ACETYLCYSTEINE – INTRAVENOUS

NEWBORN USE ONLY

2019

Alert	Paracetamol overdose may be asymptomatic initially and early assessment is recommended. Discuss all cases with the Poisons Information Centre (13 11 26 nation-wide) or local toxicology service. Check correct units are read from the nomogram (previously micromol/L and now mg/L). Anaphylactic reactions to acetylcysteine usually occur in the first few hours of infusion.

Indication	**Treatment of ORAL paracetamol overdose:**
	• **Indications for treatment:**
	  • Single acute ingestion ≥200 mg/kg and serum paracetamol concentration (taken 4–16 hours post-ingestion) is above treatment line on the nomogram (see special comments).
	  • Ingestion of liquid paracetamol with a 4-hour serum paracetamol concentration above 150 mg/L (1000 micromol/L).
	  • Ingestion of sustained release paracetamol ≥200 mg/kg or ≥ 10 gram (whichever is less) or, if ingested less than this dose, where either of two serum paracetamol concentrations (taken 4 hours apart) is above the nomogram line.
	  • Repeated supratherapeutic ingestions as per the recommended algorithm:
	    o >200 mg/kg over a single 24-hour period
	    o >300 mg/kg over a 48-hour period for the preceding 48 hours
	    o >60 mg/kg per 24-hour period for more than 48 hours
	    o If above criteria met, measure serum paracetamol and ALT concentrations. If ALT above upper limit of normal or paracetamol concentration >20 mg/L (132 micromol/L), commence acetylcysteine.
	  • Established hepatotoxicity (deranged transaminases or coagulations studies).
	  • When serum paracetamol concentrations will not be available for >8 hours post-acute ingestion
	  • Massive acute ingestion (more than 400mg/kg or paracetamol concentration is greater than twice the nomogram value at that time) needs special attention and urgent consultation
	  • Discuss other presenting scenarios with a Toxicologist.
	
	Treatment of INTRAVENOUS paracetamol overdose:
	• **Consider acetylcysteine treatment for**:
	  • Single IV dose of >60 mg/kg
	  • Serum paracetamol concentration above 50 mg/L (330 micromol/L) at 4 h after exposure
	  • Evidence of acute liver injury

Action	Acetylcysteine prevents glutathione depletion and minimises hepatocyte injury caused by paracetamol overdose.
Drug Type	Antidote.
Trade Name	DBL acetylcysteine injection concentrate, Acetadote Concentrated Injection (Solution for infusion) Acetylcysteine-Link Concentrate for infusion
Presentation	DBL acetylcysteine injection concentrate 20% (200 mg/mL, 10 mL ampoule) Acetadote Concentrated Injection (Solution for infusion) 20 % (200 mg/mL, 30 mL vial) Acetylcysteine-Link Concentrate for infusion 20% (200 mg/mL, 10 mL ampoule).
Dosage/Interval	1st IV infusion – acetylcysteine 200 mg/kg infusion over 4 hours, followed by 2nd IV infusion – acetylcysteine 100 mg/kg infusion over 16 hours.
Maximum daily dose	
Route	**Intravenous**
Preparation/Dilution	**Intravenous preparation for paracetamol toxicity** 1st infusion – dilute acetylcysteine 200 mg/kg in 7 mL/kg 5% glucose (max 500 mL) and administer over 4 hours, followed by 2nd infusion – dilute acetylcysteine 100 mg/kg in 14 mL/kg 5% glucose (max 1000 mL) and administer over 16 hours.
Administration	Intravenous for paracetamol overdose: Administer via syringe driver in 2 steps over different time periods:

	1st infusion: Over 4 hours. 2nd infusion: Over 16 hours.

