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Consensus statement

Guidelines for the management of paracetamol poisoning in Australia and New Zealand — explanation and elaboration

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Summary

- Paracetamol is involved in a large proportion of deliberate self-poisoning cases. This is the 3rd edition of the guidelines for the management of paracetamol poisoning in Australia and New Zealand. The key changes from the previous guidelines released in 2008 are recommendations for liquid paracetamol ingestion in children, management of those patients taking large/massive overdoses, modified release ingestions, supratherapeutic ingestions and indications for activated charcoal.
- The paracetamol treatment nomogram has not changed and the acetylcysteine regimen remains essentially the same.
- The optimal management of most patients with paracetamol overdose is usually straightforward. Cases which require a different management pathway include modified release paracetamol overdoses, large/massive overdoses and supratherapeutic ingestions.
- This article outlines the rationale for recommendations made in these new guidelines.

Introduction

Paracetamol is the most widely used over-the-counter analgesic agent in the world. It is involved in a large proportion of accidental paediatric exposures and deliberate self-poisoning cases and is the leading pharmaceutical agent responsible for calls to Poisons Information Centres in Australia and New Zealand. Paracetamol is also the single most commonly taken drug in overdoses that lead to hospital presentation and admission.[1] Hepatic failure and death are uncommon outcomes,[2,3] although paracetamol remains the most important single cause of acute fulminant hepatic failure in Western countries.[4,5]

Acute deliberate self-poisoning, accidental paediatric exposure and inadvertent repeated supratherapeutic ingestions all require specific approaches to risk assessment and management. This guideline details management for paracetamol poisoning in all these situations. Since the previous guidelines were released in 2008, management of paracetamol poisoning has altered and the previous guidelines don't reflect the current practice by clinical toxicologists. Particular areas where management has altered include "large/massive" paracetamol overdoses and paediatric paracetamol ingestions.

Consensus process

Experts in the field of paracetamol poisoning, from Australia and New Zealand were invited to join a panel to update the current paracetamol guidelines. Various issues had been raised about the current guidelines, which required updating. Participants were asked to review the current guidelines and were invited to submit points of debate and consult the relevant medical literature. Participants were then surveyed about these issues, controversial areas were discussed point by point, using clinical scenarios to frame debate. The resulting guidelines were then circulated to the panel members for further comment and alterations. All six members of the panel are authors of this article.

The draft guidelines were distributed to clinical toxicologist and Poison Information Centre staff for comment. Areas of controversy were reviewed by the panel members. Consensus recommendations were reached in an equitable manner. Agreement of all members of the expert panel was required in order to proceed with making the recommendation.

Background: Paracetamol pharmacokinetics

Paracetamol is rapidly absorbed from the small intestine. In therapeutic doses, peak serum concentrations occur within 1–2 hours for standard tablet or capsule formulations and within 30 minutes for liquid preparations. Peak serum concentrations after therapeutic doses do not usually exceed 20 mg/L (132 μmol/L). Twenty per cent of the ingested dose undergoes first-pass metabolism in the gut wall

(sulphation). Distribution is usually within 4 hours of ingestion for standard preparations and 2 hours for liquid preparations. Volume of distribution is 0.9 L/kg.[6]

Further elimination occurs by hepatic biotransformation. After therapeutic doses, the elimination half-life is 1.5–3 hours. About 90% is metabolised to inactive sulphate and glucuronide conjugates that are excreted in the urine. Metabolism of the remainder is via cytochrome P450 (chiefly 2E1 and 3A4) and results in the highly reactive intermediary compound *N*-acetyl-*p*-benzoquinone imine (NAPQI). In normal conditions, NAPQI is immediately bound by intracellular glutathione and eliminated in the urine as mercapturic adducts.[6]

With increased paracetamol doses, greater production of NAPQI may deplete glutathione stores. When glutathione depletion reaches a critical level (thought to be about 30% of normal stores), NAPQI binds to other proteins, causing damage to the hepatocyte. Glutathione depletion itself may also be injurious.[7,8]

General principles of paracetamol overdose management

Resuscitation

Immediate threats to the airway, breathing and circulation are extremely rare in isolated paracetamol overdose. In exceptional cases, massive ingestion causing extremely high serum paracetamol concentrations (usually above 800 mg/L or > 5000 μmol/L) may be associated with an early decrease in level of consciousness and with lactic acidosis.[9,10] This is secondary to a direct mitochondrial effect, rather than hepatotoxicity. Supportive management is appropriate in such cases; acetylcysteine is the mainstay of treatment. For specific treatment see section on "large/ massive" paracetamol ingestion. Haemodialysis has been described in this setting, but is not generally required; clinical toxicology advice should be sought if this is considered.

Any alteration of conscious state should prompt bedside testing of the patient's serum glucose level and correction of hypoglycaemia, if present. This is only likely to be due to paracetamol if there is hepatic failure.

Risk assessment

A risk assessment, in which the clinician attempts to predict the most likely clinical course and potential complications of the patient's presentation, should occur as soon as possible in the management of all poisoned patients. The key factors to consider for paracetamol poisoning are the ingested dose and serum concentration (early), clinical and laboratory features suggesting liver damage (late).

Serum paracetamol concentrations should be used to assess the need for acetylcysteine administration in all patients presenting with deliberate paracetamol self-poisoning, regardless of the stated dose. All those patients presenting more than

8 hours post ingestion also require an alanine aminotransferase (ALT), which is also used to guide management.

Clinical or biochemical evidence of liver injury may not be apparent for up to 24 hours after acute paracetamol overdose. The best surrogate marker indicating the potential for injury is a timed serum paracetamol concentration plotted on a nomogram. However, the nomogram cannot be applied in those presenting more than 24 hours post ingestion or if the time of ingestion cannot be determined with confidence by the treating clinician or in supratherapeutic ingestions.

The most important risk factor for liver damage and death after acute paracetamol ingestion, is the extent of delay beyond 8 hours of commencing treatment with acetylcysteine. Treatment within 8 hours will prevent serious hepatic injury, in almost all patients.

