Paracetamol (Acetaminophen, APAP)

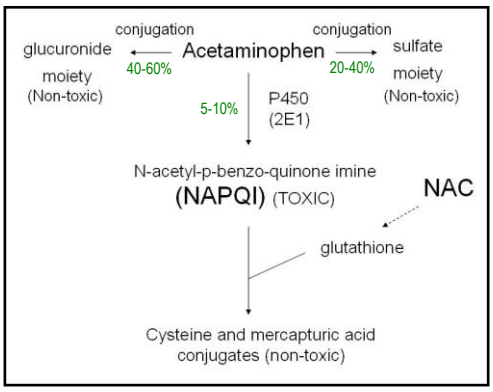
Overview/Risk assessment

Most commonly used OTC analgesic and OD needing hospital presentation & admission. Paediatric accidental overdose is also common. Hepatic failure & death uncommon and preventable by early NAC. Acute, staggered, repeated supratherapeutic, paediatric and modified-release preparation ingestions all require different strategies. Risk assessment based on dose, preparation, single or staggered od, time to presentation, investigation results, and clinical features.

Toxicokinetics

Rapid oral abs with peak levels at 1-2hrs for tablets (30mins for elixir). Extended release preparations may be absorbed over 12hrs or longer in OD esp if pharmacobezoars form. VD is 0.9-1L/kg. 20% is metabolised by gut wall, rest by the liver by conjugation & cytochrome P450 (chiefly 2E1 and 3A4). Elim. $T_{\frac{1}{2}}$=~2hrs, but may reach ≥4hrs in OD where ↑$T_{\frac{1}{2}}$ reflects saturation of conjugation & more P450 metabolism.

Toxic mechanism



In OD, SO_4^{2-} conjugation can become saturated & ↑NAPQI depletes glutathione stores. If ~<30% normal, NAPQI can bind to cell proteins → Zone 3 centrilobular liver necrosis ± renal or myocardial injury. Low levels of glutathione may expose cell to other oxidative damage. NAC is a glutathione & SO_4^{2-} source. Potential ↑toxicity if on specific cytochrome P450 inducers (For CYP2E1: chronic EtOH, isoniazid, rifampin, carbamazepine, **not** phenytoin nor phenobarbital. For CYP3A4: phenytoin, phenobarbital, glutacorticoids & rifampicin), or pre-existing low glutathione stores (genetic variation, malnutrition, pregnancy, HIV+ve, and EtOH-related or other liver disease). Malnutrition may ↓P450 enzyme production, mitigating induction. Young children have ↓toxicity (?↑sulphonation, ↑detox of NAPQI & ↑glutathione).

Clinical features

Split into 4 clinical phases:

1. *<1 day* - Asymptomatic, anorexia, nausea, vomiting (esp. large overdose or children), malaise, pallor, diaphoresis. *(NB caution with **ondansetron** as may ↑liver injury)*
2. *1-3 days* - Resolving Phase 1 symptoms, RUQ abdominal pain, elevated transaminases/INR
3. *3-4 days* - Peak hepatic enzyme (AST>10,000, ALT>100x normal), jaundice, nausea and vomiting, oliguria, metabolic acidosis, coagulopathy, encephalopathy
4. *4-21 days* - Either resolution in 1- 3 weeks, or progressive liver +/- renal failure

Investigations

Screening: BSL & ECG should be performed.
Specific: Serum APAP level/s & LFTs. Rarely avail APAP-cysteine adduct level is marker for sev.
Other tests: INR, UEC, glucose, VBG may be indicated if toxic or presenting>24hrs post-OD.

Risk factors for acute liver failure (ALF) & referral to specialist unit:

- INR>3.0 at 48hr or >4.5 at any time
- pH<7.3 or lac>3 post resus
- BPsys<80mmHg
- Oliguria or Cr>200micromol/L
- Encephalopathy or GCS<15
- ↓↓Plts or ↓BSL

Kings College Hospital (O'Grady) Criteria for liver transplantation in paracetamol-induced ALF:

- Arterial pH <7.30 post-resus OR
- PT>100s (or INR>6.5), Cr>300micromol/L and Grade III/IV encephalopathy OR
- Arterial lactate>3.5 at 4hrs or >3.0 at 12hrs (Bernal modification)

Guidelines for the Management of Paracetamol Poisoning in Australia & New Zealand

Adapted from 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; 212(4) + Online Appendix

- In **accidental** overdose when the amount ingested is accurately known, if the dose is less than the thresholds in Table 1 below then serum paracetamol levels, LFTs or follow-up are **not** required.