Monitoring	Near the completion of acetylcysteine infusion (i.e., 2 hours before completion of infusion), measure serum ALT and paracetamol concentrations. Infants with acute liver injury:
	o Monitoring:
	    o ALT – every 12 hours
	    o INR – every 12 hours
	    o Paracetamol concentration – every 12 hours
	    o EUC/BGL – daily
	    o ABG if clinical deterioration
	o Acetylcysteine should be continued (at the dose and rate of the 2nd infusion) until the patient is clinically improving, ALT levels are decreasing, the INR is improving and <2 and the paracetamol concentration is less than 10 mg/L (66 mmol/L).
	o Regular clinical review and 12-hourly (or more frequent) blood tests are to be performed until acetylcysteine is ceased.

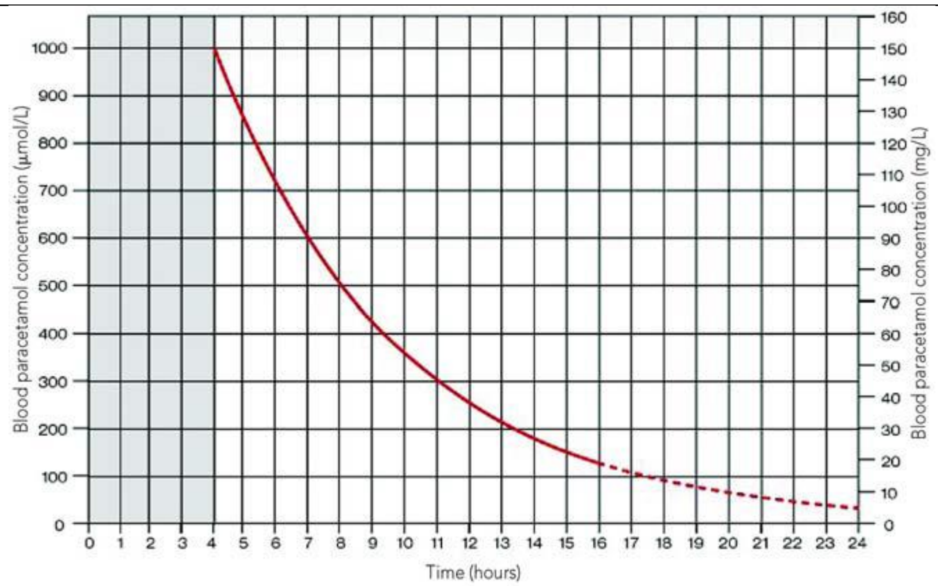
Precautions	Hypersensitivity or previous anaphylactic reaction to acetylcysteine or any component of the preparation. Note that non-IgE-mediated anaphylactic reactions are common, usually occur during loading doses and can be managed with discontinuation of the infusion, administration of antihistamines and then restarting the loading dose at a slower infusion rate.
Drug Interactions	No information is available on the interaction of acetylcysteine with other medicines.
Adverse Reactions	Gastrointestinal effects such as nausea and vomiting. The rate of anaphylactic reactions is low with the current 2-bag infusion. Adverse reactions range from mild cutaneous reactions (rashes, flushing/erythema and urticaria) to less common and more severe reactions (angioedema, bronchospasm and hypotension). May cause hyponatraemia and fluid overload especially in sick and very preterm infants. What to do when adverse reactions to acetylcysteine occur: o Cease acetylcysteine immediately o Steroid o Antihistamine o Acetylcysteine may be recommenced after 1 hour at half the rate, if the adverse reactions have abated and clinical improvement occurs.
Compatibility	See table below. Y-site: Cefepime, ceftazidime, , heparin sodium, naloxone hydrochloride, vancomycin hydrochloride

Acetylcysteine brand	Compatibility	
	Sodium chloride 0.9%	Glucose 5%
Acetadote (Phebra)	X	√
Acetylcystenine-DBL (Hospira)	√	√
Acetylcysteine-Link (Link)	√	√

Incompatibility

Acetylcysteine brand	Compatibility	
	Sodium chloride 0.9%	Glucose 5%
Acetadote (Phebra)	X	√
Acetylcystenine-DBL (Hospira)	√	√
Acetylcysteine-Link (Link)	√	√

