MJA
The Medical Journal of Australia

Supporting Information

Full guidelines

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Appendix to: Chiew Al, Reith D, Pomerleau A, et al. Updated guidelines for the management of paracetamol poisoning in Australia and New Zealand. *Med J Aust* 2019; doi: 10.5694/mja2.50428.

Consensus statement

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

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Published: December 2019

Abstract

Introduction:

Paracetamol is a very common agent taken in deliberate self-poisoning, and a common agent in accidental overdoses in adults and children. Paracetamol poisoning is the most common cause of severe acute liver injury. Since previous guidelines were published in the MJA in 2015, several studies have changed practice. A working group of experts in the area with representation from all Poisons Information Centres of Australia and New Zealand were brought together to produce an updated evidence-based guidance.

Main recommendations (unchanged from previous guidelines):

- The optimal management of most patients with paracetamol overdose is usually straightforward. Patients who present early should be given activated charcoal. Patients at risk of hepatotoxicity should receive intravenous acetylcysteine.
- The paracetamol nomogram is utilised to assess need for treatment in acute immediate-release paracetamol ingestions with a known time of ingestion.
- Cases which require a different management pathway include modified-release paracetamol overdoses, large/massive overdoses, accidental liquid ingestion in children, and repeated supra-therapeutic ingestions (e.g. excessive use of paracetamol as an analgesic).

Major changes in management in the guideline:

- The new guidelines recommend a two-bag acetylcysteine infusion regimen (200 mg/kg over 4 h, then 100 mg/kg over 16 h). This has similar efficacy but significantly reduced adverse reactions (compared to the previous 'three-bag' regimen).
- "Massive" paracetamol overdoses which result in high paracetamol concentrations more than double the nomogram line should be managed with an increased dose of acetylcysteine.
- All potentially toxic modified-release paracetamol ingestions (≥ 10 g or 200 mg/kg whichever is less) should receive a full course of acetylcysteine. Those who ingest ≥ 30 g or ≥ 500 mg/kg should receive increased doses of acetylcysteine. These patients having a higher risk of acute liver injury and may need repeated tests and prolonged therapy.

Keywords: paracetamol, guideline, poisoning, overdose

Introduction

Paracetamol is one of the commonest drugs taken in overdoses, leading to hospital presentation and admission and is the commonest cause of severe acute liver injury in Western countries [1, 2]. Fortunately, hepatic failure and death are uncommon outcomes [1, 2]. Paracetamol poisoning is also the most common reason for calls to Poisons Information Centres in Australia and New Zealand [3]. Not only is it one of the commonest medications involved in deliberate self-poisoning, it is also involved in a large proportion of accidental paediatric exposures, and overdoses with therapeutic intent when taken for symptoms such as pain or fever (repeated supratherapeutic ingestions).

Since the previous guidelines were published in the MJA in 2015, further research has emerged particularly regarding

acetylcysteine regimens, massive paracetamol ingestions and modified release paracetamol ingestion. These have led to a change in management of paracetamol poisoning and the 2015 guidelines do not reflect the current practice recommended by clinical toxicologists. This guideline details management for paracetamol poisoning in all these situations. The key changes from the previous guidelines are acetylcysteine regimen (two bag regimen) and dosage, management of patients taking large/massive overdoses, staggered ingestions, modified-release paracetamol ingestions and repeated supratherapeutic ingestion (RSTI).

Methods

The Treatment of Paracetamol Poisoning Writing Group comprised of Clinical Toxicologists and Pharmacologists from Australia and New Zealand. All members completed a detailed literature review and critically appraised existing evidence, including reviewing the relevant chapters from the newly updated Australian Therapeutic Guidelines: Toxicology & Toxinology [4]. Drafts of evidence-based recommendations, practice points and background manuscript were developed. We conducted a face-to-face meeting in May 2019 to draft the guideline. Further revisions were made via email and teleconference. The summary recommendations follow the National Health and Medical Research Council levels of evidence (www.mja.com.au.acs.hcn.com.au/sites/default/files/NHMRC.levels.of.evidence.2008-09.pdf) and the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system (www.gradeworkinggroup.org) to determine the strength of the recommendations.

Recommendations

Acute deliberate self-poisoning, accidental paediatric exposure and inadvertent repeated supratherapeutic ingestions all require specific approaches to risk assessment and management.

The initial approach focuses on risk assessment (**Box 1**); key factors to consider for paracetamol poisoning are the formulation and dose ingested, time since ingestion and serum paracetamol concentration (early), or clinical and laboratory features suggesting acute liver injury (late). Serum paracetamol concentration(s) should be used to assess the need for acetylcysteine administration in all patients presenting with deliberate self-poisoning with paracetamol, regardless of the stated dose.

We have summarised with flow charts the management of acute paracetamol exposure with known time of ingestion (**Flowchart 1**), modified release (**Flowchart 2**) and repeated supra-therapeutic ingestion (**Flowchart 4**). We have also developed a flowchart for the management of acute paracetamol poisoning for centres with limited resources (**Flowchart 3**).

Where there are any concerns regarding the management of paracetamol ingestion advice can always be sought from a clinical toxicologist or Poisons Information Centre (13 11 26 in Australia, 0800 764 766 in New Zealand).

Box 1: Paracetamol dosing that may be associated with acute liver injury.

Acute Single Ingestion *	≥ 10 g or ≥ 200 mg/kg (whichever is less)
Repeated Supra-therapeutic Ingestion (RSTI) #	≥ 10 g or ≥ 200 mg/kg (whichever is less) over a single 24-hour period. OR ≥ 12 g or ≥ 300 mg/kg (whichever is less) over a single 48-hour period. OR **≥ a daily therapeutic dose^ per day** for more than 48 hours in those who also have abdominal pain or nausea or vomiting.

*Acute ingestion is defined as any intentional/ deliberate paracetamol overdose, including staggered or multiple paracetamol ingestions over more than 2 hours.

Repeated supra-therapeutic ingestion is any patient who ingests paracetamol for therapeutic intent. These doses are a guide for asymptomatic patients at risk for acute liver injury. All symptomatic patients should be assessed with a paracetamol concentration and ALT.

^ Therapeutic daily dose of paracetamol in adults is a total dose of 60 mg/kg over 24 hours and up to a maximum dose of 4 g/day. For paediatric dosage refer to local guidelines.

Background: Paracetamol kinetics

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 [5, 6].

In 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 enzymes (chiefly CYP2E1 and CYP3A4) and results in the highly reactive intermediary compound N-acetyl-p-benzoquinone imine (NAPQI). NAPQI is detoxified by irreversible glutathione-dependent conjugation reactions to mercapturic acid and cysteine conjugates [7, 8]. In overdose, the increased formation of NAPQI depletes hepatic glutathione stores and NAPQI covalently binds to critical cellular proteins [9], causing damage to hepatocytes and acute liver injury.