Paracetamol treatment nomogram

The current nomogram for assessing requirement to treat paracetamol overdose (Figure 1) has been used in Australia since 2008.[11] It is based on the Prescott and Rumack Matthew nomograms. The Prescott nomogram was based on a cohort of patients in Edinburgh and extends from 200 mg/L (1320 µmol/L) at 4 hours to 30mg/L (200 µmol/L) at 15 hours.[12] The Rumack–Matthew nomogram is based on the same data, but extrapolated to 24 hours. It also uses a "treatment line" that is plotted starting 25% lower (150 mg/L [1000 µmol/L] at 4 hours) to comply with a United States Food and Drug Administration requirement to provide a "safety buffer" for research and clinical purposes.[13] The efficacy and safety of dosing acetylcysteine according to the Rumack–Matthew nomogram has been demonstrated in a study of more than 11 000 patients, with no deaths among patients who were treated within 15 hours.[14] The 150 mg/L at 4 hours nomogram is currently used in the USA, Canada, Australia and New Zealand.

The nomogram line remains unchanged in Australia despite the fact that in the UK and Ireland there has been a change in the paracetamol nomogram treatment line. We considered the risks versus the benefits in changing the nomogram and they were not favourable. In 2012 in the UK, the decision-to-treat line on the paracetamol nomogram was lowered to start at 100 mg/L (660 µmol/L) at 4 hours, following a directive from the Medicines and Healthcare Products Regulatory Authority (MHRA).[15] This occurred due to concerns from the coroner following a death of a young woman after a paracetamol overdose from complications of management. This has resulted in tens of thousands of very low risk patients in the UK receiving acetylcysteine treatment, exposing them to the risks of treatment; anaphylactoid reactions in particular.[16,17] These changes have resulted in significant increases in rates of hospital presentations and admission, severe adverse reactions to acetylcysteine, and a very substantial cost.[16] It is clear this change has not been

strongly endorsed by all toxicologists in the UK. We do not believe this change is necessary nor does it have a favourable risk benefit.

Management of paracetamol overdose

Gastrointestinal decontamination

Significant hepatic injury is extremely rare after acute single accidental paracetamol ingestion in children under 6 years of age, and it is very uncommon for them to have concentrations that require acetylcysteine treatment. Therefore, in children under 6 years of age with potential accidental paracetamol intoxication, gastrointestinal decontamination with syrup of ipecac, activated charcoal or gastric lavage is not indicated.

In awake, cooperative adults, 50 grams(g) of activated charcoal should be administered within 2 hours of ingestion of a toxic dose of paracetamol (more than 10 g or greater than 200 mg/kg (whichever is lower). Activated charcoal administered within 2 hours of ingestion reduces the absorbed paracetamol dose and the likelihood that acetylcysteine will subsequently be required.[18] An exception to this is immediate-release paracetamol overdose of greater than 30 g, where activated charcoal should be administered up to 4 hours post-ingestion. Similarly for modified-release paracetamol ingestions activated charcoal should be administered for up to 4 hours post-ingestion and even longer in larger overdoses. (See section: modified-release paracetamol overdose).

Nevertheless, if activated charcoal cannot be administered, treatment with acetylcysteine within 8 hours guarantees survival in almost all cases. Therefore, activated charcoal alone is not a life-saving treatment that may be imposed under a duty-of-care principle.

Acute paracetamol exposure with known time of ingestion

Treatment with acetylcysteine ensures survival if administered within 8 hours of paracetamol ingestion.[14,19] Beyond 8–10 hours after ingestion, efficacy decreases with increasing delay to treatment.[14] If the result of a paracetamol determination can be obtained **within 8 hours** of ingestion, acetylcysteine administration may be delayed until a serum paracetamol concentration plotted on the nomogram confirms it is indicated. This is provided treatment can still be commenced within the 8-hour window if it is required. If a paracetamol concentration will not be available until > 8 hours post ingestion, commence acetylcysteine while awaiting a paracetamol concentration.

For patients that present within 8 hours, with a known time of ingestion, risk assessment is based on the serum paracetamol concentration plotted on the nomogram. Supplementary investigations such as liver function tests or a coagulation

profile do not refine the risk assessment and do not provide useful baseline data or change management in this group of patients. These tests are therefore not indicated unless risk assessment for another agent requires them. Follow-up tests are only required at the conclusion of the 20-hour acetylcysteine infusion, in cases of modified-release ingestions or very large overdoses. (See section: large/massive paracetamol ingestions and modified-release paracetamol overdose).

In patients in whom a paracetamol concentration cannot be obtained until 8 or more hours after ingestion, acetylcysteine should be commenced immediately, if the reported dose exceeds the threshold for possible toxicity (Table 1) or the patient shows clinical signs suggestive of paracetamol hepatotoxicity (nausea, vomiting, right upper quadrant pain or tenderness). Evaluation of serum paracetamol concentration and ALT should then be performed as soon as possible. If the serum paracetamol concentration is subsequently found to be below the nomogram line and ALT concentration is < 50 U/L, acetylcysteine may be ceased. If the paracetamol concentration is above the nomogram line or ALT > 50 U/L, acetylcysteine should be continued. The baseline serum ALT assists risk assessment and provides useful baseline data if acetylcysteine is indicated.

Figure 2 summarises the steps for management of acute paracetamol exposure with known time of ingestion.

Large/massive paracetamol ingestions

The majority of patients take less than 30g of paracetamol and of those that have toxic paracetamol concentrations the majority are just above the treatment nomogram line.[20,21] Patients, who take much larger overdoses may have decreased paracetamol clearance and increased risk of hepatotoxicity despite usual treatment and may benefit from changes to the standard paracetamol management.[22] Patients who have ingested greater than 30g of paracetamol should be given activated charcoal up until 4 hours post ingestion if awake and co-operative.

The current acetylcysteine regimen is adequate for the majority of overdoses, but many clinical toxicologists feel that simply following the standard three bag intravenous(IV) protocol may not be adequate in large/massive paracetamol overdoses.[23] Patients who have a paracetamol concentrations double the nomogram are considered at higher risk of hepatotoxicity. In some studies, 5-7% of these patients will still develop hepatotoxicity despite being treated within 8 hours with acetylcysteine.[14,22]

Only a small percentage of paracetamol overdoses will have a paracetamol concentration greater than double the nomogram line.[19,21] Although there are no randomised control trials investigating optimum acetylcysteine dose in large overdoses, it is the practice of many clinical toxicologists to adjust the dose of acetylcysteine in these patients.[24] It has not yet been determined who might benefit

from an increase in acetylcysteine or what the optimum dose is. One approach in those patients with a paracetamol concentration more than double the nomogram line, is to double the concentration of the 16 hour infusion of acetylcysteine from 100mg/kg (current standard acetylcysteine 3rd bag infusion) to 200mg/kg IV acetylcysteine. The Poisons Information Centre or clinical toxicologist may be consulted for the most current advice on these patients.

