SESLHDMG/114

Medicine Guideline

Acetylcysteine IV in Acute Immediate Release Paracetamol Overdose

Health
South Eastern Sydney
Local Health District

Areas where Protocol/Guideline applicable	All hospital inpatient wards/units/departments
Authorised Prescribers:	Medical Officers familiar with the product
Indication for use	Antidote treatment of acute immediate release paracetamol overdose (≥ 10g or ≥ 200mg/kg whichever is less) to protect against hepatotoxicity. Timed plasma paracetamol concentration is on or above the treatment line on the paracetamol nomogram (Appendix 2). **For guidance on the management of massive paracetamol overdose (≥30g) or paracetamol level more than double the nomogram or modified release paracetamol overdose seek expert advice. Consult toxicology.**
Clinical condition Patient selection: Inclusion criteria (list investigations necessary and relevant results)	To be most effective in protecting against liver damage, therapy with acetylcysteine should be started within 8 hours of paracetamol ingestion or injection. Acetylcysteine therapy in high-risk patients presenting later than 15 hours after paracetamol ingestion has been shown to improve prognosis. Dosing and administration of acetylcysteine in staggered/chronic paracetamol overdose or in gastroenterology patients may vary. Please, contact toxicologist or gastroenterologist, respectively. Patients can be unreliable as to the amount of paracetamol ingested and time of ingestion. It should be noted that, after a toxic dose of paracetamol, the patient may appear relatively well initially and may even continue normal activities for a day or two before the onset of hepatic failure. Hepatic damage is more likely with a lower dosage of paracetamol in chronic alcoholic, malnourished or hepatic enzymes induced patients. Hepatic necrosis is preventable if treatment is instituted within 8 hours of overdose Perform plasma paracetamol levels – no earlier than 4 hours after any history of ingestion, or immediately if time of ingestion is unknown.
Proposed Place in Therapy	First line treatment. Do not delay therapy whilst awaiting the results of plasma assay if result is expected to return >8 hours post ingestion.
Adjunctive Therapy If part of combination therapy, list other drugs	Give activated charcoal (50g) to a cooperative, awake adult if they present within 2 hours of ingestion of a toxic dose of immediate release paracetamol (≥ 200 mg/kg or ≥10g whichever is less) or within 4 hours of a massive ingestion of immediate release paracetamol (≥30g).
Contra-indications	Patients with hypersensitivity or previous anaphylactic reaction to acetylcysteine or any component of the preparation.

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Precautions	Acetylcysteine should be used with caution in asthmatics or history of bronchospasm (risk of bronchospasm), or with past history of oesophageal varices and peptic ulceration (treatment induced vomiting may increase risk of haemorrhage) Category B2 use in pregnancy. May be used during pregnancy as an antidote for paracetamol poisoning. Bodyweight less than 40 kg or fluid restriction may require adjustment of total fluid volume to minimise risk of hyponatraemia, seizure and death.
Important Drug Interactions	Nil known
Dosage (Include dosage adjustment for specific patient groups)	Total dose of 300 mg/kg actual body weight infused over 20 hours (See Administration Section for dosing tables)
Duration of therapy	Single treatment of 2 sequential infusions over 20 hours (See Administration Section for details)
Prescribing Instructions	Must be prescribed on the eMR or eRIC. In the absence of eMM systems, the appropriate paper medication chart may be used.

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Administration Instructions

ACETYLCYSTEINE is available in 200 mg/mL ampoules (2 g/10 mL)

- 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.
- Use dosage tables to determine appropriate volume of acetylcysteine to be added to infusion diluent for each of the infusion periods.
- Two infusions given sequentially without any break in between infusions. Infusion 1 over 4 hours immediately followed by Infusion 2 over 16 hours

INFUSION 1:

Acetylcysteine 200 mg/kg to be added to 500 mL of sodium chloride 0.9% and infused over 4 hours (125 mL/hour)

Actual body weight (kg)	Volume of acetylcysteine (mL) to be added to 500 mL of sodium chloride 0.9%
50	50 mL
60	60 mL
70	70 mL
80	80 mL
90	90 mL
100	100 mL
110 **(ceiling weight)**	110 mL **(maximum dose)**