Management of acute paracetamol ingestion

Acute paracetamol ingestion refers to any deliberate or intentional ingestions of paracetamol usually for the purpose of self-harm. This ingestion may be a single ingestion over less than 2 hours or staggered or multiple ingestions over greater than 2 hours (see **Multiple or "Staggered" Immediate-Release Paracetamol Ingestions**). Those patients who ingest extra doses of paracetamol for therapeutic intent (e.g. pain such as toothache, back pain or flu symptoms) should be managed as per repeated supratherapeutic ingestion (see **Repeated Supratherapeutic Ingestion**).

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:

- Ingested dose (**Box 1**)
- Time of ingestion
- Preparation ingested (e.g. immediate-release or modified-release)
- Single or staggered ingestion

The most important risk factor for liver damage and death after acute paracetamol ingestion is the time before treatment with acetylcysteine commences. Treatment started within 8 hours will prevent serious hepatic injury, in almost all patients [10].

Key investigations for the management of an acute paracetamol ingestion are shown in **Box 2**. All patients who present with paracetamol self-poisoning regardless of the stated dose should be assessed with a serum paracetamol concentration and alanine aminotransferase (ALT). These results are utilised to guide management, the serum paracetamol concentration is utilised in conjunction with the paracetamol treatment nomogram in those presenting within 24 hours post-ingestion. The initial ALT helps guide management in those presenting greater than 8 hours post-ingestion. An ALT is now suggested to be taken in all patients including those presenting within 8 hours post-ingestion, as in these patients it will serve as a baseline. Clinical or biochemical evidence of liver injury may not be apparent for up to 24 hours after acute paracetamol overdose.

Box 2: Recommended investigations for acute immediate and modified release paracetamol ingestion according to time from ingestion to acetylcysteine treatment.

Time (hours) from paracetamol ingestion to acetylcysteine	Investigations on admission	Investigations at the completion of acetylcysteine
Less than 24 hours	ALT and serum paracetamol concentration	ALT*
Greater than 24 hours	Serum paracetamol concentration, ALT and INR#	ALT and INR#
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 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 initial paracetamol concentration was ≥ double the nomogram line (e.g. 300 mg/L at 4 h) or modified-release preparation ingested, then repeat paracetamol concentration at the completion of acetylcysteine.

A mild elevation in international normalised ratio (INR) no greater than 2.0, may occur early in those without hepatic injury. This is due to direct inhibition of clotting factor production and activity, by paracetamol and acetylcysteine, respectively.[11-13]

Paracetamol treatment nomogram

The paracetamol treatment nomogram (**Figure 1: Rumack–Matthew nomogram**) is used to decide whether to start or continue acetylcysteine therapy. Acute liver injury can occur if a patient's serum paracetamol concentration is above the nomogram line. The current nomogram for assessing requirement to treat paracetamol overdose has been used in Australia since 2008 [14]. The paracetamol treatment nomogram has been validated as an excellent predictor of risk, but only for acute ingestions of immediate release paracetamol with a known time of ingestion. 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 below the line, or above the line and treated within 15 hours [15].

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 modified-release or supratherapeutic ingestions. The current nomogram utilised in Australia and New Zealand has not changed (Figure 1). It is important to check the units utilised with many laboratories recently changing from µmol/L to mg/L. As most laboratories utilise mg/L these units now appear on the left axis, previously in the 2015 guidelines they appeared on the right.

The 150 mg/L (1000 µmol/L) at 4 hours nomogram is currently used in the USA, Canada, Australia and New Zealand. This contrasts with the United Kingdom that utilises a lower nomogram treatment line of 100 mg/L (660 µmol/L) at 4 hours. This has resulted in tens of thousands of very low risk patients in the UK receiving acetylcysteine exposing them to the risks of treatment and increasing rates of hospital admissions at a very substantial cost [16, 17].

GRADE: Strong; Evidence: Strong.