Furthermore those patients with very high concentrations often still have elevated paracetamol concentrations or develop abnormal liver function tests (LFTs) at the completion of treatment and may require prolonged acetylcysteine treatment.[22] They should have an ALT and paracetamol concentration checked near the completion of IV acetylcysteine (ie, 2 hours prior to completion of the acetylcysteine infusion). Acetylcysteine should be continued if they have an increasing ALT (greater than 50 U/L), or a paracetamol concentration greater than 10 mg/L (66 µmol/L). Acetylcysteine can be continued at a rate of 100 mg/kg of acetylcysteine in 1000 mL of 5% dextrose over 16 hours.

Acute paracetamol exposure with unknown time of ingestion

If the time of ingestion is unknown, or the treating clinician is not confident of the history of ingestion, it is safest to treat the patient as a delayed presentation. Thus, the recommendation is to follow the > 8 hours scenario in Figure 2; that is to commence acetylcysteine. If the serum paracetamol concentration is greater than 10 mg/L (66 µmol/L) or the ALT is elevated > 50 U/L, acetylcysteine treatment should be continued. Serum ALT should be repeated at the end of the acetylcysteine infusion and then if the ALT is < 50 U/L or decreasing, acetylcysteine may be discontinued.

If further history becomes available and the serum paracetamol concentration can be accurately plotted on the nomogram, this should be done and acetylcysteine discontinued if the paracetamol concentration is below the treatment line.

Modified-release paracetamol overdose

Modified-release paracetamol in Australia and New Zealand is currently marketed in a formulation containing 665 mg of paracetamol, of which 69% is slow-release and 31% is immediate release paracetamol. The kinetics of modified-release paracetamol preparations after deliberate self-poisoning has not been defined. Studies in volunteers confirm there is a potential for slow absorption and thus a delayed peak serum paracetamol concentration above the nomogram line.[25]

We recommend administration of 50 g activated charcoal, in cooperative adults, who can receive the dose within 4 hours of modified-release paracetamol ingestion of greater than 10 g or 200 mg/kg whichever is lower. In massive overdoses, absorption

may continue for up to 24 hours, so patients will likely benefit from activated charcoal even beyond 4 hours.[26]

If more than 200 mg/kg or 10 g (whichever is lower) has been ingested, acetylcysteine treatment should be started immediately. Serum paracetamol concentrations should be taken at 4 hours or more post-ingestion (as with standard preparations) and repeated 4 hours later. If either concentration is above the nomogram line, acetylcysteine should be continued. Acetylcysteine may be discontinued if serial concentrations, taken 4 hours apart are below the nomogram line and are decreasing. Otherwise continue the full 21 hour course of acetylcysteine to its completion.

If less than a toxic dose is ingested (10 g or greater than 200 mg/kg (whichever is lower)), serum paracetamol concentrations may be used to determine the need for acetylcysteine. Serum paracetamol concentrations should be taken at 4 hours or more post-ingestion (as with standard preparations) and repeated 4 hours later. If either concentration is above the nomogram line, acetylcysteine should be commenced.

Near the completion of acetylcysteine the patient should have a repeat ALT and paracetamol concentration. Acetylcysteine should be continued if the ALT is increasing (greater than 50 U/L) or paracetamol concentration is greater than 10 mg/L (66 µmol/L). Acetylcysteine can be continued at a rate of 100 mg/kg of acetylcysteine in 1000 mL of 5% dextrose over 16 hours.

Paediatric (< 6yrs) liquid paracetamol ingestion

Paediatric patients (children < 6 years) are thought to be less susceptible to paracetamol toxicity than older children and adults.[27] Furthermore they usually present with accidental liquid paracetamol ingestions. Activated charcoal is not indicated in this group as liquid preparations have rapid absorption.

The eTG complete (Internet: Therapeutic Guidelines - Toxicology and Wilderness) recommend a 2 hour concentration in children who ingest liquid paracetamol; and if the 2-hour concentration is above 225 mg/L (1500 µmol/L) acetylcysteine should be administered.[28] This recommendation is based on a population pharmacokinetic study by Anderson et al. that found 95% of children would reach a maximum paracetamol concentration under 2 hours.[29] Young children who ingest liquid paracetamol have rapid absorption and an earlier time to peak paracetamol concentration because of shorter elimination half-lives. They concluded that a 2 hour concentration would shorten the length of time children spend in the emergency department. This recommendation has not been validated in a larger cohort.

A 2 hour concentration will allow for early discharge and to ensure a further element of safety this paracetamol concentration has been lowered. Hence it is recommended that a paracetamol concentration can be measured at least 2 hours after ingestion of liquid preparations in children < 6 years, if they have possibly ingested more than 200 mg/kg.[29] Note in obese children this should be based on an ideal body weight.

If a child has ingested a liquid paracetamol preparation and the 2 (to 4) hour concentration is below 150 mg/L (1000 µmol/L), acetylcysteine is not required. This represents the majority of unintentional liquid paediatric ingestions and allows for early discharge. If the paracetamol concentration at 2 hours is greater than 150 mg/L (1000 µmol/L) then it should be repeated at 4 hours. Acetylcysteine should be commenced if the 4 hour concentration is **greater than** 150 mg/L (1000 µmol/L).

A 2 hour paracetamol concentration should only be utilised in a well-child with an isolated accidental liquid paracetamol ingestion, in all other cases a 4 hour paracetamol assay should be performed. Furthermore, for children presenting later than 4 hours post ingestion or who are older than 6 years of age, treat as per adult acute paracetamol exposure.

Multiple or "staggered" overdoses

In this scenario, if it has been *less* than 8 hours since the first dose, the patient can safely be treated as per the 1–8 hours scenario in Figure 2. Provided a paracetamol concentration can be obtained within 8 hours of ingestion. The rationale for this is that due to the rapid absorption of paracetamol, any later doses will only lead to overestimation of the risk. However, if it has been more than 8 hours since the first dose, treat the patient as per the > 8 hours scenario in Figure 2. The paracetamol concentration should be plotted on the nomogram at the earliest time of ingestion.

