Paracetamol ingestion - Emergency management in children

Purpose

This document provides clinical guidance for all staff involved in the care and management of a child presenting to an Emergency Department (ED) in Queensland following a paracetamol ingestion.

This guideline has been developed by senior ED clinicians and Paediatricians across Queensland, with input from Clinical Toxicology, Princess Alexandra Hospital and Pharmacy, Gastroenterology and PICU, Queensland Children's Hospital, Brisbane. It has been endorsed for use statewide by the Queensland Emergency Care of Children Working Group in partnership with the Queensland Emergency Department Strategic Advisory Panel and the Healthcare Improvement Unit, Clinical Excellence Queensland.

Key points

- Toxic paracetamol ingestions require prompt treatment with N-Acetylcysteine (NAC) infusion to avoid serious hepatic injury and death.
- The need for NAC is guided by serum paracetamol concentration levels using a treatment nomogram.
- Administer NAC **immediately** if paracetamol concentration levels are not likely to be available within eight hours of a potentially toxic ingestion (due to delay in presentation to ED or time for testing or uncertain time of ingestion) or patient has symptoms of hepatic injury (abdominal pain, nausea and anorexia).
- Careful attention is required to avoid NAC dosing errors. Fluid adjustment is required for children.
- Seek urgent toxicological advice from Poisons Information (Ph: 131126) for IV or very large overdoses (50 g or 1 g/kg), or if evidence of hepatotoxicity (ALT greater than 1,000 IU/L). Critical care may be required.

Introduction

Paracetamol is a widely used analgesic that is readily available in many different preparations. Accidental or deliberate overdose can cause hepatic failure and death. This can be prevented by the early administration of N-acetyl cysteine (NAC).[1]

This guideline is based on the recommendations made in 2015 by a group of Australasian Clinical Toxicologists consulting to the Poisons Information Centre.[1,2]

While there are certain groups who are at higher risk of hepatotoxicity (such as those with malnutrition, eating disorders, cystic fibrosis or acute viral infections) the recommended management is conservative and so remains unchanged.

Pharmacokinetics

Paracetamol is rapidly absorbed in the small intestine and reaches peak concentrations within 30 minutes for liquid preparations and one to two hours for standard tablet preparations. Distribution then occurs within two hours for liquid preparations and four hours for standard tablet preparations.[1] Hepatic biotransformation results in 90% of paracetamol being metabolised to inactive sulphate and glucuronide conjugates which are then excreted by the kidneys. The remaining 10% requires cytochrome p450 to make an intermediary compound of N-Acetyl-p-benzoquinone imine (NAPQI) which then in turn binds to intracellular glutathione for renal excretion. Depletion of glutathione occurs with higher production of NAPQI which subsequently binds to other proteins and thus damages hepatocytes. Clinical or biochemical evidence of this damage may take up to 24 hours post overdose to become apparent.[1,3]

NAC is an effective antidote to paracetamol toxicity by increasing the synthesis and availability of glutathione and directly binding to NAPQI. Appropriate treatment commencing within eight hours of the overdose will prevent almost all serious hepatic injury.

Assessment

The aim of the initial assessment is to determine the risk of hepatic injury following paracetamol ingestion.

History

History-taking should include information on:

- number, quantity and timing of ingestions
- symptoms of hepatic injury (such as abdominal pain, nausea or vomiting, anorexia)

Examination

Full examination focussing on eliciting any toxidromes to suggest co-ingestion, neurological status for co-ingestion risk and hepatic encephalopathy, and serial abdominal examinations which can elicit right upper quadrant tenderness.

Calculation of ingested dose

Use the available information to calculate the dose per kilogram of paracetamol ingested. When in doubt of the quantity, use the maximum possible ingested dose to determine the potential for hepatic injury.

