## Acetylcysteine for mucolysis

Newborn use only

### Alert
Also known as N-acetylcysteine (NAC).
Refer to acetylcysteine intravenous for paracetamol overdose.
Safety data for acetylcysteine as a mucolytic agent in newborn infants is limited and the dosage recommendation was on the basis of consensus.
Injection preparations are safe to use as oral preparation.

### Indication
- Meconium ileus secondary to cystic fibrosis
- Meconium-related ileus of preterm infants
- Distal intestinal obstruction secondary to cystic fibrosis
- Gastric or intestinal milk curd obstruction (lactobezoar)

### Action
Reduces the viscosity of mucus by cleaving disulphide bonds in the mucoprotein

### Drug type
Mucolytic agent

### 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 ampoule
- Acetadote Concentrated Injection (Solution for infusion) 20%; 200 mg/mL vial
- Acetylcysteine-Link Concentrate for infusion 20%; 200 mg/mL ampoule

### Dosage
**Intragastric**
- Meconium ileus: 400 mg/dose (4 mL/dose of acetylcysteine 10%) (range 100–500 mg/dose, 1–5 mL/dose of acetylcysteine 10% 6–8 hourly\(^3\)). Acetylcysteine 10% = 100 mg/mL
- Distal intestinal obstruction secondary to CF in 1–3-month old: 400 mg/dose (8 mL of acetylcysteine 5% (50 mg/mL) daily\(^9\)). Acetylcysteine 5% = 50 mg/mL

**Rectal enema OR via distal intestinal stoma**
- 40–200 mg/dose of acetylcysteine 4% (1–5 mL of acetylcysteine 4%) 6–8 hourly. Acetylcysteine 4% = 40 mg/mL
- 50–100 mg/dose of acetylcysteine 1% (5–10 mL/kg of acetylcysteine 1%) 6–8 hourly has also been reported. Acetylcysteine 1% = 10 mg/mL

**Dose adjustments – special scenarios**
No information.

**Maximum dose**
400 mg/dose orally

**Total cumulative dose**

### Route
- Oral via gastric tube
- Rectal
- Distal intestinal stoma or via T-tube ileostomy
- Irrigation through Replogle tube

### Preparation
**Intragastric preparation\(^4,5\)**
- Acetylcysteine 10%: Dilute 5 mL of acetylcysteine 20% (200 mg/mL) with 5 mL of glucose 5% or sodium chloride 0.9%* to make a final volume of 10 mL with a concentration of acetylcysteine 10% (100 mg/mL)
  *For Acetadote Concentrated Injection – use glucose 5% only

**Rectal or stoma administration\(^22,23\)**
- Acetylcysteine 4%: Dilute 1 mL of acetylcysteine 20% (200 mg/mL) with 4 mL of glucose 5% or sodium chloride 0.9%* to make a final volume of 5 mL with a concentration of acetylcysteine 4% (40 mg/mL)
  *For Acetadote Concentrated Injection – use glucose 5% only.

### Administration
- Intragastric/rectal/stoma: Administer slowly
- Irrigation via Replogle tube: As a continuous irrigation with suction applied

### Monitoring
Cardiorespiratory, serum electrolytes, liver function

### Contraindications
- Hypersensitivity to acetylcysteine or any component of the preparation

### Precautions
- Do not use if intestinal perforation is suspected
- Abnormal liver and/or renal function
Evidence

Acetylcysteine is used for acetaminophen poisoning and as adjuvant therapy in respiratory conditions in paediatric patients. It also exhibits a mucoytic action through its free sulfhydryl group, which opens up the disulfide bonds in mucoprotein to decrease mucus viscosity. For treatment of meconium ileus (MI) or distal intestinal obstruction syndrome (DIOS), acetylcysteine can be given enterally by mouth or by feeding tube. When administered orally, acetylcysteine has been associated with uncommon adverse effects including nausea, vomiting, diarrhea, dyspepsia and skin rashes. Repeated administration by enema has been associated with hypernatraemia and liver injury.