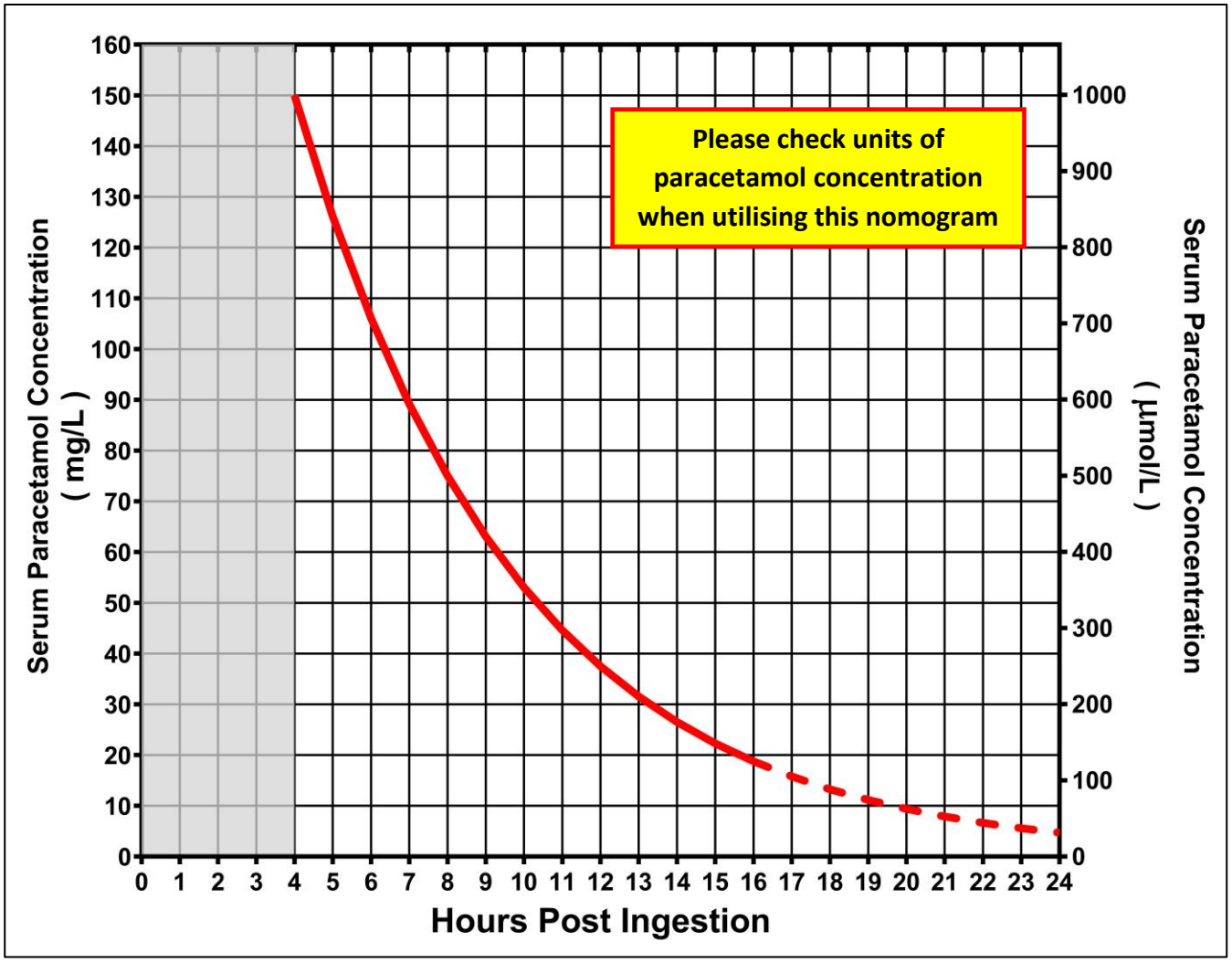


Figure 1: Paracetamol Treatment Nomogram (Rumack-Matthew Nomogram)

Note: µmol/L = micromol/L = nmol/mL

General 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 lactic acidosis [18]. 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 for severe metabolic acidosis 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.

Gastrointestinal decontamination

Activated charcoal (50 g in an adult) is recommended in awake and cooperative patients in the following ingestions:

- Within 2 hours of ingesting a toxic dose of paracetamol [≥ 10 g or ≥ 200 mg/kg (whichever is less)].
- Within 4 hours of ingesting ≥ 30 g of immediate-release paracetamol (see **large/massive paracetamol overdose**).
- Within 4 hours of ingesting a toxic dose [≥ 10 g or ≥ 200 mg/kg (whichever is less)] of modified-release paracetamol. Note in larger overdoses activated charcoal may be indicated up to 24 hours post-ingestion.

Activated charcoal administered within 2 hours of an immediate release paracetamol ingestion reduces the absorbed paracetamol dose and the likelihood that acetylcysteine will subsequently be required [19, 20]. In those who ingest greater than 30 g of paracetamol, activated charcoal within 4 hours of ingestion is associated with a reduced risk of acute liver injury [21].

Modified-release paracetamol ingestions, particularly large doses, may result in prolonged and erratic paracetamol absorption [22, 23]. Activated charcoal should be administered for up to 4 hours post-ingestion and even longer in larger overdoses (see **Modified-release paracetamol overdose**) [22].

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.

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, gastrointestinal decontamination with activated charcoal is not indicated in children under 6 years of age, even if they might have ingested a toxic dose of paracetamol.

GRADE: Strong; Evidence: Low.

Management of immediate release paracetamol overdose

The management of an acute immediate release paracetamol ingestion (defined as any intentional or deliberate self-poisoning) is summarised in **Flowchart 1**. Management is dependent on time post-ingestion and if the ingestion was single or staggered.

A. Acute immediate release paracetamol exposure with known time of ingestion

Treatment with acetylcysteine ensures survival if administered within 8 hours of paracetamol ingestion [15, 24]. Beyond 8–10 hours after ingestion, efficacy decreases with increasing delay to treatment [15]. If the result of a paracetamol concentration 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. Supplementary investigations such as liver function tests or a coagulation profile do not refine the initial risk assessment or change management in this group. However, a baseline ALT is performed for comparison to the ALT at the completion of acetylcysteine.

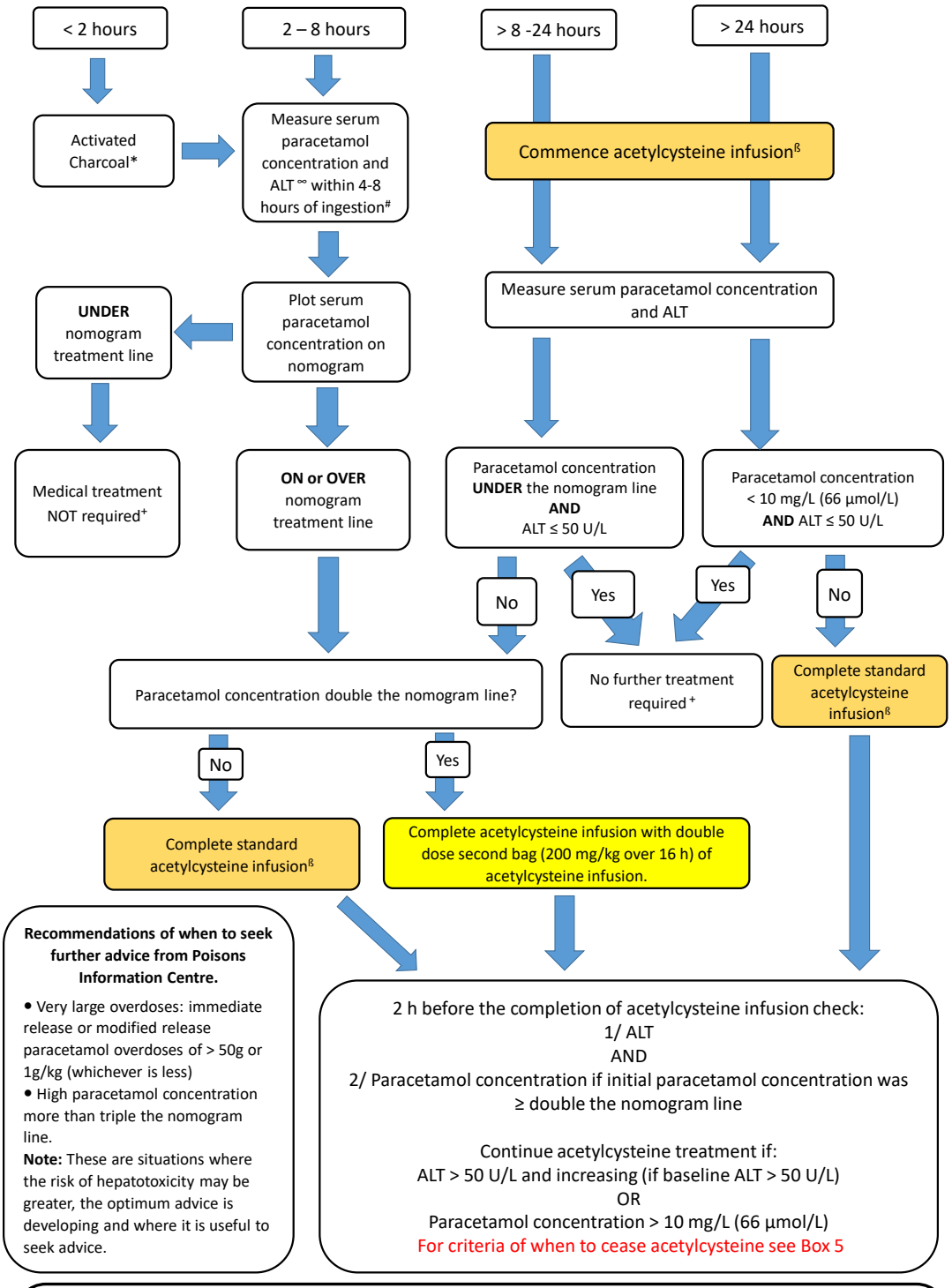
If a paracetamol concentration cannot be obtained until 8 or more hours after ingestion, acetylcysteine should be commenced immediately if the reported dose exceeds the threshold for possible toxicity (**Box 1**), or the patient shows clinical signs suggestive of paracetamol hepatotoxicity (nausea, vomiting, 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 line OR ALT > 50 U/L (and increasing if baseline ALT > 50 U/L), acetylcysteine should be continued.

