Guidelines for the management of paracetamol overdose

For Poisons Information Call
Australia 13 11 26
New Zealand 0800 764 766

General Information

1. Paracetamol overdose is a significant cause of hospital admission, but severe liver injury is rare and even when it does occur the prognosis is usually good.[1]
2. Signs consistent with paracetamol poisoning include repeated vomiting, abdominal tenderness in the right upper quadrant or mental status changes.[2]
3. Any patient should be considered to be at risk of severe liver injury if they have ingested paracetamol above the thresholds shown in **TABLE 1**.[2]
   - > Regardless of the potential ingested dose, all patients with deliberate-self poisoning should have a serum paracetamol level measured to further refine the risk of hepatic injury and thus the need for acetylcysteine.
   - > Adult and paediatric patients without deliberate self-poisoning who are not considered at risk according to the thresholds in Table 1 do not require a serum paracetamol level or LFTs.
4. Following acute overdose, **the most important factor that determines prognosis is the delay beyond 8 hours before the initiation of acetylcysteine**.[2,3]
5. Acetylcysteine is an effective antidote that prevents mortality if administered within 8 hours of an acute overdose. It has also been shown to improve prognosis if administered at any time (beyond 8 hours) following overdose.

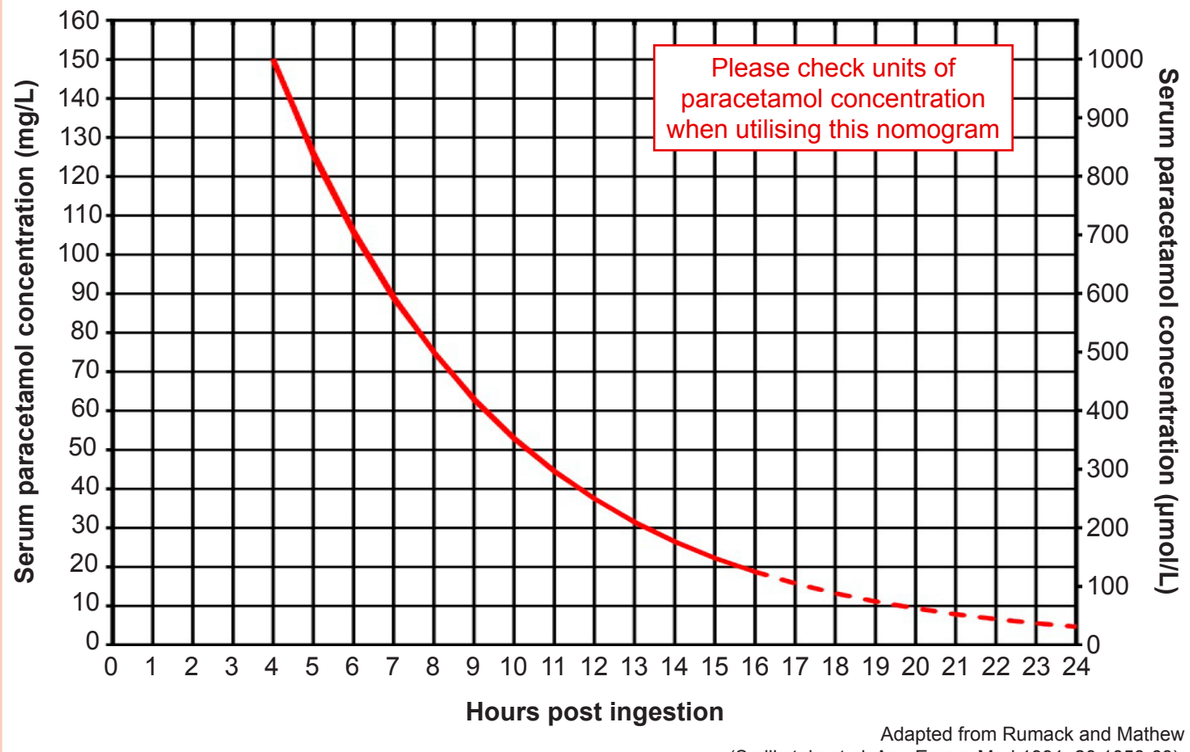
TABLE 1. Paracetamol dosing that may be associated with hepatic injury

	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 over a period of < 8 hours.
Repeated Supra-therapeutic Ingestion (RSI)	> 200 mg/kg or 10 g (whichever is lower) over a single 24-hour period. > 150 mg/kg or 6 g (whichever is lower) 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 eg. abdominal pain, nausea or vomiting.	> 200 mg/kg over a single 24-hour period. > 150 mg/kg per 24-hour period for the preceding 48 hours. > 100 mg/kg per 24-hour period for more than 48 hours.