Paracetamol dosing that may be associated with hepatic injury*		
Age	**Acute single ingestion**	**Repeated supratherapeutic ingestion**
0 - 6 years	Greater than 200 mg/kg over a period of eight hours	Any of the following: • greater than 200 mg/kg over a single 24-hour period • greater than 150 mg/kg per 24-hour period for the preceding 48 hours • greater than 100 mg/kg per 24-hour period for greater than 48 hours (may have abdominal pain, nausea or vomiting)
Over 6 years	Greater than 200 mg/kg or 10g (whichever is lower) over a period of eight hours	Any of the following: • greater than 200 mg/kg or 10 g (whichever is lower) over a single 24-hour period • greater than 150 mg/kg or 6 g (whichever is lower) per 24-hour period for the preceding 48 hours • greater than 100 mg/kg or 4 g (whichever is lower) per 24-hour period for greater than 48 hours AND symptoms indicating possible liver injury (such as abdominal pain, nausea or vomiting)

*Use the ideal body weight for body weight calculations in obese children

Investigations

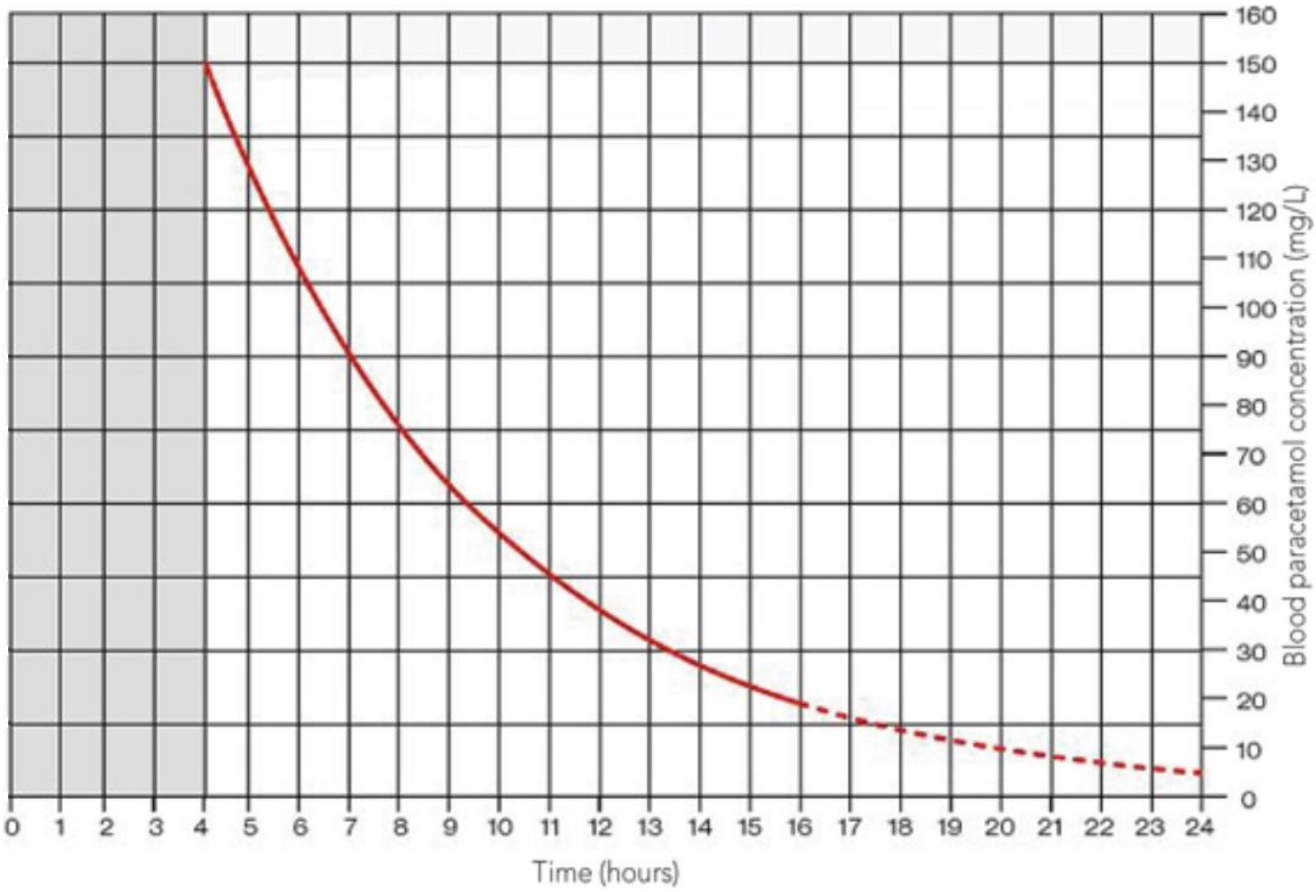
ALERT – Administer NAC immediately if paracetamol concentration levels are not likely to be available within eight hours of a potentially toxic ingestion (due to delay in presentation to ED or time for testing or uncertain time of ingestion) or patient has symptoms of hepatic injury (abdominal pain, nausea and anorexia). Do not delay for paracetamol concentration levels.