There is a small (< 1%) risk of patients developing acute liver injury despite having a paracetamol concentration below the 150 mg/L (1000 μmol/L) at 4 hours nomogram line. Hence patients not given acetylcysteine should be advised to return for further assessment if they develop abdominal pain, nausea or vomiting after discharge.

B. Large/massive paracetamol ingestion

Most patients ingest less than 30 g of paracetamol. The majority of those given acetylcysteine have paracetamol concentrations just above the treatment nomogram line [20, 25]. A small percentage of patients, usually ingesting ≥ 30 g, have a high initial paracetamol concentration greater than double the nomogram line and are at increased risk of acute liver injury if given standard acetylcysteine regimens (300 mg/kg of acetylcysteine over 20 h) [21, 26, 27]. In some studies, 5-7% of these patients will still develop hepatotoxicity despite being treated within 8 hours with acetylcysteine [15, 28]. This risk of acute liver injury increases with increasing paracetamol concentrations [27]. In patients with high paracetamol concentrations, the standard acetylcysteine regimen is not adequate to detoxify increasing amounts of

Flowchart 1: Acute Immediate Release Paracetamol Ingestion Management Flowchart



NOTE:

*Cooperative adult patients who have potentially ingested ≥ 10g or 200 mg/kg (whichever is less). Paracetamol ingestions ≥ 30 g activated charcoal should be offered until 4 hours post ingestion.

If paracetamol concentration will not be available until ≥ 8 h post ingestion, commence acetylcysteine while awaiting paracetamol concentration.

∞ Baseline ALT measurement.

ß For acetylcysteine infusion dosage see Box 3

+ Patients should be advised if they develop abdominal pain, nausea or vomiting further assessment is required.

Note: for those in rural or remote regions where pathology is not available see alternative flowchart and text.

NAPQI produced in large overdoses and hence higher doses of acetylcysteine are warranted [29, 30].

Those with an initial paracetamol concentration greater than double the nomogram line have been shown to benefit from an increased dose of acetylcysteine [21]. The second bag in the two-bag acetylcysteine regimen should be doubled to 200 mg/kg IV acetylcysteine over 16 hours (instead of 100 mg/kg over 16 hours) (**Box 3**). Patients with even higher concentrations (e.g. ≥ triple the nomogram line) may benefit from even higher acetylcysteine doses [29, 30]. These patients should be discussed with a clinical toxicologist or Poisons Information Centre.

GRADE: Strong; Evidence: Low.

C. *Multiple or "staggered" immediate-release paracetamol ingestion*

This covers any staggered or multiple paracetamol ingestions over more than 2 hours for the purpose of deliberate self-harm. This is distinct from repeated-supratherapeutic ingestion which is ingestion of excessive paracetamol for therapeutic purposes (**Flowchart 4**). Staggered ingestions should be treated as per acute immediate release ingestion (**Flowchart 1**) utilising the earliest time of ingestion for the paracetamol nomogram. Hence, if it is more than 8 hours since the first dose of paracetamol or the paracetamol concentration cannot be obtained within 8 hours, then commence acetylcysteine. If the first paracetamol concentration was measured within 2 hours of the last ingested paracetamol dose it should be repeated after 2 hours to ensure there is no ongoing absorption. If either concentration is above the nomogram line (using time from the earliest ingestion), start/continue treatment with acetylcysteine.

GRADE: Weak; Evidence: Very low.

D. *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 **Flowchart 1**; that is to commence acetylcysteine. If the serum paracetamol concentration is greater than 10 mg/L (66 µmol/L) or the ALT is > 50 U/L, acetylcysteine treatment should be continued.

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.

Investigations near the completion of acetylcysteine for acute immediate release ingestion and criteria for ongoing acetylcysteine:

Near the completion of acetylcysteine (i.e. 2 hours before completion of the infusion), ALT should be repeated in all patients. For those with an initial paracetamol greater than double the nomogram line a paracetamol concentration should also be repeated. Acetylcysteine should be continued if the paracetamol concentration is > 10 mg/L (66 µmol/L) or ALT is elevated (> 50 U/L) and increasing (if baseline ALT > 50 U/L). Small fluctuations in ALT (e.g. +/- 20 U/L or +/-10%) are common and do not on their own indicate the need for ongoing acetylcysteine.

This is a change from previous guidelines, where ALT was only repeated in those commencing acetylcysteine ≥ 8 hours post ingestion and those with a high initial paracetamol concentration. ALT should be measured in all patients at the completion of acetylcysteine as there is a small (< 1%) risk of developing acute liver injury despite treatment with acetylcysteine within 8 hours [27, 29, 31, 32].

GRADE: Strong; Evidence: Low.