Stability	To reduce microbiological hazard, use as soon as practicable after dilution. If storage is necessary, hold at 2 to 8°C for not more than 24 hours.
Storage	Store the unopened vial below 25°C. Protect from light. Product is for single use in one patient only. Discard any residue.
Special Comments	Paracetamol treatment nomogram for acute paracetamol ingestion with known time of ingestion [2]

	 Notes: The paracetamol nomogram is only validated for single acute ingestions in adults. Beware units are different on right and left axes.
Evidence summary	**Paracetamol overdose** Paracetamol (acetaminophen) is involved in a large proportion of accidental paediatric over-exposures and deliberate self-poisoning cases, although subsequent hepatic failure and death are both uncommon outcomes [2]. Paracetamol overdose is less common in neonatal care with case reports related to maternal ingestion whilst pregnant with delivery of an infant with high paracetamol concentrations [3-7], and both oral [8-12] and intravenous (IV) [13-18] paracetamol use in the neonate. Paracetamol is rapidly absorbed from the small intestine with peak serum concentrations 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 (130 micromol/L). Twenty per cent of the ingested dose undergoes first-pass metabolism in the gut wall (sulfation). Further elimination occurs in the liver with about 90% metabolised to inactive sulfate and glucuronide conjugates that are excreted in the urine. Metabolism of the remainder is via cytochrome P450 and results in the highly reactive compound N-acetyl-p-benzoquinone imine (NAPQI). In normal conditions, NAPQI is immediately bound by intracellular glutathione and eliminated in the urine as mercapturic adducts. With increased paracetamol doses, greater production of NAPQI may deplete glutathione stores. When glutathione depletion reaches a critical level (about 30% of normal stores), NAPQI binds to other proteins, causing damage to the hepatocyte. Glutathione depletion may also be injurious. [2] Paracetamol clearance is lower in neonates than in children and adults. The volume of distribution was 70.4 L/70 kg and the clearance increased from 2.85 L/h/70 kg at 27 weeks to 7.05 L/h/70 kg by 42 weeks PMA. Clearance increased only slightly with PMA (0.138 L/kg/h at 28 weeks PMA to 0.167 L/kg/h at 44 weeks PMA). Paracetamol clearance in neonates was one third of the mature value reported in adults (16.2 L/h/70 kg). [19] Reported paracetamol elimination half-life has ranged from 11 hours in premature infants to 4 to 5 hours in term neonates after rectal dosing, compared to adult values of 2 to 4 hours. [20] Elimination half-life after IV administration day of life 1 ranged from 4.6 hours in preterm newborns to 2.9 hours in term newborns. [20] However, much slower clearance rates have been reported in newborn infants after paracetamol overdose, including in a 585 g infant after a cumulative dose of only 29.1 mg/kg within 3 hours, with a peak paracetamol concentration of (51.1 mg/L (338 micromol/L) at 30 minutes after the last dose, with an apparent half-life of 14.8 hours [8, 9, 14].

Individual cases with hepatic toxicity related to paracetamol in newborns have been reported. Overall, the number of cases reported is limited to significant overdoses (75–446 mg/kg), most commonly as a result of an in-hospital 10-fold drug dosing error [19]. In infants and children, hepatotoxicity has been reported over a dosage range of 60–420 mg/kg/day for 1–42 days [1].

Prediction of paracetamol toxicity
Several nomograms that provide a treatment threshold related to time of single ingestion have been developed for prediction of paracetamol toxicity but have not been validated in newborns. [21] The original Prescott line commenced at 200 mg/L at 4 hours and reached 10 mg/L at approximately 22 hours. Rumack and Matthew amended this to start at 150 mg/L at 4 hours and reach 10 mg/L at approximately 20 hours to provide a safety buffer. The current UK nomogram commences at a paracetamol concentration 100 mg/L at 4 hours and reaches 10 mg/L at approximately 18 hours, lowered due to a case fatality report [22]. 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 treated within 15 hours [23]. The 150 mg/L at 4 hours nomogram is currently recommended for use in the USA, Canada, Australia and New Zealand [22, 24].