Repeated supratherapeutic ingestion

There is little evidence to guide risk assessment for repeated ingestion of high doses of paracetamol. The margin of safety has for many years been assumed to be high.[30] However, recent data suggest that minor subclinical elevations of serum ALT may be quite common with prolonged therapy.[31] Conversely, studies of "high-risk" patients who have taken supratherapeutic doses over 3–4 days have suggested significant hepatotoxicity is uncommon.[32] Therefore, the threshold for the reported dose that causes toxicity has been made deliberately and conservatively low (see Table 1 and Figure 3). However, there is evidence that the combination of a low paracetamol concentration and an ALT less than 50 U/L at any time indicates there is no risk of subsequent hepatotoxicity.[33] In most cases, this rule precludes the need for prolonged treatment in this group.

Patients should have a paracetamol concentration and ALT measured if they meet the criteria for supratherapeutic ingestion.

Criteria for supratherapeutic ingestion:

- more than 10 g or 200 mg/kg (whichever is lower) in a single 24-hour period

- more than 6 g or 150 mg/kg (whichever is lower) per 24 hours for the preceding 48 hours
- more than 4 g/day or 100 mg/kg/day (whichever is lower) for more than 48 hours, in those who **also have** symptoms indicating possible liver injury, e.g., abdominal pain, nausea or vomiting.

Recommended investigations

Table 2 gives a summary of recommended tests and when they should be done. For ease of reference, these are presented according to the time from ingestion to administration of acetylcysteine.

A mild elevation in international normalised ratio (INR) no greater than 2.0, may occur early in those without hepatic injury or liver failure, due to direct inhibition of clotting factor production by paracetamol and acetylcysteine.[34-36]

Acetylcysteine

Acetylcysteine is an effective antidote and should be administered to all patients judged to be at risk of developing hepatotoxicity after paracetamol overdose. With acetylcysteine therapy, morbidity from overdose can be minimised. Oral acetylcysteine and methionine have also been used to prevent hepatotoxicity.[19,37] Neither is registered for use in Australasia and the oral regimens often provoke vomiting.

Non-IgE mediated anaphylactic (anaphylactoid) reactions manifested by rash, wheeze or mild hypotension occur in 10%–50% of patients during the first two acetylcysteine infusions.[38-40] Management is supportive, with temporary halting or slowing of the infusion and administration of antihistamines and bronchodilators if required.[41] The occurrence of a non-IgE mediated anaphylactic reaction does not preclude the use of acetylcysteine on another occasion if indicated. Severe life-threatening reactions are very rare and should be treated with adrenaline as required. Once the symptoms settle acetylcysteine can be recommenced. Reactions are more likely to occur in predisposed individuals, such as patients with asthma.[42]

Acetylcysteine reduces mortality if commenced in late presenting patients with established paracetamol-induced fulminant hepatic failure, although mechanisms of action in this period may be different. In this setting, acetylcysteine reduces inotrope requirements, decreases cerebral oedema and increases the rate of survival by about 30%.[43]

Dose calculations for acetylcysteine

When risk assessment indicates that acetylcysteine is required, it is administered as a three-stage infusion (Table 3). Each stage contains different doses, totalling

300 mg/kg over 21 hours,[12] or in cases of massive overdose where a 200 mg/kg third bag maybe appropriate, totalling 400mg/kg over 21 hours. If hepatic injury is suspected after the third infusion, acetylcysteine is continued at the rate of the last infusion stage (100 mg/kg acetylcysteine over 16 hours or 150 mg/kg/24 hours) until there is clinical and biochemical evidence of improvement. (See section: Subsequent management of hepatotoxicity and liver failure)

Acetylcysteine is packaged for intravenous infusion in ampoules, each containing a 20% solution (i.e. 200 mg acetylcysteine per 1 mL). Prescription of acetylcysteine requires a two-stage calculation to compute the appropriate weight-based dose and then the volume required. Calculation or transcription errors may lead to potentially fatal dosing errors.[44] It is recommended that dosing tables providing the required volume of 20% acetylcysteine by weight, are used to chart the volume required in each infusion. This precludes the need for calculations and decreases the potential for error. Such tables are found in the acetylcysteine product information and have also been reproduced in this guideline (Table 4). Furthermore it is also important to ensure adequate mixing of acetylcysteine and fluid when preparing the infusion.[45]

Calculation of acetylcysteine doses is based on actual bodyweight rounded up to the nearest 10 kg, but with a ceiling weight of 110 kg.[46] For children, the dose of acetylcysteine is calculated in the same way, but with the volume reduced appropriately (Table 5).

Different rates of initial infusions (using the same total dose) are increasingly being used.[47-49] For example, some toxicology units use 200 mg/kg over the first 4 hours (50 mg/kg/h), and a similar adjusted regimen has been trialled in the UK. These have the demonstrated advantage of lower rates of acetylcysteine non-IgE mediated anaphylactic reactions. Efficacy data to date is similar but this has not been clearly established in large studies.

Subsequent management of hepatotoxicity and liver failure

Only a small proportion of patients develop hepatotoxicity, early symptoms include nausea, vomiting, abdominal pain and right upper quadrant tenderness. The majority of these still do not develop fulminant hepatic failure and recover fully.[1,14] Patients who develop abnormal liver biochemistry require an extended duration of IV acetylcysteine. Acetylcysteine is continued at the rate of the last infusion stage (100mg/kg acetylcysteine over 16 hours or 150 mg/kg/24 hours).

Most experts would continue acetylcysteine until:

- The patient is clinically improving and
- ALT is decreasing and
- INR is improving and < 2 and

- The paracetamol concentration is less than 10 mg/L (66 µmol/L).

These patients require regular clinical review and 12-hourly blood tests, or more frequently if there is clinical deterioration. Blood investigations that indicate prognosis should be performed. These include electrolytes, urea, creatinine, liver function tests, INR, blood sugar, phosphate and venous blood gas (looking at the pH and lactate).[50,51] Advice may be sought from a clinical toxicologist or local Poisons Information Centre. A markedly prolonged INR is common in patients with severe hepatotoxicity and correction is not required, unless there is evidence of bleeding. Avoid correction of INR until discussion with a Liver Transplant Unit.