* For obese children, the body weight used for calculations should be an ideal body weight.

Paracetamol Treatment Nomogram[9]

> Treat ALL patients with serum paracetamol concentration above the nomogram treatment line.
> Ensure that correct units are used (ie. µmol/L or mg/L).



Adapted from Rumack and Mathew
(Smilkstein et al. Ann Emerg Med 1991; 20:1058-63).

Management of Acute Single Ingestions

Decontamination

> Decontamination using 50 g activated charcoal is indicated in cooperative adult patients:
  - > Immediate-release paracetamol preparations:
    - > Administer within 2 hours if ingestion greater than 10 g or 200 mg/kg (whichever is less).
    - > Administer within 4 hours if ingestion greater than 30 g.
  - > Modified-release paracetamol preparations:
    - > Administer within 4 hours if ingestion greater than 10 g or 200 mg/kg (whichever is less).
    - > Administer beyond 4 hours if massive doses ingested.
> Activated charcoal is not indicated in paediatric liquid preparation ingestions.

Liquid Paracetamol Ingestion

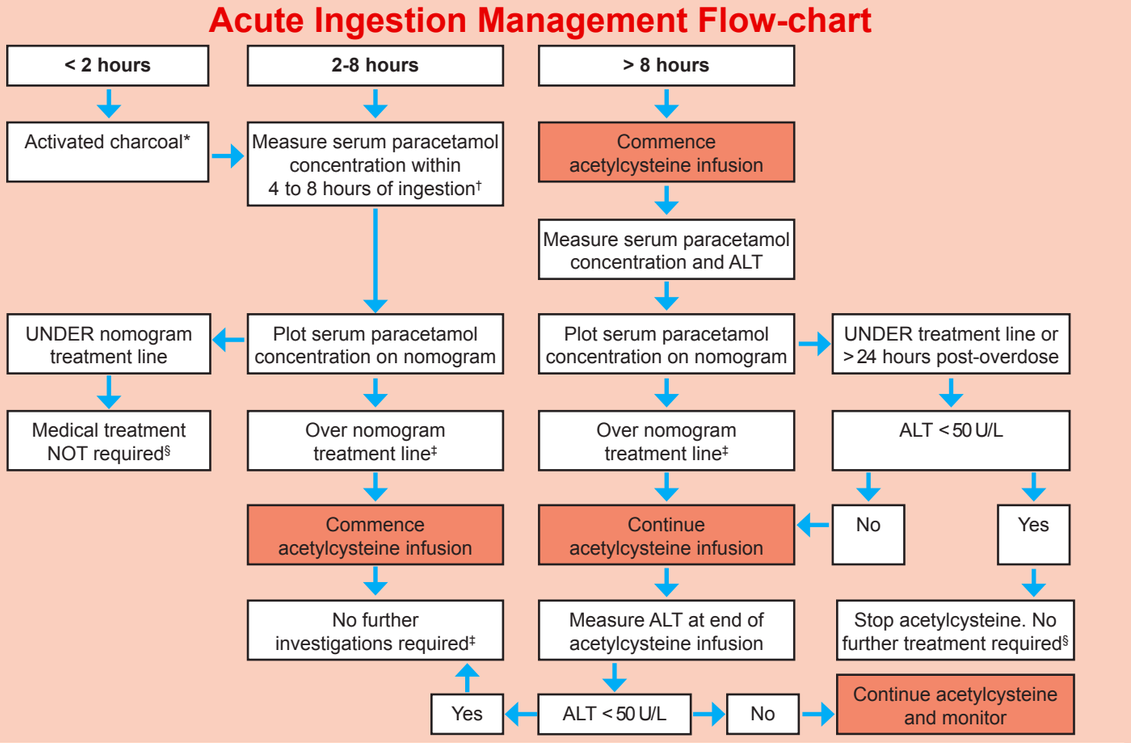
Paediatric (< 6 years) liquid paracetamol ingestion