Acetylcysteine pharmacokinetics
Acetylcysteine prevents glutathione depletion and minimises hepatocyte injury caused by a number of different toxins including NAPQI [25]. There are few studies on the pharmacokinetics of acetylcysteine and the pharmacokinetics of paracetamol are dose dependent and altered by liver injury [21]. An IV acetylcysteine regimen was first described by Prescott in 1977 [26], with limited pharmacokinetic data reported in 17 patients with severe paracetamol poisoning treated with a mean volume of distribution 0.5 litre/kg and mean elimination half-life of 5.7 hours [27]. Similar data suggested the initial loading regimen resulted in excessively high maximal concentrations (C_{max}) and then declining plasma concentrations despite the 16-hour maintenance infusion [25, 28].

Safety and adverse reactions
Adverse reactions to IV acetylcysteine include gastrointestinal effects such as nausea and vomiting and non-allergic (non-IgE mediated) anaphylactic reactions in 14% to 75% of patients ranging from mild cutaneous reactions (rashes, flushing/erythema and urticaria) to less common and more severe reactions (angioedema, bronchospasm and hypotension). [29] The incidence and severity of non-allergic anaphylactic reactions may be influenced by the rate of acetylcysteine infusion. Anaphylactic reactions usually occur during loading doses and can be managed with discontinuation of the infusion, administration of antihistamines and then restarting the loading dose at a slower infusion rate [30]. Gastrointestinal effects are more common with oral dosing.

The dosing regimen for IV acetylcysteine is complicated and prone to errors in preparation and administration. The proprietary acetylcysteine solution is 10 mg/ml, and may be subject to potentially hazardous administration of inadequate dosages and 10-fold excess dose calculation errors. Reported adverse reactions to overdose include haemolysis and acute kidney injury, cerebral oedema and seizures, and ST-elevation myocardial infarction with subsequent death due to heart failure. [25]

Premature infants are at risk for fluid overload, hyponatraemia, and blood loss with frequent blood draws, when administered NAC IV for paracetamol toxicity [31]. Hyponatraemia associated with acetylcysteine in glucose 5% infusion in children was reduced by using sodium chloride 0.18% + glucose 5% infusions [LOE III-3 GOR C]. Due to incompatibility, this cannot be done with the Phebra product (Acetadote).

Efficacy: Treatment of paracetamol overdose
Current management of paracetamol poisoning involves the administration of IV or oral acetylcysteine which is based mainly on observational studies. Results from these observational