Acute modified-release paracetamol ingestion

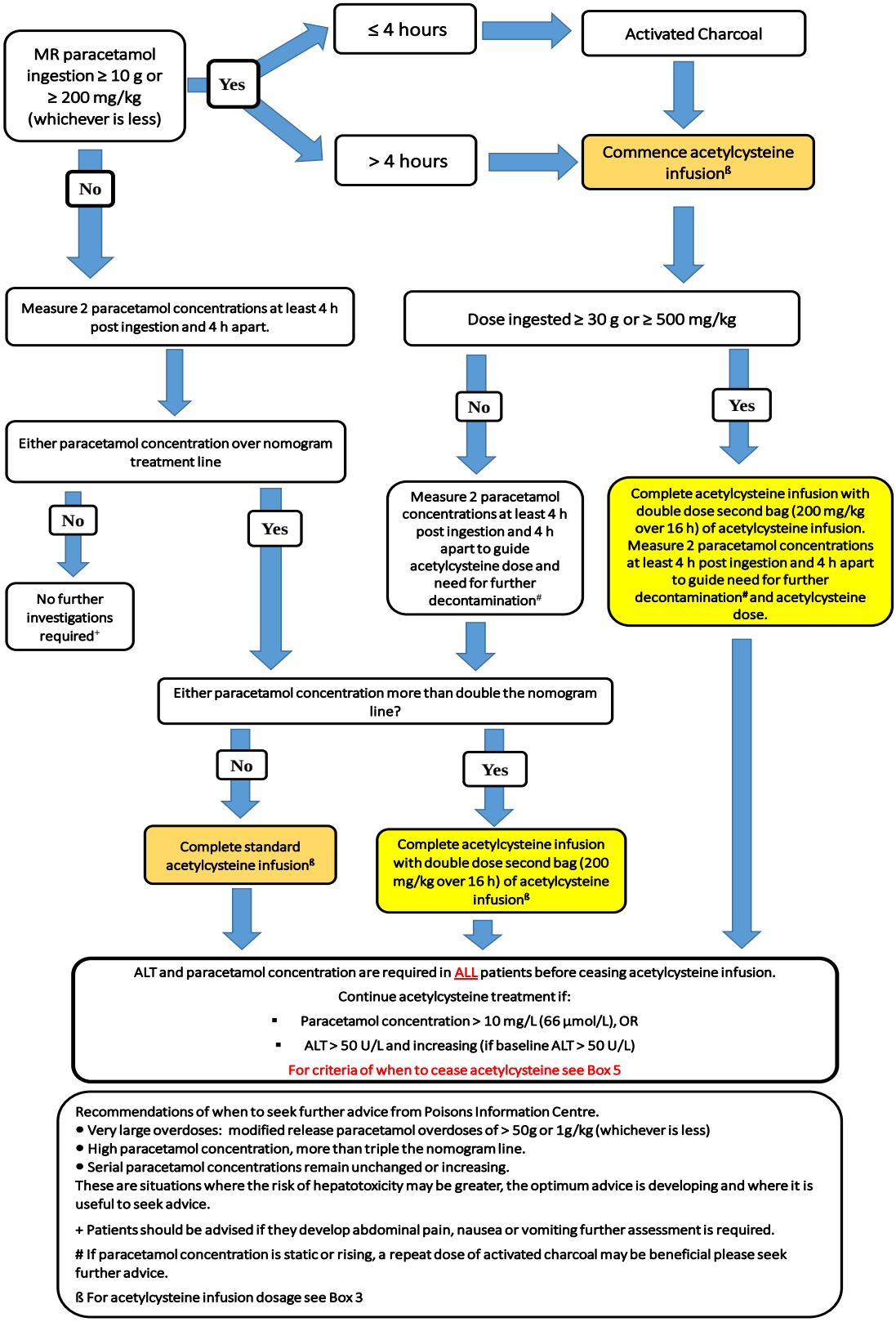
Modified-release paracetamol contains 69% modified-release and 31% immediate-release paracetamol in a 665 mg tablet. In the last guidelines, management was very similar to that for immediate-release paracetamol. However, evidence from studies and case series from both Australia and Europe have shown that this approach appears inadequate [22, 23, 33]. A recent observational study from Australia found that following an acute overdose of modified-release paracetamol patients may have persistently high paracetamol concentrations, double paracetamol peaks, and ongoing absorption [22]. Many patients required prolonged acetylcysteine treatment and treatments such as activated charcoal and increased acetylcysteine did not appear to substantially mitigate the risk of acute liver injury [22]. Hence the recommended management has changed considerably (**Flowchart 2**).

All modified-release paracetamol overdose (including mixed ingestion of immediate and modified release paracetamol) of ≥ 10 g or 200 mg/kg (whichever is less) should be offered activated charcoal up to 4 hours post-ingestion. For massive (≥ 30 g) modified-release paracetamol overdoses, absorption may continue up to 24 hours post-ingestion; patients may benefit from activated charcoal beyond 4 hours [22].

The nomogram should not be used to assess need for treatment of potentially toxic modified-release ingestions. Paracetamol concentrations are useful to guide further management such as acetylcysteine dosage (e.g. the need for increased or prolonged treatment) and need for further decontamination (e.g. further doses of activated charcoal if paracetamol concentrations remain unchanged or rise). Importantly, all those who ingest ≥ 10 g or 200 mg/kg (whichever is less) should immediately commence acetylcysteine (**Flowchart 2**) and receive a full 20 hour course of acetylcysteine regardless of their serum paracetamol concentration(s).

All patients who ingest ≥ 30 g or ≥ 500 mg/kg of modified release paracetamol or have a paracetamol concentration greater than double the nomogram line should receive an increased dose of acetylcysteine.

Flowchart 2: Acute Ingestion Modified-Release Paracetamol Management Flowchart



The second bag in the current standard IV acetylcysteine regimen should be doubled to 200 mg/kg IV acetylcysteine over 16 hours. This is because the majority of the preparation is modified-release and initial paracetamol concentrations may only reflect the immediate-release component of the preparation. Hence, following large MR paracetamol ingestions acetylcysteine doses may be inadequate due to ongoing paracetamol absorption.

Those who report ingesting less than a toxic dose (< 10 g AND < 200 mg/kg) should have two serum paracetamol concentrations 4 hours apart, starting at least 4 h post-ingestion. If either is above the nomogram line, a standard course of acetylcysteine should be given.