Serum paracetamol concentration testing is used to determine the need for NAC (by plotting on the treatment nomogram provided below). Testing is recommended for patients with a history of:

- ingesting a toxic dose (refer to table in Assessment section)
- deliberate self-poisoning regardless of the stated ingested dose
- accidental exposures if uncertain of ingested dose

<table>
<tr><th colspan="2">Investigations recommended for the management of paracetamol overdose</th></tr>
<tr><td>Children aged less than 6 years post-ingestion of liquid paracetamol</td><td>Serum paracetamol concentration at 2 hours post-ingestion.
Concentrations less than 150 mg/L require no further treatment. Repeat at four hours post-ingestion if two-hour level is greater than or equal to 150 mg/L.</td></tr>
<tr><td>Patients with single potentially toxic paracetamol ingestion</td><td>
<table>
<tr><th>Time of presentation</th><th>Testing</th></tr>
<tr><td>Within 8 hours of ingestion</td><td>Serum paracetamol concentration at 4-8 hours post-ingestion.
If initial paracetamol concentration is more than double the nomogram line, at end of NAC infusion repeat level and measure ALT.</td></tr>
<tr><td>8-24 hours post-ingestion</td><td>Serum paracetamol concentration and ALT on presentation and commence NAC while awaiting level
If initial paracetamol concentration is above the nomogram treatment line measure ALT at end of NAC infusion.</td></tr>
<tr><td>Greater than 24 hours post-ingestion</td><td>Serum paracetamol concentration, transaminases (ALT/AST), INR/PT, creatinine, urea, glucose and arterial or venous blood gas on presentation.
Follow up as clinically indicated.</td></tr>
<tr><td>Unknown</td><td>Serum paracetamol concentration and ALT on presentation.
Seek toxicologist advice for further testing.</td></tr>
</table>
</td></tr>
<tr><td>Patients post-ingestion of sustained release paracetamol (e.g. Panadol Osteo® and Osteomol®)</td><td>Serum paracetamol concentration minimum of four hours post-ingestion.
ALT and repeat serum paracetamol concentration four hours after initial testing to capture the delayed release. Repeat paracetamol levels and ALT again two hours prior to cessation of the infusion.</td></tr>
<tr><td>Patients with potentially toxic repeated supratherapeutic ingestions</td><td>Serum paracetamol concentration and ALT on presentation.
Repeat at eight hours after initial measurement if either serum paracetamol concentration greater than 20 mg/L or ALT greater than 50 U/L.
Check ALT every twelve hours if ALT greater than 50 U/L or paracetamol concentration is greater than 10 mg/L.</td></tr>
</table>

Paracetamol treatment nomogram



Reproduced from Daly FF 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 (5): 296-301 with permission from John Wiley and Sons. Link to article.

Management

Refer to Appendix 1 for a summary of the emergency management for a child following a paracetamol ingestion.

Contact a Clinical Toxicologist via Poisons Information Centre (ph.: 131126) urgently for:

- overdoses of 50 g or 1 g/kg (always use lower threshold)
- tested paracetamol concentration is double the nomogram line
- IV overdoses
- evidence of hepatotoxicity (ALT greater than 1,000 IU/L)

Higher concentrations of NAC may be required. Contact paediatric critical care specialist (onsite or via Retrieval Services Queensland (RSQ)) as advised by Poisons Information Centre/Clinical Toxicologist

Refer patients with a deliberate overdose for a psychiatric assessment as per local practices

Activated charcoal

Activated charcoal is not a life-saving treatment but may prevent or reduce the need for treatment with NAC if used appropriately.