	studies indicate that treatment with acetylcysteine seems to result in a decrease in morbidity and mortality. [32] There are no clinical trials of acetylcysteine treatment for paracetamol poisoning in newborn infants. Current observations are limited to case reports. ***Acetylcysteine versus placebo:*** A single RCT in adults with paracetamol-induced fulminant hepatic failure (n = 50) using a 20.15 hour IV protocol with total dose 300 mg/kg reported increased survival was higher in the acetylcysteine group (48% vs 20%) with a lower incidence of morbidity including cerebral oedema and hypotension needing inotropic support. [33] ***Oral versus intravenous acetylcysteine***: Oral regimens for treatment of paracetamol overdose have not been reported in newborn infants and therefore are not recommended. In adults, a systematic review and meta-analysis of observation studies identified 16 reports including 5164 cases, with direct comparisons lacking. [34] Overall, there was no difference in overall rate of paracetamol-induced hepatotoxicity after use of oral versus IV routes (12.6% and 13.2% respectively). In a stratified analysis by timing of treatment, there was no difference in hepatotoxicity for infants with treatment commenced prior to 8 to 10 hours of paracetamol overdose (5.3% versus 5.9%) and no difference in hepatotoxicity for patients treated late (23.3% versus 26.3%). Two RCTs have compared IV acetylcysteine regimens to regimens including oral treatment in adults with paracetamol overdose. Eizadi-Mood, 2013 [35] compared an IV protocol with a total dose of 300 mg/kg over 20.30 hours including 150 mg/kg loading dose over 30 minutes versus an oral loading dose 140 mg/kg regimen then IV infusion to a total dose 290 mg/kg over 20 hours. Anaphylactic reactions were observed in 60.7% of the IV group and 13.3% of the oral group (P value = 0.004). Efficacy was not reported. [LOE II] Arefi, 2013 [36] compared a 20-hour IV protocol with the 72-hour US oral protocol. There were no differences in liver function tests and prothrombin index 24, 48 and 72 hours after treatment, but nausea and hypotension occurred more frequently in the oral group (57.6% vs. 33.3%, and 12.1% vs. 0% respectively; $p < 0.05$). ***Different acetylcysteine dosage regimens:*** There are insufficient data from RCTs to determine the relative efficacy of different IV acetylcysteine regimens. Children were not included in the majority of trials. Hence, the evidence pertains only to adults. [32] Several studies have assessed the effect of longer loading-dose regimens for reducing side effects due to anaphylactic reactions and shorter total duration of infusion in lower-risk patients with paracetamol overdose. In an RCT, Kerr 2005 [37] compared a loading dose regimen of 150 mg/kg IV in 200 mL of glucose 5% over 60 min versus the same over 15 minutes as part of a 20-hour IV regimen with total dose 300 mg/kg. There was no mortality in either group (slower 0/71 versus rapid 0/109), no difference in hepatotoxicity (slower 5/68 versus rapid 6/107; RR 1.34, 95%CI 0.39, 4.56), but reduced adverse events with a slower loading regimen (slower 43/71 versus rapid 82/109; RR 0.51, 95%CI 0.27, 0.96). [LOE II] In an RCT, Bateman 2014 [38] compared the UK standard IV schedule consisting of 150 mg/kg in 200 mL over 15 min, then 50 mg/kg in 0·5 L over 4 hours, then 100 mg/kg in 1 L over 16 hours IV [total dose 300 mg/kg over 20.25 hours] versus a modified short IV protocol consisting of 100 mg/kg in 200 mL over 2 hours, then 200 mg/kg in 1 L over 10 hours [total dose 300 mg/kg over 12 hours]. The shorter 12-hour regimen resulted in reduced vomiting, retching or use of antiemetics from 0 to 12 hours (60/101 versus 80/102; RR 0.40, 95%CI 0.22, 0.75) and reduced anaphylactic symptoms (58/108 versus 75/100; R 0.39, 95%CI 0.21, 0.70). There was no difference in hepatotoxicity (2/100 versus 3/101; RR 0.67, 95%CI 0.11, 4.08) and no mortality in either group (0/112 versus 0/110). [LOE II]