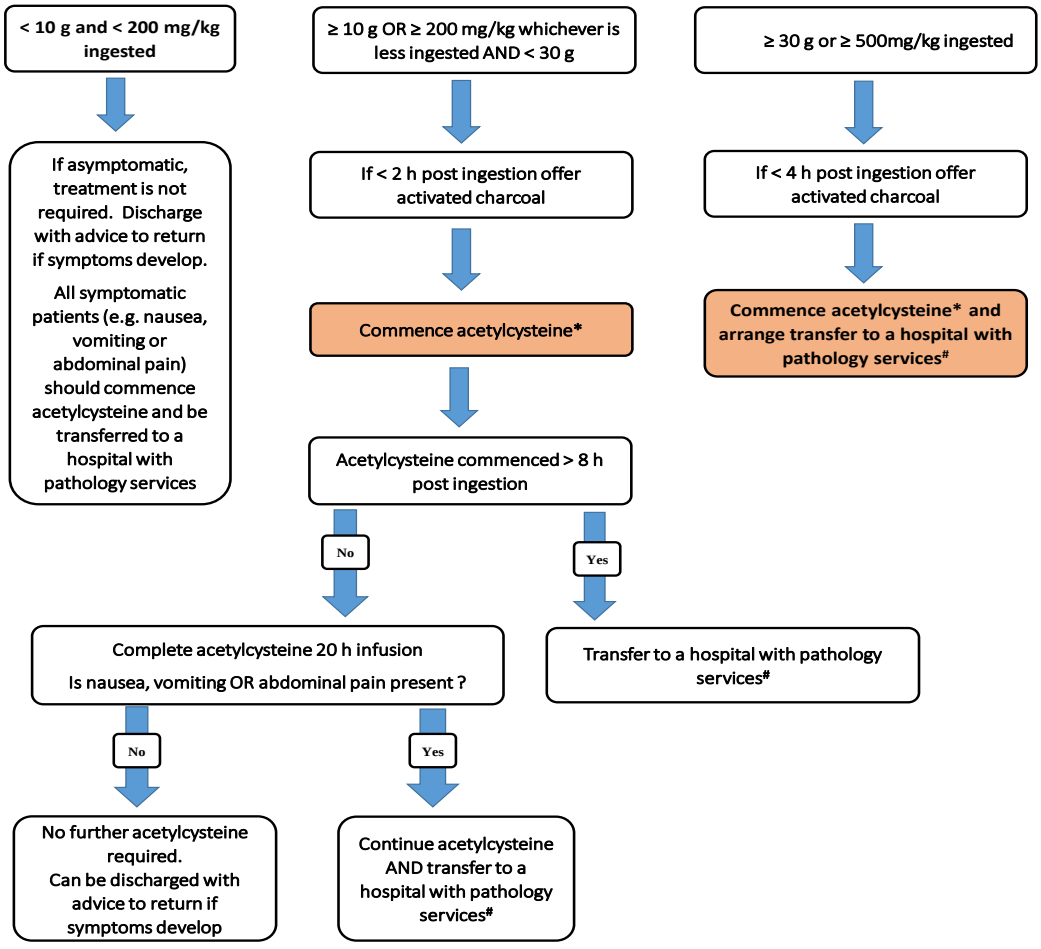
Acetylcysteine is often required for much longer durations. ALT and a paracetamol concentration should be checked near the completion of the second bag of acetylcysteine. Acetylcysteine should be continued if the paracetamol concentration is ≥ 10 mg/L (66 µmol/L) OR ALT is elevated (> 50 U/L) and increasing (if baseline ALT > 50 U/L). Small fluctuations in ALT (e.g. +/- 20 U/L or +/-10%) are common and don't on their own indicate the need for ongoing acetylcysteine. Higher doses of acetylcysteine may be required in subsequent infusions if the paracetamol concentration remains ≥ 100 mg/L (660 µmol/L) and further advice should be sought.

GRADE: Strong; Evidence: Very low.

Rural and Remote Centres

Many rural and remote health care facilities do not have access to 24-hour pathology or have very limited pathology (e.g. point of care testing only). These facilities can still manage

Flowchart 3: Acute Immediate Release Paracetamol Ingestion Management Flowchart for Rural/ Remote Facilities^ (no pathology availability)



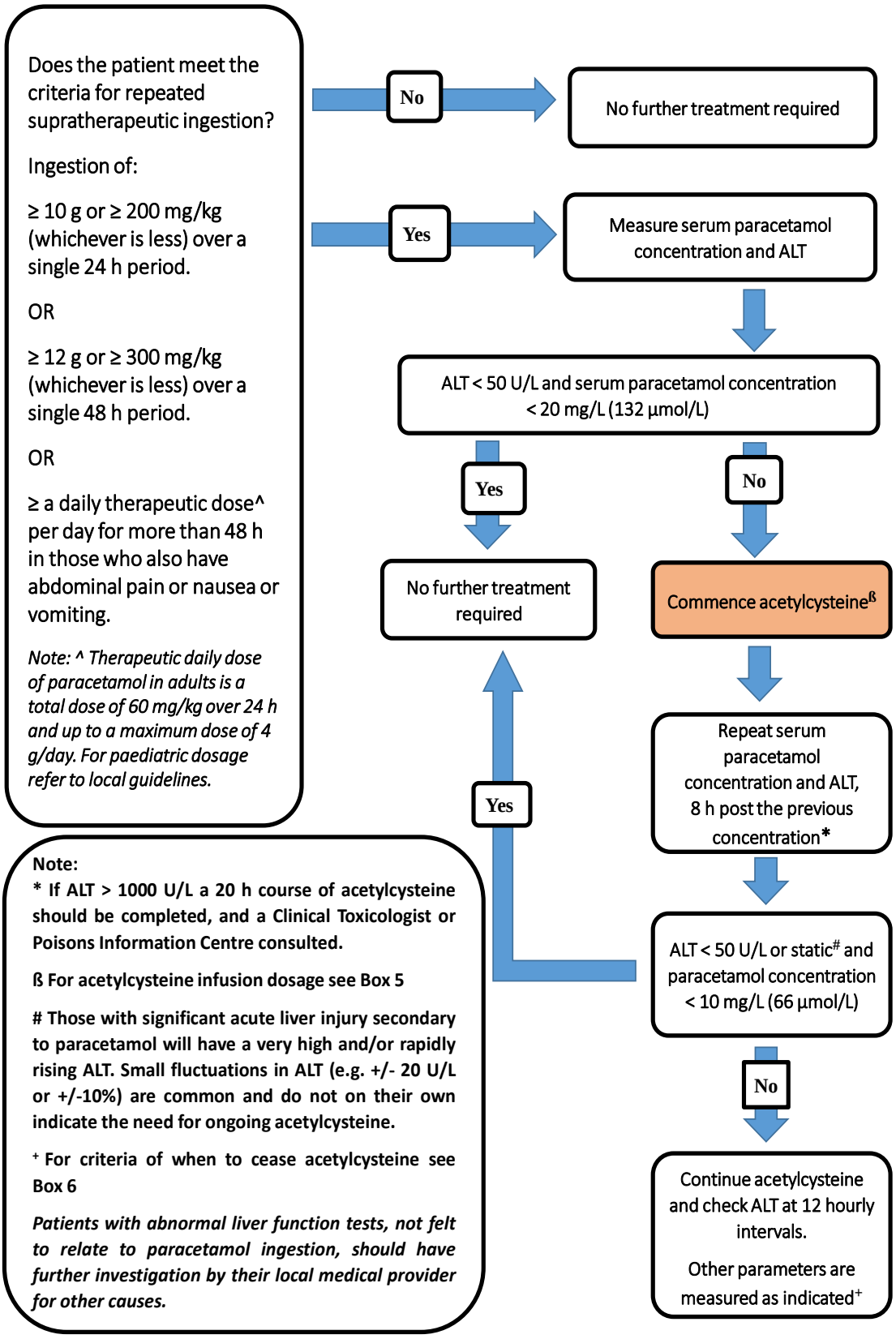
Note: This flowchart applies to facilities that do not have the capacity to measure a paracetamol concentration and/or ALT but are able to administer IV acetylcysteine. All other facilities should follow Flowchart 1: Immediate Release Paracetamol Ingestion Management Flowchart.

Patients who have ingested modified release paracetamol overdoses ≥ 10 g or ≥ 200 mg/kg (whichever is less) should have activated charcoal and acetylcysteine started and transfer arranged.