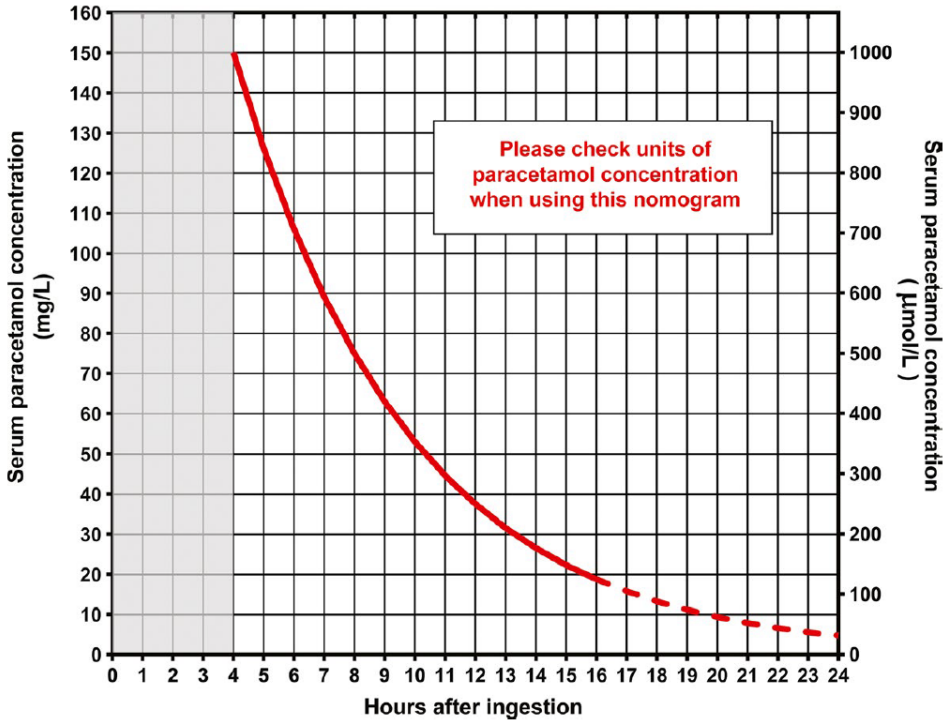
1 Paracetamol dosing that may be associated with acute liver injury

Acute single ingestion*	Repeated supratherapeutic ingestion†
≥ 10g or ≥ 200 mg/kg (whichever is less)	≥ 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 patients who also have abdominal pain or nausea or vomiting

*Acute ingestion is defined as any intentional or deliberate paracetamol overdose, including staggered or multiple paracetamol ingestions over more than 2 hours. † Repeated supratherapeutic ingestion refers to 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 alanine aminotransferase (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, please refer to local guidelines. ◆