	Both Wong 2016 [39] and McNulty 2017 [40] compared patients treated with 200 mg/kg over 4 hours followed by 100 mg/kg over 16 hours to a historical cohort treated with 150 mg/kg over 1 hour, then 50 mg/kg over 4 hours and 100 mg/kg over 16 hours. Both studies reported reduced non-allergic anaphylactic reactions with the longer duration loading dose and no difference in rate of gastrointestinal side effects or hepatotoxicity between groups. [LOE III-3] In a cluster RCT of 6 hospitals including 100 adult patients with paracetamol overdose, Wong 2019 [41] compared a shorter protocol of 200 mg/kg over 4 hours, then 6.25 mg/kg/hour in 1 L with cessation of infusion after 8 hours of the second bag if the serum ALT was <40 IU/L, the creatinine was normal and paracetamol concentration was less than 20 mg/L [total dosage 250 mg/kg over 12 hours], versus a longer protocol of 200 mg/kg over 4 hours, then 100 mg/kg over 16 hours [6.25 mg/kg/hour in 1 L] [total dosage 300 mg/kg over 20 hours]. There was no difference in ALT (18 IU/L versus 16 IU/L) or INR (1.2 versus 1.2) at 20 hours. No patients developed hepatic injury or hepatotoxicity in either group (OR 1.0, 95%CI 0.02, 50). No patients represented with liver injury, none died and 96 of 96 were well at day 14. [LOE I] ***Acetylcysteine use in newborn infants:*** Intravenous acetylcysteine use in newborn infants is restricted to case reports with variable outcome including hepatotoxicity and death and variable reporting of adverse effects [19]. A case report of an 895 g infant with a paracetamol concentration of 1140 mg/L post-delivery used an IV acetylcysteine loading dose of 150 mg/kg over an hour, then 50 mg/kg over 4 hours and 100 mg/kg over 16 hours. A fourth dose was administered at 6.25 mg/kg/h for 16 hours. The observed half-life of elimination of acetaminophen was 15 hours. Acetylcysteine was well tolerated. [31] Another case report in a 585 g infant used a loading dose of 150 mg/kg IV over 30 minutes, followed by 50 mg/kg over 4 hours and 100 mg/kg over 16 hours. The infant developed hypotension requiring inotropes after 5 hours of infusion. [14] **Recommendation** In infants and children, hepatotoxicity has been reported over a dosage range of 60–420 mg/kg/day for 1–42 days [1]. A lower treatment threshold of 60 mg/kg following IV paracetamol overdose should be considered. If there is uncertainty about the dose received, treat if paracetamol concentration is above 50 mg/L (330 micromol/L) at 4 hours after exposure. Until further pharmacokinetic data and trials are available in newborn infants, infants should be commenced on a regimen of 200 mg/kg over 4 hours followed by 100 mg/kg over 16 hours. Near the completion of acetylcysteine infusion (i.e., 2 hours before completion of infusion), measure serum ALT and paracetamol concentrations. Acetylcysteine infusion should be continued if the ALT level is increasing (>50 U/L) or the paracetamol concentration is >10 mg/L (66 mmol/L). Discontinue acetylcysteine if serial paracetamol concentrations measured 4 hours apart are below the nomogram line and decreasing and the ALT or AST and INR are all falling. [22, 24]
References	1. Heubi JE, Barbacci MB, Zimmerman HJ. Therapeutic misadventures with acetaminophen: Hepatoxicity after multiple doses in children. Journal of Pediatrics. 1998;132:22-7. 2. Daly FFS, Fountain JS, Murray L, Graudins A, Buckley NA. Guidelines for the management of paracetamol poisoning in Australia and New Zealand - Explanation and elaboration. Medical Journal of Australia. 2008;188:296-301. 3. Aw MM, Dhawan A, Baker AJ, Mieli-Vergani G. Neonatal paracetamol poisoning [4]. Archives of Disease in Childhood: Fetal and Neonatal Edition. 1999;81:F78. 4. Bharmappanavara G, Childs A, Gallichan J, Maxwell N. Paracetamol overdose in a mother requiring treatment of the neonate using N-acetylcysteine: A Case Report. Archives of Disease in Childhood: Fetal and Neonatal Edition. 2014;1):A63-A4. 5. Noble C, Loveless R, Chuang R. Peripartum acetaminophen overdose with IV N-acetylcysteine treatment in neonate. Clinical Toxicology. 2017;55 (7):718-9. 6. Roberts I, Robinson MJ, Mughal MZ, Ratcliffe JG, Prescott LF. Paracetamol metabolites in the neonate following maternal overdose. British Journal of Clinical Pharmacology. 1984;18:201-6.