*For acetylcysteine regimen see Box 3

These patients are at increased risk of acute liver injury and so require further assessment at a hospital that has pathology services.

Flowchart 4: Repeated Supratherapeutic Ingestion Management Flowchart



acute paracetamol poisoning provided acetylcysteine is available (Flowchart 3). As a paracetamol concentration is not easily available in these facilities the need for acetylcysteine is based on ingested dose and the time of ingestion < 8 hours. Patients at high risk of acute liver injury (e.g. acetylcysteine > 8 hours post-ingestion, symptomatic or large ingestions [≥ 30 g]) require transfer to a larger facility with pathology capabilities. Patients who have ingested a toxic dose of modified release paracetamol overdoses should have activated charcoal and acetylcysteine commenced and transfer arranged.

Paediatric (< 6 years) liquid paracetamol ingestion

Paediatric patients (children < 6 years) are thought to be less susceptible to paracetamol toxicity than older children and adults [34]. Furthermore, they usually present with accidental liquid paracetamol ingestions. Young children who ingest liquid paracetamol have rapid absorption and an earlier time to peak paracetamol concentration because of shorter elimination half-lives. Activated charcoal is not indicated in this group as liquid preparations have rapid absorption.

In children less than 6 years of age, where ingestion of greater than 200 mg/kg of liquid paracetamol is suspected, a serum paracetamol concentration should be measured at least 2 hours post-ingestion [35]. If the 2 (to 4) hour concentration is below 150 mg/L (1000 µmol/L), acetylcysteine is not required. If the 2-hour paracetamol concentration is greater than 150 mg/L (1000 µmol/L), this should be repeated 4 hours post-ingestion and acetylcysteine commenced if this is ≥ 150 mg/L (1000 µmol/L).

A 2-hour concentration should only be utilised in a well-child < 6 years of age with an isolated liquid paracetamol ingestion. In all other cases a 4-hour concentration should be performed. Further, for those children who present later than 4 hours post-ingestion or in children older than 6 years of age, treatment is as per the adult acute paracetamol exposure guideline.

GRADE: Strong; Evidence: Very low.

Repeated supra-therapeutic ingestion (RSTI)

Patients who ingest excessive paracetamol for a therapeutic purpose (e.g. pain, viral illness) or ingest therapeutic doses of paracetamol and have symptoms of acute liver injury (e.g. abdominal pain, nausea and vomiting) are managed as RSTI (**Flowchart 4**).

If the ingestion is deliberate/intentional they should be managed as per acute intentional 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 [36]. Minor subclinical elevations of serum ALT are quite common with prolonged therapy [37]. However, hepatotoxicity has been reported at doses within the therapeutic range of paracetamol (in some cases at doses less than the recommended 4 g/day). The reasons why certain individuals are at greater risk of toxicity are unclear [38], but toxicity could be influenced by age, comorbidities, alcohol use, nutritional status (e.g., prolonged fasting), concurrent medicine use and genetics. Some patients are likely to be at increased risk for acute liver injury following RSTI due to glutathione depletion or CYP450 induction. Clinical flags would include pregnancy, prolonged fasting, chronic alcoholism, febrile illness and chronic use of CYP450 inducing drugs such as carbamazepine [39]. Hence, the threshold for potentially toxic dose has been made deliberately and conservatively low in this and previous guidelines.

Those patients who meet the criteria for supratherapeutic ingestion (**Box 1**) should have a paracetamol concentration and ALT measured. There is evidence that the combination of a low paracetamol concentration and normal ALT at any time indicates there is minimal risk of subsequent hepatotoxicity [40-42]. If the paracetamol concentration is > 20 mg/L (132 µmol/L) or ALT > 50 U/L, then acetylcysteine is commenced, and pathology repeated 8 hours after the initial sampling. Those with significant acute liver injury secondary to paracetamol will have a very high and/or rapidly rising ALT [41, 43]. Small fluctuations in ALT (e.g. +/- 20 U/L or +/- 10%) are common and do not on their own indicate the need for ongoing acetylcysteine. All patients with an initial ALT > 1000 U/L should receive at least a full 20 h course of IV acetylcysteine.

GRADE: Strong; Evidence: Very low.

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 [24, 44]. Neither is registered for use in Australasia and the oral regimens often provoke vomiting.

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% [45].

A. Acetylcysteine infusions

The standard (traditional) three-bag intravenous (IV) weight-based acetylcysteine dosage regimen (150 mg/kg body weight over 15-60 minutes, then 50 mg/kg over 4 hours and 100 mg/kg over 16 hours [300mg/kg total]) was developed in the 1970's. It was empirically derived and not subject to dose ranging studies [29]. This regimen has proven to be highly efficacious when compared to no treatment but causes frequent adverse reactions and the dosing regimen is complex and prone to error [10, 46]. Various acetylcysteine dosing regimens have been proposed and studied worldwide with the aim to decrease the rate of adverse effects [46]. These regimens include the Scottish and Newcastle Anti-emetic Pre-treatment for Paracetamol Poisoning (SNAP) 12-hour regimen and the two-bag acetylcysteine protocol. Both have

shown to decrease the rate of adverse events [47-50], with similar efficacy to the standard regimen [51, 52].

A two-bag acetylcysteine regimen (Box 3) will now replace the three-bag regimen recommended in previous guidelines. The two-bag acetylcysteine regimen slows the initial loading dose and simplifies the protocol (i.e. 200mg/kg over 4 hours followed by 100 mg/kg over 16 hours). This is widely used in toxicology units around Australia and has been shown to significantly reduce the rates of adverse reactions [48-50, 52, 53].

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. It is recommended that dosing tables providing the required dose and volume of 20% acetylcysteine by weight, are used to chart each infusion. This precludes the need for calculations and decreases the potential for error (Box 4). Furthermore, it is also important to ensure adequate mixing of acetylcysteine and fluid when preparing the infusion [54].

Calculation of acetylcysteine doses is based on actual bodyweight rounded up to the nearest 10 kg, but with a ceiling weight of 110 kg [55]. For children, the dose of acetylcysteine is calculated in the same way, but with the volume reduced appropriately (Box 3).

GRADE: Strong; Evidence: low.

B. Acetylcysteine Adverse Reactions

Non-IgE mediated anaphylactic (anaphylactoid) reactions manifested by rash, wheeze or mild hypotension occurred in 10%–50% of patients administered the traditional three bag IV acetylcysteine regimen [56-58]. With a two-bag regimen this rate is significantly lower (~5%) [48, 50]. Management of these reactions is supportive, with temporary halting or slowing of the infusion and administration of antihistamines and bronchodilators if required [59]. 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 symptoms settle acetylcysteine can be recommenced. Reactions are more likely to occur in predisposed individuals, such as patients with asthma [60].