> In children suspected of ingesting > 200 mg/kg, measure serum paracetamol level at least 2 hours post-ingestion:
  - > If the concentration 2-4 hours after ingestion is < 150 mg/L (1000 µmol/L), acetylcysteine is not required.
  - > If the 2 hour concentration is > 150 mg/L (1000 µmol/L), measure again at 4 hours post-ingestion. If the 4 hour concentration is still > 150 mg/L (1000 µmol/L), commence acetylcysteine infusion as per the paracetamol nomogram.
> For children presenting later than 4 hours post ingestion, treat as per the **Acute Ingestion Management Flow-chart**

Paediatric (≥ 6 years) liquid paracetamol ingestion

> In all cases, other than an isolated accidental liquid paediatric ingestion (< 6 years), treat as per the **Acute Ingestion Management Flow-chart.**

Acute Ingestion Management Flow-chart



NOTE: Treatment recommendations are based on the time elapsed from the paracetamol ingestion.
* Cooperative adult patients who have potentially ingested greater than 10 g or 200 mg/kg, whichever is less. For paracetamol ingestions ≥ 30 g 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 serum paracetamol and ALT concentrations should be checked at the end of acetylcysteine infusion.
§ Patients should be advised that if they develop abdominal pain, nausea or vomiting further assessment is required.

What To Do When The Nomogram Does Not Apply

Staggered Overdose

> A staggered overdose comprises several ingestions over a period of less than 24 hours. The paracetamol concentration should be plotted on the nomogram from the earliest time of ingestion.
> If the patient has taken a staggered overdose of paracetamol at multiple time intervals within the last 8 hours, treat the patient as per the < 8 hours scenario in the **Acute Ingestion Management Flow-chart**.
> If it has been MORE than 8 hours since the first dose, treat the patient as per the > 8 hours scenario in the **Acute Ingestion Management Flow-chart**.

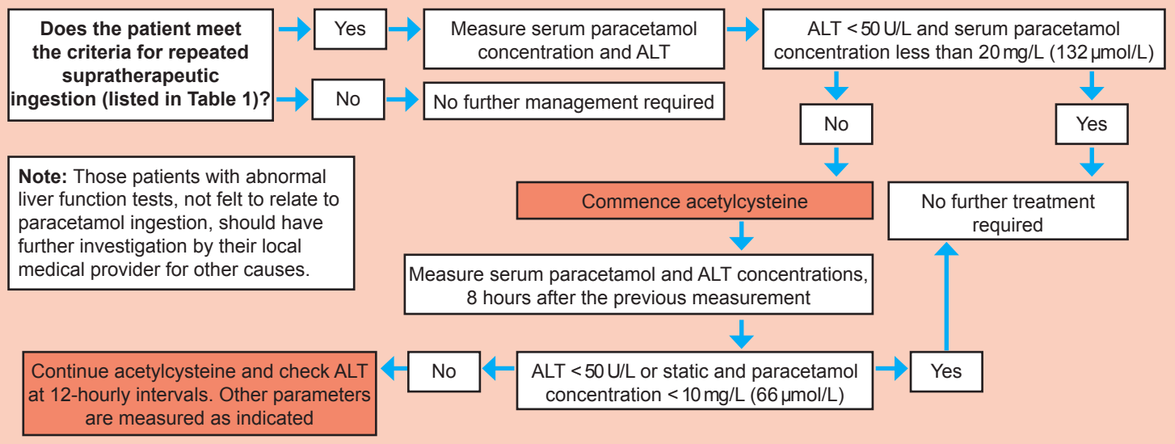
Unknown Time of Paracetamol Ingestion

> If the time of ingestion is unknown, it is safest to treat the patient as a delayed presentation and commence acetylcysteine. If the serum paracetamol concentration is > 10 mg/L (66 µmol/L) or the ALT is elevated > 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.

Sustained-Release Paracetamol Preparations

> If more than 10 g or 200 mg/kg (whichever is less) has been ingested commence acetylcysteine.
  - > Measure serum paracetamol concentration at 4 or more hours post-ingestion, then again 4 hours later if the first concentration is below the nomogram line.
  - > If serial paracetamol concentrations taken 4 hours apart are below the nomogram line and decreasing, acetylcysteine may be discontinued, otherwise continue the full 21 hour course of acetylcysteine to its completion.
> If < 10 g and < 200 mg/kg has been ingested, measure serum paracetamol levels 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 (> 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.