7. Wong C, Watson D. Favourable maternal and fetal outcome following antenatal paracetamol overdose with timely n-acetylcysteine infusion. Journal of Paediatrics and Child Health. 2019;55 (Supplement 1):113.
8. Abadier M, Wong A, Graudins A. Accidental repeated supratherapeutic overdose of paracetamol in a neonate with prolonged paracetamol elimination half-life. Clinical Toxicology. 2019;57 (6):547.
9. Chiew A, Buckley N, Pao LT, Roberts D. Pharmacokinetics of acetaminophen and metabolites after accidental acute overdose in a neonate. Clinical Toxicology. 2018;56 (10):951-2.
10. Bektas MS. Multidrug toxicity in a newborn: A case report. Current Pediatric Research. 2017;21:375-8.
11. Bucaretchi F, Fernandes CB, Branco MM, De Capitani EM, Hyslop S, Caldas JPS, Moreno CA, Porta G. Acute liver failure in a term neonate after repeated paracetamol administration. Revista Paulista de Pediatria. 2014;32:144-8.
12. Isbister GK, Bucens IK, Whyte IM. Paracetamol overdose in a preterm neonate. Arch Dis Child Fetal Neonatal Ed. 2001;85:F70-2.
13. Figueroa-Uribe AF, Perez-Sandoval LL. Paracetamol overdose in a newborn: A case report. Revista Mexicana de Pediatria. 2017;84:66-71.
14. Tynjala PI, Backman JT, Karjalainen M, Hoppu K. Paracetamol toxicity in an extremely preterm neonate after an inadvertent intravenous overdose: A case report. Clinical Toxicology. 2015;53 (4):285-6.
15. Broeks IJ, Van Roon EN, Van Pinxteren-Nagler E, De Vries TW. Intravenous paracetamol overdose in a paediatric patient. [Dutch]. Pharmaceutisch Weekblad. 2013;148:56-8.
16. Porta R, Sanchez L, Nicolas M, Garcia C, Martinez M. Lack of toxicity after paracetamol overdose in a extremely preterm neonate. European Journal of Clinical Pharmacology. 2012;68:901-2.
17. Nevin DG, Shung J. Intravenous paracetamol overdose in a preterm infant during anesthesia. Paediatr Anaesth. 2010;20:105-7.
18. de la Pintiere A, Beuchee A, Betremieux PE. Intravenous propacetamol overdose in a term newborn. Arch Dis Child Fetal Neonatal Ed. 2003;88:F351-2.
19. Pacifici GM, Allegaert K. Clinical Pharmacology of Paracetamol in Neonates: A Review. Current Therapeutic Research - Clinical and Experimental. 2015;77:24-30.
20. Cuzzolin L, Antonucci R, Fanos V. Paracetamol (acetaminophen) efficacy and safety in the newborn. Current Drug Metabolism. 2013;14:178-85.
21. Bateman DN, Dear JW. Acetylcysteine in paracetamol poisoning: A perspective of 45 years of use. Toxicology Research. 2019;8:489-98.
22. Chiew AL, Fountain JS, Graudins A, Isbister GK, Reith D, Buckley NA. Consensus statement. Guidelines for the management of paracetamol poisoning in Australia and New Zealand — explanation and elaboration. https://www.mja.com.au/sites/default/files/issues/203_05/Guidelines_paracetamol_Aus_NZ_2015.pdf. 2015.
23. Smilkstein MJ, Knapp GL, Kulig KW, Rumack BH. Efficacy of oral N-acetylcysteine in the treatment of acetaminophen overdose. Analysis of the national multicenter study (1976 to 1985). N Engl J Med. 1988;319:1557-62.
24. Chiew AL, Fountain JS, Graudins A, Isbister GK, Reith D, Buckley NA. Summary statement: New guidelines for the management of paracetamol poisoning in Australia and New Zealand. Medical Journal of Australia. 2015;203:215-8.
25. Waring WS. Novel acetylcysteine regimens for treatment of paracetamol overdose. Therapeutic Advances in Drug Safety. 2012;3:305-15.
26. Prescott LF, Park J, Ballantyne A, Adriaenssens P, Proudfoot AT. Treatment of paracetamol (acetaminophen) poisoning with N-acetylcysteine. Lancet. 1977;2:432-4.
27. Prescott LF, Donovan JW, Jarvie DR, Proudfoot AT. The disposition and kinetics of intravenous N-acetylcysteine in patients with paracetamol overdosage. European Journal of Clinical Pharmacology. 1989;37:501-6.