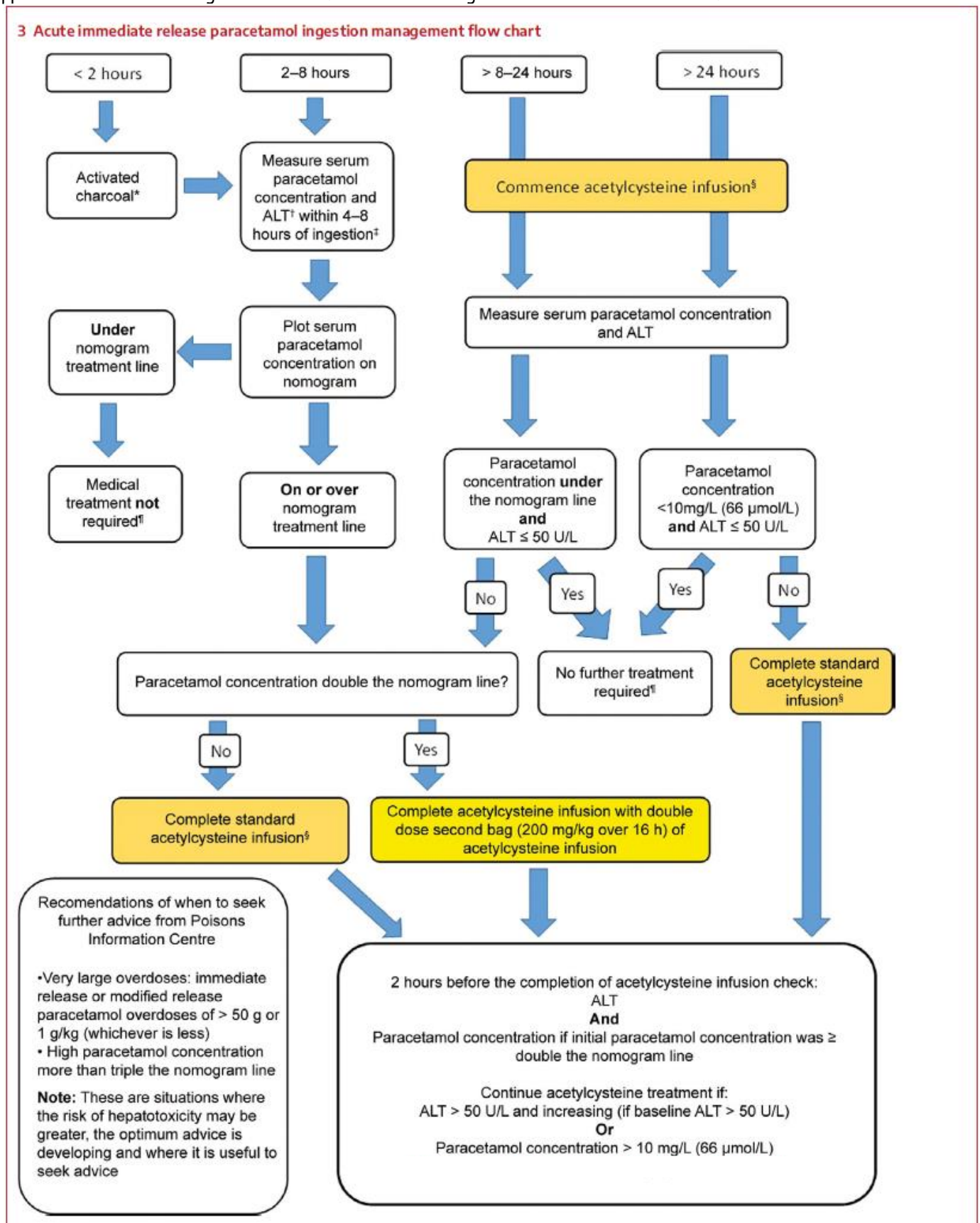
- All patients with **deliberate** self-poisoning, or when an accidental dose cannot be estimated, require a serum paracetamol level to refine the risk of hepatic injury and requirement for the antidote N-acetylcysteine.
- Decontamination with charcoal only indicated in patients >6 years, who present within 2h of a toxic dose of immediate-release paracetamol (4+h if modified-release paracetamol or if >30g) and are co-operative.

2 Paracetamol treatment nomogram (Rumack–Matthew nomogram)



Acute Ingestion

Applies to all deliberate single overdoses & all accidental single overdoses above thresholds.



ALT = alanine aminotransferase. * Cooperative adult patients who have potentially ingested ≥ 10 g or ≥ 200 mg/kg (whichever is less). For paracetamol ingestions ≥ 30 g, activated charcoal should be offered until 4 hours after ingestion. † Baseline ALT measurement. ‡ If paracetamol concentration will not be available until ≥ 8 hours after ingestion, commence acetylcysteine while awaiting paracetamol concentration. § For acetylcysteine dosage, see below. ¶ Patients should be advised that if they develop abdominal pain, nausea or vomiting, further assessment is required.

Staggered Overdose

Multiple doses taken >2hrs apart. If all doses taken within the last 8 hrs, follow 2-8 hrs path in acute ingestion flow-chart & interpret the level as if all doses were taken at the earliest dose time. If >8 hrs since the first dose, follow >8 hrs path in flow-chart. If the first paracetamol level was taken within 2 hrs of the last ingested paracetamol, rpt after 2 hrs to ensure no ongoing absorption. If either level is above the nomogram line start or continue NAC.

Modified-Release Paracetamol [665mg tabs (69% MR & 31% IR)]

Commence NAC if:

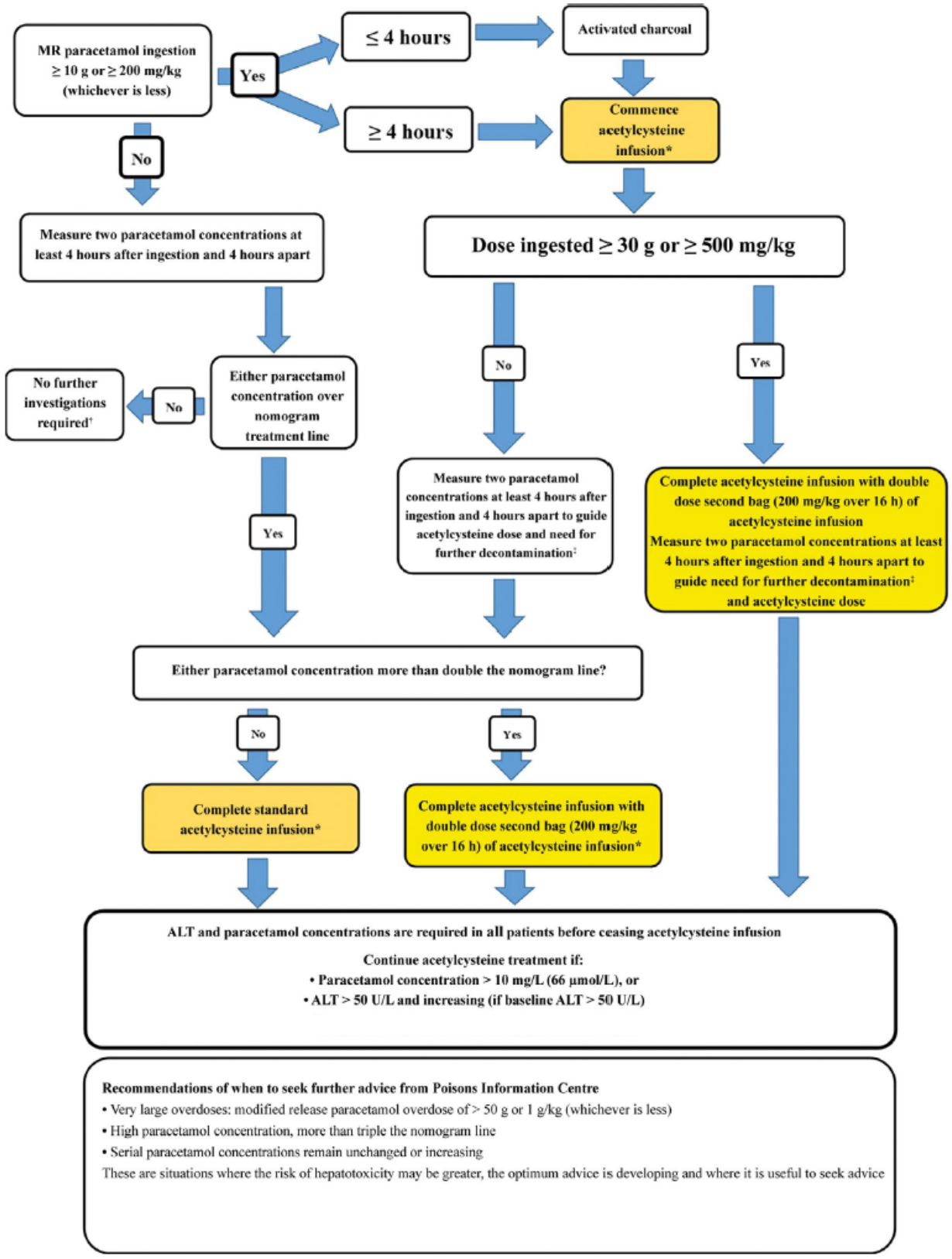
- Significant OD (≥10g or ≥200mg/kg) OR
- Low dose ingestion (<10g and <200mg/kg) and either of 2 paracetamol levels taken at least 4hrs post-OD and 4hr apart is over the nomogram line value

Use a double dose 2nd bag if:

- Massive OD (≥30g or ≥500mg/kg)
- Low dose ingestion (<10g and <200mg/kg), but one of the paracetamol levels 4hrs apart is >double the nomogram line OR

If massive OD (≥30g or ≥500mg/kg) may benefit from activated charcoal beyond 4hrs.

4 Acute ingestion modified release paracetamol management flow chart



ALT = alanine aminotransferase; MR = modified release. * Patients should be advised that if they develop abdominal pain, nausea or vomiting, further assessment is required. † If paracetamol concentration is static or rising, a repeat dose of activated charcoal may be beneficial; please seek further advice. ‡ For acetylcysteine dosage, see below.

Repeated Supertherapeutic Ingestion

Manage as per the flow-chart on the right:

Notes:

ALT = alanine aminotransferase.

*** 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.**

† Patients with abnormal liver function tests, not felt to relate to paracetamol ingestion, should have further investigation by their local medical provider for other causes.