Repeated Supratherapeutic Ingestion Management Flow-chart in Adults and Children



Note: Those 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.

Administration of Acetylcysteine

> When required, acetylcysteine is infused in a 3 stage intravenous infusion giving a total dose of 300 mg/kg over 21 hours.[4]
  - > **First Infusion:** The initial dose (150 mg/kg) is diluted in 200 mL of 5% glucose and infused over 60 minutes under close medical supervision due to the incidence of anaphylactoid reactions.
  - > **Second Infusion:** The second dose (50 mg/kg) is diluted in 500 mL of 5% glucose and infused over the next 4 hours.
  - > **Third Infusion:** The third dose (100 mg/kg) is diluted in 1000 mL of 5% glucose is infused over the next 16 hours.
> Acetylcysteine is usually well tolerated. A non-IgE mediated anaphylactic (anaphylactoid) reaction can occur during the initial infusions in 10-50% of patients, manifested by rash, bronchospasm, and rarely, hypotension.[5,6] Management is supportive, with temporary halting or slowing of the infusion and administration of antihistamines and bronchodilators if required.[7] Severe life-threatening reactions are very rare and should be treated with adrenaline as required. Once the symptoms settle acetylcysteine can be recommenced.
> Patients who have serum paracetamol concentrations more than double the nomogram line may benefit from doubling the concentration of the 16 hour infusion of acetylcysteine from 100 mg/kg (current standard acetylcysteine 3rd bag infusion) to 200 mg/kg IV acetylcysteine totalling 400 mg/kg over 21 hours. Serum ALT and paracetamol levels should be checked near the completion of acetylcysteine infusion. Acetylcysteine should be continued if the ALT level is increasing (greater than 50 U/L) or the paracetamol concentration is greater than 10 mg/L (66 µmol/L).
> 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.

Acetylcysteine Intravenous Infusion Dosage Guide

> Acetylcysteine is packaged for intravenous infusion in ampoules, each containing a 20% solution (ie. 200 mg acetylcysteine per 1 mL).
> Prescription errors can occur when calculating the dose of acetylcysteine using the recommended mg/kg dose. Using the "Acetylcysteine intravenous infusion dosage guide" allows the dose in mgs and mLs to be calculated and charted in one step, reducing the potential for calculation and transcription errors.[4]
> **TABLE 2** allows calculation of the dose and volume required for each infusion. Patient actual body weight is estimated to the nearest 10 kg.
> The occurrence of a previous reaction does not preclude the use of acetylcysteine on another occasion if indicated.
> It is also important to ensure adequate mixing of acetylcysteine and fluid when preparing the infusion.

TABLE 2. Adult Acetylcysteine Intravenous Infusion Dosage Guide

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.

> In children the volume of 5% glucose into which acetylcysteine is diluted should be an appropriate volume for the patient's weight. Eg.:
  - > **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 body weight:**

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.

Recommendations of when to call the 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, > double the nomogram line.
Intravenous paracetamol errors/overdoses.
Patients with hepatotoxicity (e.g. ALT > 1000 IU/L).

*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.

> This guideline addresses the majority of paracetamol ingestion scenarios encountered. However not all clinical scenarios can be addressed, or the management remains controversial.
> Where there are any concerns regarding the management of paracetamol ingestion, advice should always be sought from a clinical toxicologist or local Poisons Information Centre.

References
1. Sheen CL et al. (2002) QJM 95(9):609-619. **2.** Dart RC et al. (2006) Clin Toxicol (Phila) 44(1):1-18. **3.** Smilkstein MJ et al. (1988) N Engl J Med 319(24):1557-1562. **4.** Little M et al. (2005) Med J Aust 183(10):535-536. **5.** Sandilands EA & Bateman DN. (2009) Clin Toxicol (Phila) 47(2):81-88. **6.** Lynch RM & Robertson R. (2004) Accid Emerg Nurs 12(1):10-15. **7.** Bailey B & McGuigan MA. (1998) Ann Emerg Med 31(6):710-715. **8.** Ferner RE et al. (2001) Br J Clin Pharmacol 52(5):573-577. **9.** Chiew AL et al. (2015) Med J Aust 203(5):215-218.

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