28. Pakravan N, Waring WS, Sharma S, Ludlam C, Megson I, Bateman DN. Risk factors and mechanisms of anaphylactoid reactions to acetylcysteine in acetaminophen overdose. Clinical Toxicology. 2008;46:697-702.
29. Wong A, Graudins A. N-acetylcysteine regimens for paracetamol overdose: Time for a change? EMA - Emergency Medicine Australasia. 2016;28:749-51.
30. Fisher ES, Curry SC. Evaluation and treatment of acetaminophen toxicity. Advances in Pharmacology. 2019;85:263-72.
31. Jahne C, Baum C, Doyon S. Administration of IV N-acetylcysteine in a premature infant weighing 895 g. Clinical Toxicology. 2018;56 (10):1071.
32. Chiew AL, Gluud C, Brok J, Buckley NA. Interventions for paracetamol (acetaminophen) overdose. Cochrane Database Syst Rev. 2018;2:CD003328.
33. Keays RT, Cove C, Forbes A, Alexander GJM, Williams R. Use of late N-acetyl cysteine in servere paracetamol overdose. Gut. 1989;30:A1512.
34. Green JL, Heard KJ, Reynolds KM, Albert D. Oral and Intravenous Acetylcysteine for Treatment of Acetaminophen Toxicity: A Systematic Review and Meta-analysis. West J Emerg Med. 2013;14:218-26.
35. Eizadi-Mood N, Sabzghabaee AM, Siadat S, Yaraghi A, Shariati M, Gheshlaghi F, Massoumi G, Movahedi D, Baradaran S. Intravenous acetylcysteine versus oral and intravenous acetylcysteine: Does a combination therapy decrease side effects of acetylcysteine? Pakistan Journal of Medical Sciences. 2013;29:308-11.
36. Arefi M, Behnoush B, Pouraziz H, Yousefinejad V. Comparison of oral and intravenous N-acetylcysteine administration in the treatment of acetaminophen poisoning. [Persian]. Scientific Journal of Kurdistan University of Medical Sciences. 2013;18:36-43.
37. Kerr F, Dawson A, Whyte IM, Buckley N, Murray L, Graudins A, Chan B, Trudinger B. The Australasian Clinical Toxicology Investigators Collaboration randomized trial of different loading infusion rates of N-acetylcysteine. Annals of emergency medicine. 2005;45:402-8.
38. Bateman DN, Dear JW, Thanacoody HKR, Thomas SHL, Eddleston M, Sandilands EA, Coyle J, Cooper JG, Rodriguez A, Butcher I, Lewis SC, Vliegenthart ADB, Veiraiah A, Webb DJ, Gray A. Reduction of adverse effects from intravenous acetylcysteine treatment for paracetamol poisoning: A randomised controlled trial. The Lancet. 2014;383:697-704.
39. Wong A, Graudins A. Simplification of the standard three-bag intravenous acetylcysteine regimen for paracetamol poisoning results in a lower incidence of adverse drug reactions. Clin Toxicol (Phila). 2016;54:115-9.
40. McNulty R, Kirby A, Gunja N. Fewer adverse drug reactions to acetylcysteine in paracetamol overdose using a reduced bolus 2-bag protocol compared to the traditional 3-bag protocol: A meta-analysis. Clinical Toxicology. 2018;56 (6):524-5.
41. Wong A, McNulty R, Taylor D, Sivilotti M, Greene S, Gunja N, Koutsogiannis Z, Graudins A. The NACSTOP Trial: A Multicenter, Cluster-Controlled Trial of Early Cessation of Acetylcysteine in Acetaminophen Overdose. Hepatology. 2019;69:774-84.

Original version Date: 29/08/2019	**Author: ANMF Consensus Group**
Current Version number: 1.0	**Current Version Date: 29/08/2019**
Risk Rating: Medium	**Due for Review: 29/08/2024**

Authors Contribution

Original author/s	Srinivas Bolisetty, David Osborn
Evidence Review	David Osborn, Himanshu Popat
Expert review	Angela Chiew, Naren Gunja
Nursing Review	Eszter Jozsa
Pharmacy Review	Jing Xiao, Michelle Jenkins, Cindy Chen
ANMF Group contributors	Nilkant Phad, Himanshu Popat, James Marceau
Final editing and review of the original	Ian Whyte
Electronic version	Cindy Chen, Ian Callander
Facilitator	Srinivas Bolisetty