INFUSION 2:

Acetylcysteine 100 mg/kg to be added to 1000 mL of sodium chloride 0.9% and infused over 16 hours (63 mL/hour)

Actual body weight (kg)	Volume of acetylcysteine (mL) to be added to 1000 mL of sodium chloride 0.9%
50	25 mL
60	30 mL
70	35 mL
80	40 mL
90	45 mL
100	50 mL
110 **(ceiling weight)**	55 mL **(maximum dose)**

	Preparation: Calculate volume of acetylcysteine required. **Infusion 1**: Remove the corresponding volume of sodium chloride 0.9% from a 500 mL bag of sodium chloride 0.9%, and then add acetylcysteine to that sodium chloride 0.9% bag. (e.g. for a 50 kg patient, withdraw 50 mL from a 500 mL bag of sodium chloride 0.9%, and replace with 50 mL of acetylcysteine). Mix well and run **over 4 hours** (rate of 125 mL/hour). **Infusion 2:** Add acetylcysteine to 1000 mL bag of sodium chloride 0.9%. Mix well and run **over 16 hours** (rate of 63 mL/hour). **Invert all prepared solutions at least 10 times prior to infusing to ensure adequate mixing.** NOTE: May substitute Glucose 5% for sodium chloride 0.9% if clinically indicated
Monitoring requirements Safety Effectiveness (state objective criteria)	Plasma paracetamol concentrations should be measured no earlier than 4 hours after the ingestion of paracetamol for reliable assessment of hepatotoxicity as well as baseline EUC, LFT and coagulation profile. In those presenting more than 8 hours post ingestion, paracetamol concentration, plasma liver enzymes should also be measured. Blood urea, electrolytes, glucose, coagulation profile and venous blood gases should be obtained in those with abnormal liver function tests or as clinically indicated. ECG should be performed. Monitor hepatic and renal function and fluid/electrolyte balance. Those patients with initial paracetamol concentrations more than double the nomogram line should have EUC, LFTs, coagulation studies and paracetamol level 2 hours before the completion of the acetylcysteine infusion.
Management of Complications	Acetylcysteine is usually well tolerated. Non-IgE Anaphylaxis (anaphylactoid) reactions such as rash, bronchospasm and rarely hypotension may be seen rarely in some patients. If there is a reaction, the infusion should be temporarily stopped or slowed. An antihistamine administered or in severe reactions adrenaline administered as per anaphylaxis protocols. Once the reaction has resolved, re-institute acetylcysteine at a reduced rate and titrate up slowly. The occurrence of a non-IgE anaphylaxis (anaphylactoid) reaction does not preclude the use of acetylcysteine on another occasion if indicated. **In case of reaction consult with Toxicology.**

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Basis of Protocol/Guideline: (including sources of evidence, references)	Bateman DN, Dear JW, Thanacoody HK, et al. Reduction of adverse effects from intravenous acetylcysteine treatment for paracetamol poisoning: a randomised controlled trial. Lancet 214; 383:697-704. Chiew AL, Reith D, Pomerleau A, Wong A, Isoardi KZ, Soderstrom J, Buckley NA. Guideline summary: updated guidelines for the management of paracetamol poisoning in Australia and New Zealand. MJA 2019; 212 (4): 175-183 Graudins A, Harper A. Comparison of adverse drug reaction rates using a two-bag to a standard three-bag intravenous acetylcysteine regimen for paracetamol poisoning. Clinical Toxicology. 2015, 53: 249. MIMS online. Acetylcysteine-Link injection. Last updated 04 August 2020.
Groups consulted in development of this guideline	Prince of Wales Hospital (POWH) Emergency Department: Clinical Nurse Consultant; Senior Pharmacist; Medical Director. Emergency Department Directors, St. George and Sutherland Hospitals