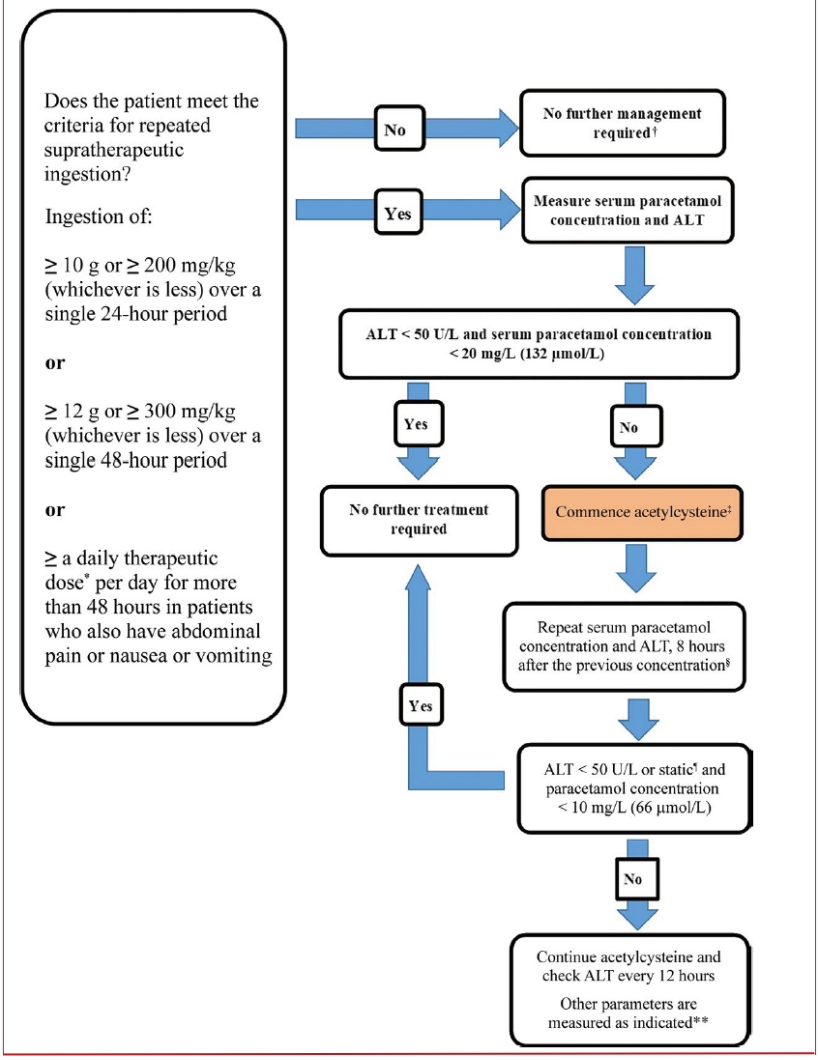
‡ For NAC dosage, see below.

§ If ALT > 1000 U/L, a 20-hour course of NAC should be completed and a clinical toxicologist or Poisons Information Centre should be consulted.

¶ Patients with significant acute liver injury secondary to paracetamol will have a very high and/or rapidly rising ALT. Small fluctuations in ALT (e.g. ± 20 U/L or ± 10%) are common and do not on their own indicate the need for ongoing NAC.

**** For criteria of when to cease NAC, see below**

5 Repeated supratherapeutic ingestion management flow chart



Unknown Time of Overdose

Commence NAC and treat the patient as per >8-24 hrs scenario on the acute ingestion pathway. If the paracetamol level is >10mg/L (66 µmol/L) or the ALT >50U/L, continue NAC. If the actual time of OD becomes clear AND the paracetamol level can be accurately plotted on the nomogram, then NAC can be discontinued if the level is below the treatment line.

N-Acetylcysteine (NAC)

Use: NAC (glutathione precursor & sulphydryl group source, also antioxidant) prevents mortality if given <8hrs & improves prognosis if given at any time following overdose. Dialysis may be alternative in massive (>1g/kg) OD, esp if RF.
Dosing: Using a 20% solution, give 200mg/kg (max 22g) in 500mL over 4hr & then 100mg/kg (max 11g) over 16hr in 1L. All in 5% glucose or NS or NS+5% glucose. Volumes for children are 7ml/kg (max 500mL) and 14ml/kg (max 1L) respectively.
Adverse effects: NAC is usually well tolerated but anaphylactoid reactions (rash, bronchospasm, & rarely ↓BP) can occur in ~5%. If this happens, stop infusion, consider antihistamines and, when resolved, restart at a reduced rate and slowly titrate back up.
Ceasing: If NAC required >20 hours, NAC can be ceased if: ALT or AST are decreasing AND INR < 2.0 AND patient clinically well AND (only for modified release OD or initial level >double the nomogram line) paracetamol level <10mg/L (66µmol/L).

When to seek further advice from toxicologist

- Very large overdoses: immediate release or modified release paracetamol overdoses of ≥50g or 1g/kg (whichever 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