C. Cessation of Acetylcysteine

Some patients will require ongoing treatment with acetylcysteine if they have a persistently high paracetamol concentration > 10 mg/L (66 µmol/L) or if the ALT is > 50 U/L and increasing. [**note:** small fluctuations in ALT (e.g. +/- 20 U/L or +/-10%)] are common and do not on their own indicate the need for ongoing acetylcysteine). In these cases, acetylcysteine should be continued until the patient has met all the criteria outlined in Box 5. Acetylcysteine is generally continued at the rate of the second infusion (e.g. 100 mg/kg over 16 hours) (Box 3). Higher infusion rates may be warranted for massive paracetamol ingestions, especially if the paracetamol concentration is ≥ 100 mg/L (660 µmol/L) at the completion of the initial acetylcysteine infusion; a clinical toxicologist should be consulted in such cases. Regular clinical review and at least 12 hourly blood tests are recommended for those requiring prolonged treatment (Box 2).

GRADE: Strong; Evidence: low

Box 3: Standard Two-Bag Acetylcysteine Regimen#^

Initial Infusion:

*acetylcysteine 200 mg/kg (maximum 22 g) in glucose 5% 500 mL (child 7 mL/kg up to 500 mL) or sodium chloride 0.9% 500 mL (child 7 mL/kg up to 500 mL) intravenously, over 4 hours.^*

Second acetylcysteine infusion:

*acetylcysteine 100 mg/kg (maximum 11 g) in glucose 5% 1000 mL (child 14 mL/kg up to 1000 mL) or sodium chloride 0.9% 1000 mL (child 14 mL/kg up to 1000 mL) intravenously, over 16 hours.^**

If ongoing acetylcysteine is required, continue at the rate of the second infusion (e.g. 100 mg/kg over 16 hours). Higher ongoing infusion rates (e.g. 200 mg/kg over 16 hours) may be required for massive paracetamol ingestions and a clinical toxicologist should be consulted.

#Acetylcysteine is also compatible with 0.45% saline + 5% dextrose.
^For adults (age ≥ 14 y) dosing should be based on actual bodyweight rounded up to the nearest 10 kg, with a ceiling weight of 110 kg. For children (age < 14 y) use actual body weight.
* If the initial paracetamol concentration was **more than double the nomogram line** following an acute ingestion increase acetylcysteine dose to 200 mg/kg (maximum 22 g) in glucose 5% 1000 mL (child 14 mL/kg up to 1000 mL) or sodium chloride 0.9% 1000 mL (child 14 mL/kg up to 1000 mL) intravenously, over 16 hours.

Note: Monitoring with pulse oximetry for the first 2 hours of the infusion is recommended.

Box 4: Dose and volume of acetylcysteine to be charted for each infusion, based on actual bodyweight in adults.

- Obtain weight of patient (kg) to determine dosage. Dosing should be based on actual body weight rounded up to the nearest 10 kg, with a ceiling weight of 110 kg.
- Acetylcysteine is packaged for intravenous infusion in ampoules, each containing a 20% solution (i.e. 200 mg acetylcysteine per 1 mL)
- Remove the corresponding volume from the infusion fluid (i.e. 5 % glucose or sodium chloride 0.9%) then add acetylcysteine. Invert all prepared solutions at least 10 times prior to infusing to ensure adequate mixing.
- Acetylcysteine is also compatible with 0.45% saline + 5% dextrose.

PATIENT'S BODY WEIGHT (kg)	INITIAL INFUSION (200 mg/kg of acetylcysteine)	SECOND (100 mg/kg of acetylcysteine)
	Dose (g) & Volume (mL) of acetylcysteine to be added to 500 mL of 5% glucose or sodium chloride 0.9%	Dose (g) & Volume (mL) of acetylcysteine to be added to 1000 mL of 5% glucose or sodium chloride 0.9%
50	10 g = 50 mL	5 g = 25 mL
60	12 g = 60 mL	6 g = 30 mL
70	14 g = 70 mL	7 g = 35 mL
80	16 g = 80 mL	8 g = 40 mL
90	18 g = 90 mL	9 g = 45mL
100	20 g = 100 mL	10 g = 50 mL
110 **(maximum dose)**	22 g = 110 mL	11 g = 55 mL

Box 5: Cessation of Acetylcysteine

In those patients who require acetylcysteine beyond 20 hours. Acetylcysteine can be ceased if **all** the following criteria have been met:

- ALT or AST are decreasing
- INR < 2.0
- Patient clinically well

AND

For modified-release ingestions and those with an initial paracetamol concentration greater than double the nomogram line: paracetamol concentration < 10 mg/L (66 µmol/L)

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Hepatotoxicity and Subsequent Liver Failure:

Only a small proportion of patients develop hepatotoxicity (ALT > 1000 U/L); early symptoms include nausea, vomiting, abdominal pain and right upper quadrant tenderness. Of these only a minority will develop fulminant hepatic failure, and most patients recover fully with standard treatments [10, 15, 61]. Typically, in those with paracetamol induced acute liver injury the ALT and AST will rise for 3 - 4 days before recovering [62]. Acetylcysteine is continued until the criteria met in **Box 5**. Investigations that monitor liver function and guide prognosis should be performed regularly in all patients with hepatotoxicity, including electrolytes, urea, creatinine, liver function tests, INR, blood sugar, phosphate and venous blood gas (looking at the pH and lactate).

A Liver Transplant Unit should be consulted if any of the following criteria are met:

- 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,
- systolic hypotension with BP < 80mmHg, despite resuscitation,
- hypoglycaemia, severe thrombocytopenia or encephalopathy of any degree,
- or any alteration of consciousness (GCS < 15) not associated with sedative co-ingestions.

DO NOT GIVE clotting factors unless bleeding or after discussion with a Liver Transplant Unit.

GRADE: Strong; Evidence: Strong.

Intravenous paracetamol medication errors:

Intravenous paracetamol medication errors are not dealt within these guidelines, as the treatment thresholds are lower than for an oral ingestion [63]. The most common are iatrogenic and due to ten-fold calculation errors in children [64]. A clinical toxicologist or Poisons Information Centre should be contacted regarding these cases.

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 less).
- High paracetamol concentration, more than triple the nomogram line.
- Intravenous paracetamol errors/overdoses, as the treatment threshold is lower.
- Patients with hepatotoxicity (i.e. ALT > 1000 IU/L).
- Neonatal paracetamol poisonings

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

***** *For Poisons Information Centre: Call 131126 in Australia* ***OR*** *0800 764766 in New Zealand*

Conclusion:

This is an up dated 2019 guideline for the management of paracetamol poisoning in Australia and New Zealand. While most paracetamol poisoning scenarios are covered, if there are any concerns regarding the management of paracetamol ingestion advice can always be sought from a clinical toxicologist or Poisons Information Centre (131126 in Australia, 0800 764766 in New Zealand).

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