Patients should be discussed with a Liver Transplant Unit if they have any of the following:

- INR > 3.0 at 48 hours or > 4.5 at any time
- Oliguria or creatinine > 200 µmol/L
- Persistent acidosis (pH < 7.3) or arterial lactate > 3 mmol/L, despite resuscitation.
- Systolic hypotension with BP < 80 mmHg
- Hypoglycaemia
- Severe thrombocytopenia
- Encephalopathy of any degree, or any alteration of consciousness (GCS < 15), not associated with sedative co-ingestions.[52]

The Liver Transplant Unit may also be called, if there are any concerns, to discuss management of these patients.

Intravenous paracetamol medication errors

Intravenous paracetamol medication errors are not dealt within these guidelines, as the treatment thresholds are different from an oral ingestion. They are usually iatrogenic errors. A clinical toxicologist or Poisons Information Centre should be contacted regarding these cases.

Recommendations of when to call the Poisons Information Centre

This guideline addresses the majority of paracetamol ingestion scenarios encountered. However not all clinical scenarios can be addressed, or the management remains controversial. Table 6 outlines those cases that we recommend contacting the Poisons Information Centre for further advice. Where there are any concerns regarding the management of paracetamol ingestion, advice should always be sort from a clinical toxicologist or local Poisons Information Centre.

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References

1. Buckley N, Eddleston M. Paracetamol (acetaminophen) poisoning. Systematic review. *BMJ Clinical Evidence* 2007; pii: 2101. http://clinicalevidence.bmj.com/x/systematic-review/2101/overview.html (accessed June 2015).
2. Dart RC, Erdman AR, Olson KR, et al. Acetaminophen poisoning: an evidence-based consensus guideline for out-of-hospital management. *Clin Toxicol* 2006; 44:1-18.
3. Linden CH, Rumack BH. Acetaminophen overdose. *Emerg Med Clin North Am* 1984; 2: 103-119.
4. Lancaster EM, Hiatt JR, Zarrinpar A. Acetaminophen hepatotoxicity: an updated review. *Arch Toxicol* 2015; 89: 193-199.
5. Larson AM, Polson J, Fontana RJ, et al. Acetaminophen-induced acute liver failure: results of a United States multicenter, prospective study. *Hepatology* 2005; 42: 1364-1372.
6. Forrest JA, Clements JA, Prescott LF. Clinical pharmacokinetics of paracetamol. *Clin Pharmacokinet* 1982; 7: 93-107.
7. Jollow DJ, Mitchell JR, Potter WZ, et al. Acetaminophen-induced hepatic necrosis. II. Role of covalent binding in vivo. *J Pharmacol Exp Ther* 1973; 187: 195-202.
8. Mitchell JR, Jollow DJ, Potter WZ, et al. Acetaminophen-induced hepatic necrosis. I. Role of drug metabolism. *J Pharmacol Exp Ther* 1973; 187: 185-194.
9. Shah AD, Wood DM, Dargan PI. Understanding lactic acidosis in paracetamol (acetaminophen) poisoning. *Br J Clin Pharmacol* 2011; 71: 20-28.
10. Flanagan RJ, Mant TG. Coma and metabolic acidosis early in severe acute paracetamol poisoning. *Hum Toxicol* 1986; 5: 179-182. 11.
11. Daly FF, Fountain JS, Murray L, et al. Guidelines for the management of paracetamol poisoning in Australia and New Zealand--explanation and elaboration. A consensus statement from clinical toxicologists consulting to the Australasian poisons information centres. *Med J Aust* 2008; 188: 296-301.
12. Prescott LF, Illingworth RN, Critchley JA, et al. Intravenous N-acetylcysteine: the treatment of choice for paracetamol poisoning. *Br Med J* 1979; 2: 1097-1100.
13. Reid D, Hazell W. Paracetamol poisoning: which nomogram should we use? *Emerg Med (Fremantle)* 2003; 15: 486-496.
14. Smilkstein MJ, Knapp GL, Kulig KW, et al. Efficacy of oral N-acetylcysteine in the treatment of acetaminophen overdose. Analysis of the national multicenter study (1976 to 1985). N Engl J Med 1988; 319: 1557-1562.
15. Medicines and Healthcare Products Regulatory Agency. Benefit risk profile of acetylcysteine in the management of paracetamol overdose 2012. http://webarchive.nationalarchives.gov.uk/20141205150130/http://www.mhra.gov.uk/home/groups/pl-p/documents/drugsafetymessage/con184709.pdf. (accessed Feb 2015).
16. Bateman DN, Carroll R, Pettie J, et al. Effect of the UK's revised paracetamol poisoning management guidelines on admissions, adverse reactions and costs of treatment. *Brit J Clin Pharmacol* 2014; 78: 610-618.
17. Bateman DN, Dear JW, Carroll R, et al. Impact of reducing the threshold for acetylcysteine treatment in acute paracetamol poisoning: the recent United Kingdom experience. *Clin Toxicol (Phila)* 2014; 52: 868-872.
18. Buckley NA, Whyte IM, O'Connell DL, Dawson AH. Activated charcoal reduces the need for N-acetylcysteine treatment after acetaminophen (paracetamol) overdose. *J Toxicol Clin Toxicol* 1999; 37: 753-757.
19. Buckley NA, Whyte IM, O'Connell DL, Dawson AH. Oral or intravenous N-acetylcysteine: which is the treatment of choice for acetaminophen (paracetamol) poisoning? *J Toxicol Clin Toxicol* 1999; 37: 759-767.
20. Duffull SB, Isbister GK. Predicting the requirement for N-acetylcysteine in paracetamol poisoning from reported dose. *Clinical Toxicology (Phila)* 2013; 51: 772-776.
21. Graudins A. Paracetamol poisoning in adolescents in an Australian setting: Not quite adults. *Emerg Med Australas* 2015; 27: 139-144.
22. Doyon S, Klein-Schwartz W. Hepatotoxicity despite early administration of intravenous N-acetylcysteine for acute acetaminophen overdose. *Acad Emerg Med* 2009: 16: 34-39.
23. Rumack BH, Bateman DN. Acetaminophen and acetylcysteine dose and duration: past, present and future. *Clin Toxicol (Phila)* 2012; 50: 91-98.
24. Juma SA , Villeneuve E, Elliot A, et al. Doubling the third dose of intravenous N-acetylcysteine survey: An international practice perspective(abstract). *Clin Toxicol (Phila)* 2015: 53: 253-254.
25. Tan C, Graudins A. Comparative pharmacokinetics of Panadol Extend and immediate-release paracetamol in a simulated overdose model. *Emerg Med Australas* 2006; 18: 398-403.
26. Roberts DM, Buckley NA. Prolonged absorption and delayed peak paracetamol concentration following poisoning with

extended-release formulation. *Med J Aust* 2008; 188: 310-311.