Efficacy

Meconium ileus secondary to cystic fibrosis

There are no trials of oral or rectal acetylcysteine for meconium ileus secondary to cystic fibrosis. Case series of use of rectal acetylcysteine in uncomplicated meconium ileus include a report of 8 infants were given an acetylcysteine 20%, only 2 were successful in relieving obstruction compared to 9 of 13 relieved with diatrizoic acid (Gastrografin) enema [1]; acetylcysteine and pancreatic enzyme irrigation of a T-tube ileostomy has been reported in two case series with resolution of meconium ileus in 20 of 23 infants using 5–10 mL of an acetylcysteine 1% solution [2]; and in 6 infants using approximately 10 mL of a acetylcysteine 4% solution via the T-tube into the distal ileum [3].

Meconium-related obstruction in preterm infants

There are no RCTs of oral or rectal acetylcysteine for meconium-related obstruction in preterm infants. Several case series [4, 5] and controlled studies [6, 7] have reported variable efficacy of acetylcysteine orally or rectally in preterm infants. In a retrospective controlled study [6], 132 preterm infants <1250 g with meconium obstruction were given first-line saline rectal irrigations 5–10 mL/kg every 6 hours and metoclopramide 0.1 mg/kg/dose PO or IV every 6 hours. Infants received either oral acetylcysteine 100 mg/kg (10% solution = 1 mL) every 6 hours (n = 34) or rectal enema (1 mL of acetylcysteine 10% [100 mg] added to 9 mL sodium chloride 0.9% ) 5–10 mL/kg every 6 hours (n = 52) or no additional treatment (n = 35). There was a reduction in mean time to resolution of obstruction (12 days oral NAC group; 10 days rectal NAC group; 15 days control group) and full enteral feeding. None of the infants was given a contrast enema. Hospital stay and mortality rate did not differ between groups.

A before and after study [7] reported 6 of 99 infants born <1500 g in the before period had a meconium-associated bowel obstruction with 4 perforated and 6 surgically managed, compared to 18
of 42 (43%) diagnosed with meconium-related bowel obstruction in the after period. Twelve of 18 resolved with sodium chloride 0.9% enemas, whilst the other 6 resolved with acetylcysteine 100 mg/mL (dose not reported) through an orogastric tube and ultrasound guided diatrizoic acid (Gastrografin) enemas. None required surgery. No complications arose relating to the conservative treatment nor were there any bowel perforations.

**Gastric or intestinal milk curd obstruction (lactobezoar)**

There are case reports [8-10] of use of acetylcysteine for both gastric and intestinal obstruction with milk curds (lactobezoar) [11]. Successful treatment of gastric lactobezoar was reported using 10 mg/kg/dose of acetylcysteine 10% diluted with 50 mL of sodium chloride 0.9% administered via nasogastric tube over 30 minutes followed by clamping of the nasogastric tube for two hours and repeated 6 hourly up to 7 doses in total [8-10]. A case series reported two extremely preterm infants with intestinal obstruction secondary to human-milk-fortifier-associated curds treated with nasogastrically instilled acetylcysteine and elimination of human milk fortifier [11]. One resolved without surgery whilst the other infant required operative treatment despite nasogastric acetylcysteine and repeated enemas.

**Distal intestinal obstruction syndrome (DIOS) secondary to cystic fibrosis**

There are no RCTs of oral or rectal acetylcysteine for DIOS associated with cystic fibrosis. The ESPGHAN Cystic Fibrosis Working Group recommend use of acetylcysteine administered orally has been superseded by diatrizoic acid (Gastrografin) in children with an acute episode of DIOS [12]. Oral osmotic laxatives containing polyethylene glycol (PEG) or lactulose are recommended alternatives when needed for prophylaxis against DIOS. [12] A recent review of acetylcysteine for management of DIOS found administration technique and monitoring parameters are not well defined in current literature and clinical trials are lacking and would be helpful to better define the role of acetylcysteine in distal intestinal obstruction syndrome [13].