Activated charcoal is only routinely recommended for cooperative patients aged greater than six years if able to be administered one to two hours post-ingestion. It may be given up to four hours post-ingestion for very large overdoses, or beyond this time frame for large overdoses of sustained release paracetamol preparations on advice from Poisons Information Centre/Clinical Toxicologist. It is not recommended in liquid preparation overdose due to the fast absorption time.

N-Acetyl Cysteine (NAC)

NAC following single toxic paracetamol ingestion

The need for NAC is guided by serum paracetamol concentration levels using a treatment nomogram (see Assessment section).

ALERT – Additional management is required for **sustained release paracetamol** ingestions. Refer to section below.

NAC administration following single toxic paracetamol ingestion		
Time from ingestion		**Indications for NAC**
	2 hours	NAC will not be required for **children aged less than 6 years** with serum paracetamol concentration less than 150 mg/L at two hours post-ingestion of liquid paracetamol. If greater than or equal to 150 mg/L do not commence NAC but repeat level at four hours.
	4-8 hours	Commence NAC if: • serum paracetamol concentration levels taken at 4 hours post-ingestion are greater than or equal to 150 mg/L or • serum paracetamol concentration levels taken 4-8 hours post-ingestion are above the nomogram treatment line. Await serum levels if results are expected within 8 hours of ingestion. If results are not expected within 8 hours, commence NAC and review serum levels when available. Continue NAC if levels taken within 4-8 hours of ingestion are above the nomogram treatment line. Otherwise cease infusion.
	Greater than 8 hours	Commence NAC immediately if present 8 -24 hours post-ingestion. If present greater than 24 hours post-ingestion, collect bloods for further testing prior to commencing NAC (refer to Investigations). Continue NAC if serum paracetamol concentration levels above the nomogram treatment line or ALT greater than 50 U/L.
Unknown		Commence NAC immediately. Continue NAC if paracetamol concentration is greater than 10 mg/L or ALT is greater than 50 U/L.

NAC following sustained release paracetamol ingestions

Sustained release paracetamol preparations (such as Panadol Osteo® and Osteomol® both with 665mg paracetamol/tablet) result in **potentially delayed** peak concentrations above the nomogram treatment line. A single measurement of paracetamol level is not adequate to make decisions around NAC administration if an unknown quantity or a potentially toxic quantity has been ingested.

NAC administration following sustained release paracetamol ingestions

In addition to the management previously described for single toxic ingestions, repeat serum level four hours after initial testing and commence NAC if level is above the treatment line.

For all patients requiring NAC:

- measure paracetamol concentration levels and ALT two hours before completion of the NAC infusion.
- continue the NAC infusion and seek toxicology advice if ALT is greater than 50 U/L or paracetamol concentration is greater than 10 mg/L

NAC following repeated supratherapeutic ingestions*

NAC administration following repeated supratherapeutic ingestions*

Commence NAC if either serum paracetamol concentration greater than 20 mg/L or ALT greater than 50 U/L.

Repeat levels at 8 hours after initial testing. Discontinue NAC if ALT is less than 50 U/L or static **AND** paracetamol concentration is less than 10 mg/L. Otherwise continue NAC and recheck ALT every twelve hours.

*Refer to Assessment section for definition

NAC administration

ALERT – Careful attention is required when ordering fluids. Fluid adjustment orders are required for smaller children due to risk of hyponatremia using the total adult fluid volume (1700mls). Secondary seizures have resulted when using 5% glucose.[4,5,6]

Refer to the NAC guideline and use the appropriate order form (based on child's weight) or the electronic ordering system.

The total NAC dosing is 300 mg/kg administered over 20 hours in two sequential IV infusions and is compatible with any glucose and/or sodium-based fluids. Dosing is calculated on actual body weight up to 110 kg (with dosing based on 110 kg weight for children over 110 kg). NAC is packaged in 10 mL ampoules each containing 2,000 mg (20%). Doses are written in mg. While the recommended regime uses two bags, some smart pumps are yet to be updated to accommodate this and, at present ieMR has both two and three-bag options. The two-bag regime can be run using the mL/hour functionality on the pumps as per the NAC forms.