27. Rumack BH, Matthew, H. Acetaminophen poisoning and toxicity. *Pediatrics* 1975; 55: 871-876.
28. Expert Group for Toxicology and Wilderness. Toxicology: paracetamol (revised June 2012, amended Oct 2014). In: Toxicology and Wilderness, version 2, eTG complete [Internet]. Melbourne: Therapeutic Guidelines Limited, 2015 Mar. http://www.tg.org.au/index.php?sectionid=170.
29. Anderson BJ, Holford NH, Armishaw JC, Aicken R. Predicting concentrations in children presenting with acetaminophen overdose. *J Pediatr* 1999; 135: 290-295.
30. Prescott LF. Therapeutic misadventure with paracetamol: fact or fiction? *Am J Ther* 2000; 7: 99-114.
31. Watkins PB, Kaplowitz N, Slattery JT, et al. Aminotransferase elevations in healthy adults receiving 4 grams of acetaminophen daily: a randomized controlled trial. *JAMA* 2006; 296: 87-93.
32. Benson GD. Acetaminophen in chronic liver disease. *Clin Pharmacol Ther* 1983; 33: 95-101.
33. Daly FF, O'Malley GF, Heard K, et al. Prospective evaluation of repeated supratherapeutic acetaminophen (paracetamol) ingestion. *Ann Emerg Med* 2004; 44: 393-398.
34. Owens KH, Medlicott NJ, Zacharias M, et al. Population pharmacokinetic-pharmacodynamic modelling to describe the effects of paracetamol and N-acetylcysteine on the international normalized ratio. *Clin Exp Pharmacol Physiol* 2015; 42: 102-108.
35. Whyte IM, Buckley NA, Reith DM, et al. Acetaminophen causes an increased International Normalized Ratio by reducing functional factor VII. *Ther Drug Monit* 2000; 22: 742-748.
36. Jang DH, Weaver MD, Pizon AF. In vitro study of N-acetylcysteine on coagulation factors in plasma samples from healthy subjects. *J Med Toxicol* 2013; 9: 49-53.
37. Hamlyn AN, Lesna M, Record CO, et al. Methionine and cysteamine in paracetamol (acetaminophen) overdose, prospective controlled trial of early therapy. *J Int Med Res* 1981; 9: 226-231.
38. Sandilands EA, Bateman DN. Adverse reactions associated with acetylcysteine. Clin Toxicol (Phila) 2009; 47: 81-88.
39. Kao LW, Kirk MA, Furbee RB, et al. What is the rate of adverse events after oral N-acetylcysteine administered by the intravenous route to patients with suspected acetaminophen poisoning? *Ann Emerg Med* 2003; 42: 741-750.
40. Lynch RM, Robertson R. Anaphylactoid reactions to intravenous N-acetylcysteine: a prospective case controlled study. *Accid Emerg Nurs* 2004; 12: 10-15.
41. Bailey B, McGuigan MA. Management of anaphylactoid reactions to intravenous N-acetylcysteine. *Ann Emerg Med* 1998; 31: 710-715.
42. Schmidt LE, Dalhoff K. Risk factors in the development of adverse reactions to N-acetylcysteine in patients with paracetamol poisoning. *Brit J Clin Pharmacol* 2001; 51: 87-91.
43. Keays R, Harrison PM, Wendon JA, et al. Intravenous acetylcysteine in paracetamol induced fulminant hepatic failure: a prospective controlled trial. *BMJ* 1991; 303: 1026-1029.
44. Little M, Murray L, McCoubrie D, Daly FF. A potentially fatal prescribing error in the treatment of paracetamol poisoning. *Med J Aust* 2005; 183: 535-536.
45. Ferner RE, Langford NJ, Anton C, et al. Random and systematic medication errors in routine clinical practice: a multicentre study of infusions, using acetylcysteine as an example. *Brit J Clin Pharmacol* 2001; 52: 573-577.
46. Duncan R, Cantlay G, Paterson B. New recommendation for N-acetylcysteine dosing may reduce incidence of adverse effects. *Emerg Med J* 2006; 23: 584.
47. Bateman DN, Dear JW, Thanacoody HK, et al. Reduction of adverse effects from intravenous acetylcysteine treatment for paracetamol poisoning: a randomised controlled trial. *Lancet* 2014; 383: 697-704.
48. Graudins A, Harper A. Comparison of adverse drug reaction rates using a two-bag to a standard three-bag intravenous acetylcysteine regimen for paracetamol poisoning (abstract). *Clin Toxicol (Phila)* 2015; 53: 249.
49. Isbister GK, Downes MA, Mcnamara K, et al. A novel infusion protocol for the administration of acetylcysteine (abstract). *Clin Toxicol (Phila)* 2015; 53: 249-250.
50. Schmidt LE, Dalhoff K. Serum phosphate is an early predictor of outcome in severe acetaminophen-induced hepatotoxicity. *Hepatology* 2002; 36: 659-665.
51. Bernal W, Donaldson N, Wyncoll D, Wendon J. Blood lactate as an early predictor of outcome in paracetamol-induced acute liver failure: a cohort study. *Lancet* 2002; 359: 558-563.
52. Devlin J, O'Grady J. Indications for referral and assessment in adult liver transplantation: a clinical guideline. British Society of Gastroenterology. *Gut* 1999; 45 (Suppl VI): VI1-VI22.