**Maintenance of patency of Replogle tube**

There are no reports of use of acetylcysteine for maintenance of patency of a Replogle tube used for suctioning of the proximal pouch in infants with oesophageal atresia.

**Safety**

In general, oral and rectal acetylcysteine use has been reported to be well tolerated, although the number of reports is insufficient to determine rates of adverse effects. Reported side effects of acetylcysteine treatment include hepatic derangement associated with use of oral acetylcysteine and acetylcysteine 0.2%/contrast enema in an infant with meconium ileus secondary to cystic fibrosis [14]; a preterm infant who developed hypernatremia with instillation of a 5% solution through a distal stoma at 2.2 mL/hour [15]. There is also a case report of a 3-year-old infant with DIOS associated with cystic fibrosis, who developed liver injury after oral and rectal administration of acetylcysteine [16].

For paracetamol overdose, acetylcysteine is recommended at a dose of 300 mg/kg (200 mg/kg over 4 hours and 100 mg/kg over 16 hours) given intravenously. Adverse reactions are uncommon except for nausea and vomiting. Rashes, erythema, angioedema and anaphylaxis are uncommon [17]. Doses of acetylcysteine are comparable to those documented for paracetamol overdose and, with repeated administration orally or rectally, may substantially exceed these.

**Pharmacokinetics/pharmacodynamics**

There are few studies on the pharmacokinetics of acetylcysteine with terminal half-life values of between 2.7 and 5.7 hours reported in adults [18]. In infants, gestational age 24.9–31.0 weeks, 2–11 hours after birth, mean elimination half-life was 11 hours (range 7.8–15.2), plasma clearance 37 mL/kg/h (range 13–62) and volume of distribution 573 mL/kg (range 167–1010 mL/kg). A steady-state concentration of acetylcysteine was reached in 2–3 days during a constant infusion. [19] The oral systemic bioavailability of – varied between 6 and 10% in adult volunteers [20, 21], with first-pass metabolism in the liver limiting systemic concentrations [18].
**Practice points**

For enemas, solutions of acetylcysteine should not exceed 4% to avoid mucosal injury and hypernatraemic dehydration. Monitor electrolytes and liver function tests particularly with repeated administration. There are insufficient data to determine the safety and efficacy of acetylcysteine via nasogastric tube or enema for meconium ileus of prematurity and gastric and intestinal milk curd obstruction (lactobezoar) in preterm infants, particularly in respect to other approaches and agents. [LOE IV, GOR D]

Acetylcysteine T-tube ileostomy irrigation has been used for infants with meconium ileus associated with cystic fibrosis. [LOE IV GOR D]

The ESPGHAN Cystic Fibrosis Working Group recommend that use of acetylcysteine administered orally has been superseded by diatrizoic acid (Gastrografin) in children with an acute episode of distal intestinal obstruction [12]. Oral osmotic laxatives containing polyethylene glycol (PEG) or lactulose are recommended alternatives when needed for prophylaxis against DIOS. [12] [LOE IV GOR D]

There are no published reports of use of acetylcysteine for irrigation of the upper pouch in infants with oesophageal atresia.

**Irrigation of upper oesophageal pouch in tracheo-oesophageal fistula – no reported evidence. For refractory cases with thick secretions not responding to sodium chloride 0.9% irrigation – subject to surgeon’s approval – 5 mL/hour of acetylcysteine 4% through Replaque tube.**

**Preparation of acetylcysteine 4%:** Dilute 20mL of acetylcysteine 20% (200 mg/mL) with 80 mL of glucose 5% or sodium chloride 0.9%* to make a final volume of 100 mL with a concentration of acetylcysteine 4% (40 mg/mL)

*For Acetadote Concentrated Injection – use glucose 5% only.

**References**
