45 mL normal saline to a final volume of 50 mL (final concentration 10 IU/mL).

Example, In a 70 kg patient, a 1.0 unit/kg/hour infusion (70 units per hour) equates to 7 mL/hour.

When higher dose infusions are required (e.g. above 500 IU/ hour), it will be more practicable to use more concentrated insulin infusions (e.g. 50 units/mL), to achieve this, take 25 mL from a vial of Actrapid (100 IU/mL) and dilute with 25 mL normal saline to a final volume of 50 mL (final concentration 50 IU/mL).

Example, In a 70 kg patient, a 10 unit/kg/hour infusion (700 units per hour) equates to 14 mL/hour.

And a continuous infusion of 10% dextrose:

- Start the infusion at 100 mL/hour and titrate the infusion rate to maintain the blood sugar.

- There is a possibility of fluid overload if high volumes of lower concentrated dextrose solutions are administered to maintain blood sugar. More concentrated dextrose infusions such as 50% dextrose may be used (via central access) to reduce the risk of fluid overload.

5. Monitor during the insulin infusion:
    - Perform capillary blood glucose every 10 minutes initially and following insulin infusion rate changes, then every 30-60 minutes when on a stable infusion rate.
    - Measure serum potassium hourly and replace potassium as required to achieve a normal serum concentration.

Stopping the high-dose insulin euglycaemic infusion:

6. Once the patient is clinically improved and haemodynamically stable, wean off vasopressor support before discontinuation of the insulin infusion.
7. Halve the dose of the insulin infusion and observe for two hours. In the absence of a fall in blood pressure, stop the infusion. If the blood pressure falls, restart the infusion and attempt to wean at a later time point.
8. Hypoglycaemia continues to be a risk after discontinuing the insulin infusion because of its long half-life following infusion. Continue to monitor capillary blood glucose for a period of 24 hours after discontinuing insulin infusion. Treat hypoglycaemia according to local protocols. In some cases, as the toxin is eliminated and patient improves, insulin resistance will reduce and dextrose requirements will increase.
9. Rebound hyperkalaemia may occur following discontinuation of the infusion. Continue to monitor potassium concentration closely.

References

1. TOXBASE®. High dose insulin euglycaemic therapy for adults updated 5/2021; Available from: http://www.toxbase.org.