Prescribe the entire treatment course at the time of the initial presentation to avoid administration delays.

Adverse drug reactions

Anaphylactoid reactions including rash, pruritus, angioedema, bronchospasm and rarely hypotension may occur following NAC administration with females and asthmatics at higher risk. Progression to a more clinically significant reaction is rare.

If drug reactions occur, slow the infusion or temporarily cease the infusion, treat with antihistamines or bronchodilators and restart once the reaction settles.

Ongoing liver impairment

Seek specialist advice (Toxicology/Gastroenterology/Critical Care) for patients with ongoing evidence of liver impairment.

For patients with ongoing liver impairment, continue NAC and 12-hourly-blood-testing until clinically improving, ALT is reducing, INR is improving and less than 2.0 and the paracetamol level is less than 10 mg/L.

Indications for referral to a liver transplant unit

- INR greater than 2.0 at any time
- oliguria or creatinine greater than 200 μmol/L
- persistent acidosis pH less than 7.3
- systolic hypotension despite resuscitation
- hypoglycaemia
- severe thrombocytopenia
- encephalopathy not otherwise explained [2]

Escalation and advice outside of ED

Clinicians can contact the services below if escalation of care outside of senior clinicians within the ED is needed, as per local practices. Transfer is recommended if the child requires a higher level of care.

Critical care is unlikely to be required following a paracetamol overdose in isolation but may be required if co-ingestions have occurred. Seek critical care advice (onsite or via RSQ) if advised by toxicologist or child is critically unwell.

Toxicology advice is required for the following:

- overdoses of more than total of 50 g or 1 g/kg (always use lower threshold)
- tested paracetamol concentration is double the nomogram line
- IV overdoses
- evidence of hepatotoxicity (ALT greater than 1,000 IU/L)

Reason for contact	Who to contact
Advice (including management, disposition or follow-up of all children requiring a NAC infusion)	Follow local practices. Options: • Poisons Information Centre 13 11 26 (24-hour service) • onsite/local paediatric service • Queensland Children's Hospital experts via Children's Advice and Transport Coordination Hub (CATCH) on 13 CATCH (13 22 82) (24-hour service) • local and regional paediatric videoconference support via Telehealth Emergency Management Support Unit TEMSU (access via QH intranet) on 1800 11 44 14 (24-hour service)
Referral	First point of call is the onsite/local paediatric service

Inter-hospital transfers

Do I need a critical transfer?	• discuss with onsite/local paediatric service • view Queensland Paediatric Transport Triage Tool
Request a non-critical inter-hospital transfer	• contact onsite/local paediatric service • contact RSQ on 1300 799 127 for aeromedical transfers • contact Children's Advice and Transport Coordination Hub (CATCH) on 13 CATCH (13 22 82) for transfers to Queensland Children's Hospital

Non-critical transfer forms	• QH Inter-hospital transfer request form (access via QH intranet)
	• aeromedical stepdown (access via QH intranet)
	• commercial aeromedical transfers:
	  ○ Qantas
	  ○ Virgin
	  ○ Jetstar

When to consider discharge from ED

Consider discharge for the following patients:

- NAC infusion not required (based on assessment of serum paracetamol concentration levels or clear history of quantity of accidental ingestion)

AND

- if ingestion deliberate, a psychiatric assessment has been conducted as appropriate.

On discharge, educate the family regarding safe paracetamol administration and storage.

Follow-up

Not routinely required.

When to consider admission

Admission to an inpatient service or SSU is recommended for patients requiring ongoing NAC infusion once serum paracetamol concentration levels are available.