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GOVERNANCE	
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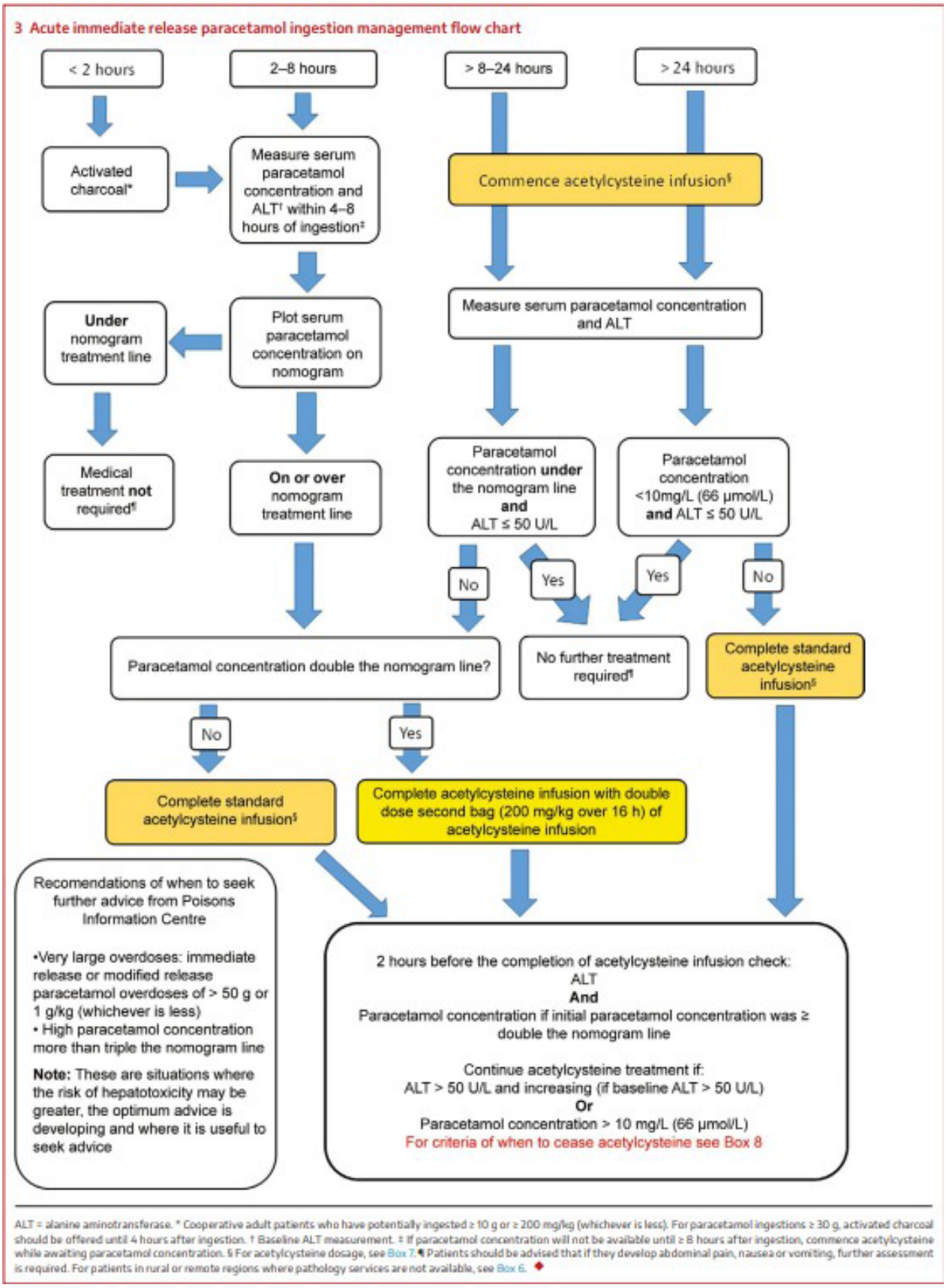
Appendix 1 Acute immediate release paracetamol ingestion management flow chart
[Updated guidelines for the management of paracetamol poisoning in Australia and New Zealand]



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Appendix 2 Paracetamol treatment nomogram (Rumack – Matthew nomogram)
Updated guidelines for the management of paracetamol poisoning in Australia and New Zealand

For the management of acute immediate release paracetamol ingestion

Please check units of paracetamol concentration when using this nomogram – Rumack – Matthew nomogram reports serum paracetamol concentration in mg/L