Table 1: Paracetamol dosing that may be associated with hepatic injury

	Adults and children over 6 years of age	Children (aged 0–6 years)*
Acute single ingestion	> 200 mg/kg or 10 g (whichever is lower) over a period of less than 8 hours	> 200 mg/kg or more over a period of less than 8 hours
Repeated Supra-therapeutic Ingestion (RSI)	> 200 mg/kg or 10 g (whichever is lower) over a single 24-hour period	> 200 mg/kg over a single 24-hour period
	> 150 mg/kg or 6 g (whichever is lower) per 24-hour period for the preceding 48 hours	> 150 mg/kg per 24-hour period for the preceding 48 hours
	> 100 mg/kg or 4 g (whichever is lower) per 24-hour period, for more than 48 hours in those who also have symptoms indicating possible liver injury e.g. abdominal pain, nausea or vomiting	> 100 mg/kg per 24-hour period for more than 48 hours

*** NOTE:** For obese children the weight used, should be based on an ideal body weight.

Table 2: Recommended investigations according to time from paracetamol ingestion to acetylcysteine treatment

Time (hours) from paracetamol ingestion to acetylcysteine	Investigations on admission	Investigations at the completion of acetylcysteine
Less than 8 hours	Serum paracetamol concentration	Nil*
8–24 hours	Serum paracetamol concentration and ALT	ALT and UEC*
Greater than 24 hours	Serum paracetamol concentration, ALT and INR	ALT, INR and UEC
Patients who have an abnormal ALT	UEC, LFTs, INR, BSL, phosphate and VBG (looking at the pH and lactate).	**Repeat investigations every 12 hours, including:** UEC, LFTs, INR, BSL, phosphate and VBG (looking at the pH and lactate).

ALT = alanine aminotransferase, BSL = blood sugar level, INR = international normalised ratio, UEC = urea, electrolytes, creatinine, VBG = venous blood gas.

*** NOTE:** If symptoms of hepatotoxicity (i.e. nausea, vomiting, abdominal pain or tenderness) then **repeat** ALT. Or if initial concentration more than double the nomogram line, then **repeat** ALT and paracetamol concentration at the completion of acetylcysteine.

Table 3: Three-stage acetylcysteine infusion

Initial Infusion	An initial dose of 150 mg/kg of acetylcysteine diluted in 200 mL of 5% glucose and infused over 60 minutes
Second Infusion	The initial infusion is followed by a continuous infusion of 50 mg/kg of acetylcysteine in 500 mL of 5% glucose over the next 4 hours
Third Infusion	The second infusion is followed by a continuous infusion of 100 mg/kg of acetylcysteine in 1000 mL of 5% glucose over the next 16 hours.*

*** Note**: Patients who have a paracetamol concentration more than double the nomogram line, may benefit from an increase in the dose of acetylcysteine in the 100 mg/kg over 16 hours infusion (third infusion) to 200 mg/kg IV acetylcysteine in 1000 mL of 5% glucose over 16 hours. (see text)

Table 4: Volume of acetylcysteine to be charted for each infusion, based on actual bodyweight and rounded up to the nearest 10 kg

Patient's body weight (kg)	Initial acetylcysteine infusion **Dose: 150 mg/kg over 60 min to be added to 200 mL of 5% glucose**	Second acetylcysteine infusion **Dose: 50 mg/kg over 4 hours to be added to 500 mL of 5% glucose**	Third acetylcysteine infusion **Dose: 100 mg/kg over 16 hours to be added to 1000 mL of 5% glucose**
	Dose acetylcysteine (g) = volume (mL)* = (*0.75 x wt [kg]*)	Dose acetylcysteine (g) = volume (mL)* = (*0.25 x wt [kg]*)	Dose acetylcysteine (g) = volume (mL)* = (*0.5 x wt [kg]*)
50	7.5 g = 37.5 mL	2.5 g = 12.5 mL	5 g = 25 mL
60	9 g = 45 mL	3 g = 15 mL	6 g = 30 mL
70	10.5 g = 52.5 mL	3.5 g = 17.5 mL	7 g = 35 mL
80	12 g = 60 mL	4 g = 20 mL	8 g = 40 mL
90	13.5 g= 67.5 mL	4.5 g = 22.5 mL	9 g = 45 mL
100	15 g= 75 mL	5 g = 25 mL	10 g = 50 mL
110†	16.5 g= 82.5 mL	5.5 g = 27.5 mL	11 g = 55 mL

* Assuming concentration of acetylcysteine is 200 mg/ml.

† **Note:** All patients weighing greater than 110 kg should be dosed according to a bodyweight of 110 kg.

Table 5: Acetylcysteine administration to children, based on body weight

Children ≤ 20 kg body weight

- 150 mg/kg acetylcysteine in 3 mL/kg 5% glucose over 60 minutes
- Followed by 50 mg/kg in 7 ml/kg 5% glucose over 4 hours
- Followed by 50 mg/kg in 7 mL/kg 5% glucose over 8 hours
- Followed by 50 mg/kg in 7 mL/kg 5% glucose over 8 hours

Children > 20 kg bodyweight

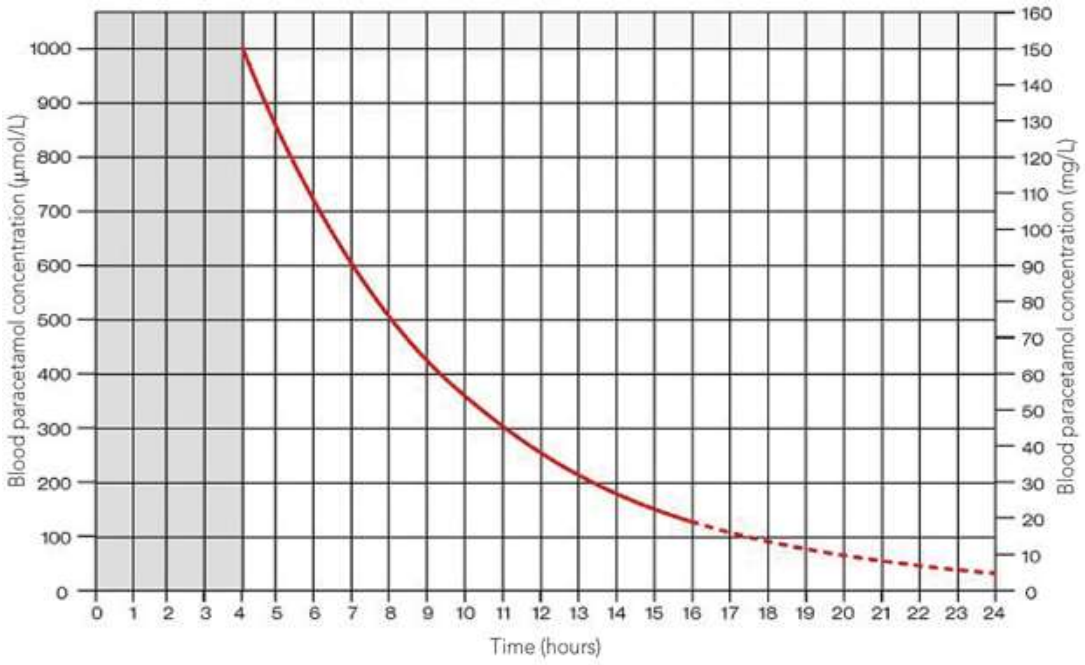
- 150 mg/kg acetylcysteine in 100 mL 5% glucose over 60 minutes
- Followed by 50 mg/kg in 250 mL 5% glucose over 4 hours
- Followed by 50 mg/kg in 250 mL 5% glucose over 8 hours
- Followed by 50 mg/kg in 250 mL 5% glucose over 8 hours