Related documents

Guidelines

- Paediatric Medication Guideline N-Acetylcysteine (Intravenous)

Forms

- N- Acetylcysteine Order form- Child (less than 20kg)
- N- Acetylcysteine Order form- Child (20-50kg)
- N- Acetylcysteine Order form- Child (greater than 50kg)

References

1. 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 (5): 296-301.
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3. Marzullo L. An update of N-acetylcysteine treatment for acute acetaminophen toxicity in children. Curr. Opin. Pediatr. 2005;17 (2): 239-45.
4. Sung L, Simons JA, Ayneka NL. Dilution of Intravenous N-Acetylcysteine as a Cause of Hyponatremia. Pediatr. 1997;100(3):389-91.
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6. Furmaga J, Wax P, Kleinschmidt K. N-Acetylcysteine (NAC)-Induced Hyponatremia Caused by an Electronic Medical Record (EMR) Order Error. J Med Toxicol. 2015;11 (3): 355-8.

Guideline approval

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Disclaimer

This guideline is intended as a guide and provided for information purposes only. The information has been prepared using a multidisciplinary approach with reference to the best information and evidence available at the time of preparation. No assurance is given that the information is entirely complete, current, or accurate in every respect. We recommend hospitals follow their usual practice for endorsement locally including presenting it to their local Medicines Advisory Committee (or equivalent) prior to use.

The guideline is not a substitute for clinical judgement, knowledge and expertise, or medical advice. Variation from the guideline, taking into account individual circumstances may be appropriate.

This guideline does not address all elements of standard practice and accepts that individual clinicians are responsible for:

- Providing care within the context of locally available resources, expertise, and scope of practice
- Supporting consumer rights and informed decision making in partnership with healthcare practitioners including the right to decline intervention or ongoing management
- Advising consumers of their choices in an environment that is culturally appropriate and which enables comfortable and confidential discussion. This includes the use of interpreter services where necessary
- Ensuring informed consent is obtained prior to delivering care
- Meeting all legislative requirements and professional standards
- Applying standard precautions, and additional precautions as necessary, when delivering care
- Documenting all care in accordance with mandatory and local requirements

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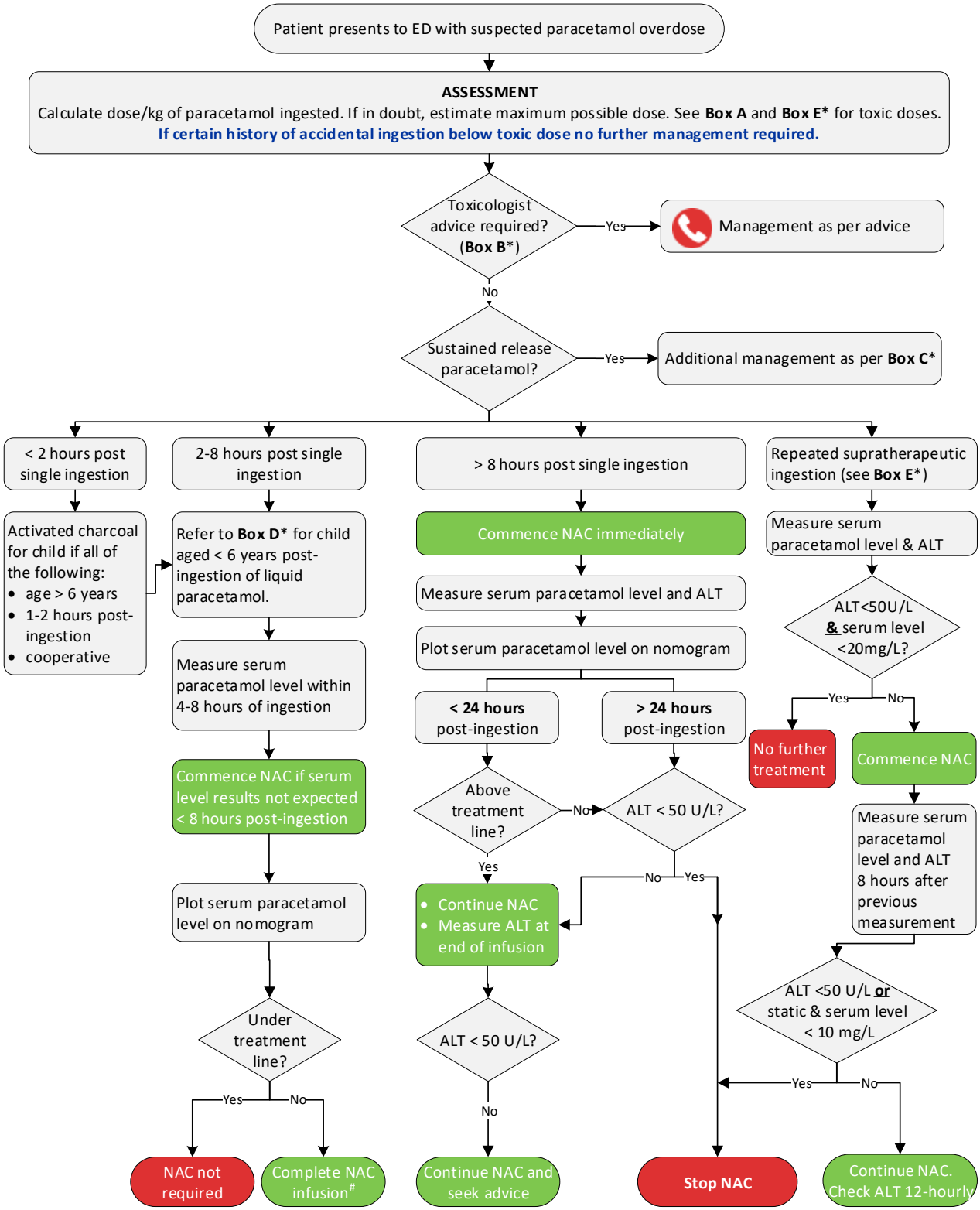

Box A: Paracetamol dosing that may be associated with hepatic injury	
Age 0-6 years:	> 200 mg/kg over 8 hour period
Age over 6 years:	> 200 mg/kg or 10 g (whichever is lower) over 8 hour period

*** Box B-E** over page

\# Seek Toxicology advice if serum paracetamol level is more than double treatment line

Seek Toxicology advice via Poisons Information Line (Ph: 13 11 26)

Box B: Criteria for toxicologist advice

Seek urgent toxicological advice via Poisons Information (ph.: 131126) for the following:

- IV overdoses
- very large overdoses (greater than 50 g or 1 g/kg) (always use lower threshold)
- evidence of hepatotoxicity (ALT greater than 1,000 IU/L)

Critical care may be required.

If unknown time of potentially toxic single ingestion, commence NAC and seek advice re testing.

Box C: NAC administration following sustained release paracetamol ingestions

Sustained release paracetamol preparations (such as Panadol Osteo and Osteomol) result in **potentially delayed** peak concentrations above the nomogram treatment line.

A single measurement of paracetamol level is not adequate to make decisions regarding NAC.

In addition to the management described for single toxic ingestions, **repeat serum level** 4 hours after initial testing and commence NAC if level is above the treatment line.

For all patients requiring NAC:

- measure paracetamol concentration levels and ALT 2 hours before completion of the NAC infusion
- continue NAC infusion and seek toxicology advice if ALT is greater than 50 U/L or paracetamol concentration is greater than 10 mg/L

Box D: NAC administration following liquid paracetamol ingestions in children aged <6 years

NAC will **not** be required for children aged less than 6 years with serum paracetamol concentration less than 150 mg/L at 2 hours post-ingestion of liquid paracetamol.

If greater than or equal to 150 mg/L do not commence NAC but repeat level at 4 hours.

Box E: Repeated supratherapeutic paracetamol ingestion that may be toxic

Age	Repeated supratherapeutic ingestion
0 - 6 years	Any of the following: • greater than 200 mg/kg over a single 24-hour period • greater than 150 mg/kg per 24-hour period for the preceding 48 hours • greater than 100 mg/kg per 24-hour period for greater than 48 hours (may have abdominal pain, nausea or vomiting)
Over 6 years	Any of the following: • greater than 200 mg/kg or 10 g (whichever is lower) over a single 24-hour period • greater than 150 mg/kg or 6 g (whichever is lower) per 24-hour period for the preceding 48 hours • greater than 100 mg/kg or 4 g (whichever is lower) per 24-hour period for greater than 48 hours AND symptoms indicating possible liver injury (such as abdominal pain, nausea or vomiting)