Table 6: Recommendations on when to seek further advice from Poisons Information Centre

- Very large overdoses:
    - Immediate release or modified release paracetamol overdoses of > 50 g or 1 g/kg (whichever is lower).
    - A very high paracetamol concentration, more than double the nomogram line.
- Intravenous paracetamol errors/ overdoses.
- Patients with hepatotoxicity (e.g. ALT > 1000 IU/L).

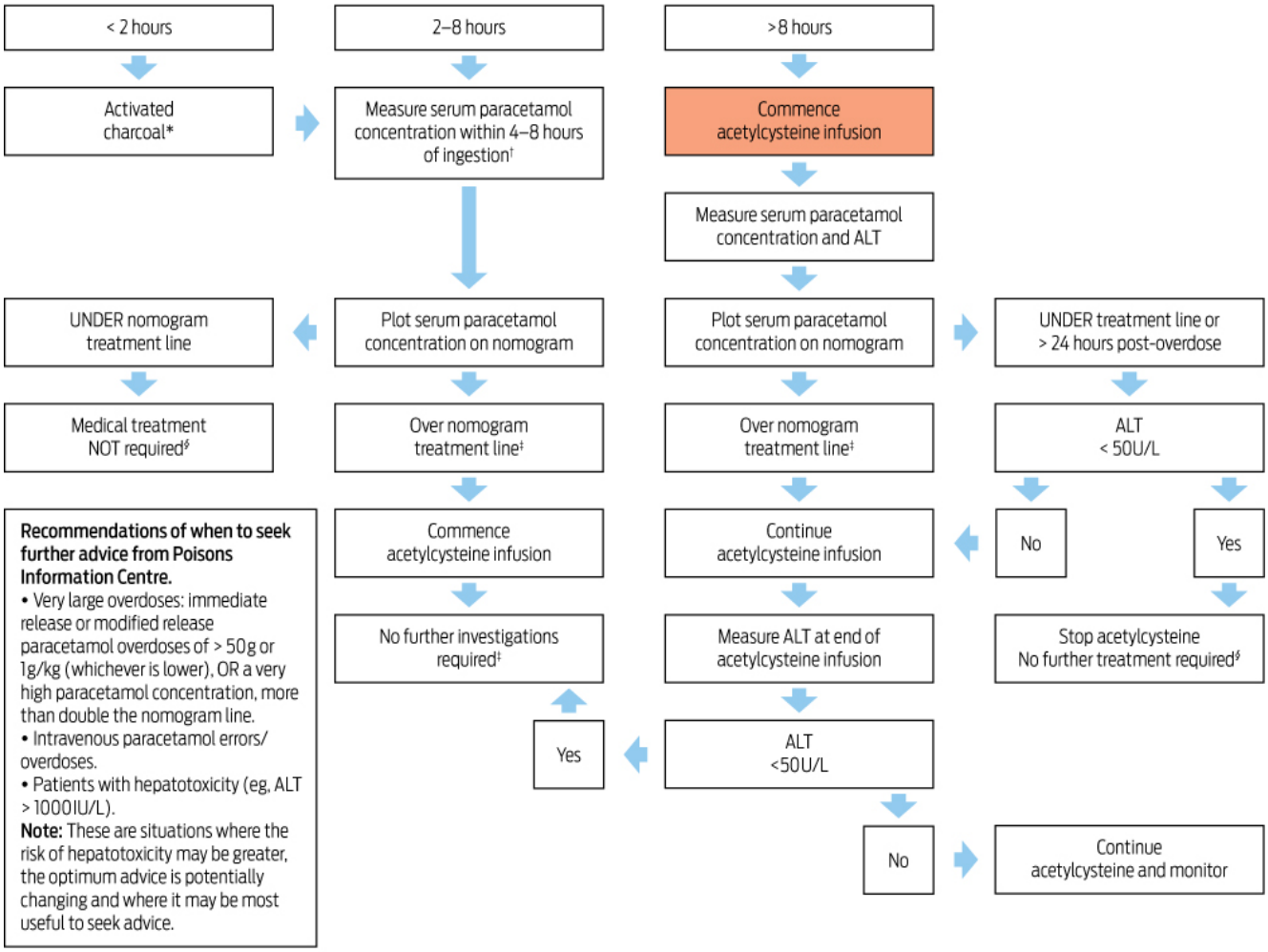
Note: These are situations where the risk of hepatotoxicity may be greater, the optimum advice is potentially changing and where it may be most useful to seek advice.

Figure 1: Paracetamol treatment nomogram



Note: Ensure correct units are used when utilising the paracetamol treatment nomogram.

Figure 2: Management flow chart for acute paracetamol exposure with known time of ingestion



NOTE:
*Cooperative adult patients who have potentially ingested greater than 10g or 200mg/kg, whichever is less. For paracetamol ingestions ≥ 30g activated charcoal should be offered until 4 hours post-ingestion.
† If paracetamol concentration will not be available until > 8 hours post-ingestion, commence acetylcysteine while awaiting paracetamol concentration.
‡Those patients with initial paracetamol concentrations more than double the nomogram line may benefit from an increase in acetylcysteine dose (see text) and a serum paracetamol and ALT concentrations should be checked at the end of the acetylcysteine infusion.
§ Patients should be advised that if they develop abdominal pain, nausea or vomiting further assessment is required.

Figure 3: Management flow chart for repeated supratherapeutic paracetamol ingestion