JPPT | Review

# *N*-acetylcysteine for Management of Distal Intestinal Obstruction Syndrome

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With the improving life expectancy of cystic fibrosis patients, new manifestations of the disease are emerging. Distal intestinal obstruction syndrome is one of the increasingly noted complications. Traditionally this syndrome was treated surgically. *N*-acetylcysteine is sometimes used as a non-surgical treatment option despite lack of definitive evidence for its efficacy and safety and not being mentioned in current treatment guidelines. The existing case reports suggest that *N*-acetylcysteine may have a place in therapy for older patients with incomplete distal intestinal obstruction syndrome to relieve the initial obstruction or following disimpaction to ensure clearance of remaining ileus and to prevent obstruction recurrence. In younger patients (e.g., <3 years of age), efficacy of *N*-acetylcysteine has been controversial and its use has been associated with drug-induced liver injury and hypernatremia. In the cases included in this review, 4% *N*-acetylcysteine was the formulation most commonly used. Since higher concentrations have been associated with increased adverse effects and mucosal injury, lower concentrations and dosages should be used when using *N*-acetylcysteine until further evidence becomes available. Proper administration technique and monitoring parameters are not well defined in current literature. Prospective, well-designed clinical trials are lacking and would be helpful to better define the role of *N*-acetylcysteine in distal intestinal obstruction syndrome.

**ABBREVIATIONS** CF, cystic fibrosis; CFTR, cystic fibrosis transmembrane conductance regulator; DILI, drug-induced liver injury; DIOS, distal intestinal obstruction syndrome; ESPGHAN, European Society for Pediatric Gastroenterology, Hepatology, and Nutrition; GI, gastrointestinal; IV, intravenous; MI, meconium ileus; NAC, *N*-acetylcysteine; NG, nasogastric

**KEYWORDS** cystic fibrosis; distal intestinal obstruction syndrome; meconium ileus; mucolytic; *N*-acetylcysteine; pediatric

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## Introduction

Cystic fibrosis (CF) is an autosomal recessive disease characterized by exocrine pancreatic insufficiency and progressive pulmonary disease. According to the CF Foundation, it affects approximately 70,000 people worldwide and 30,000 people in the United States. Cystic fibrosis is caused by a mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene, which codes for a protein whose main function is to regulate chloride ion transport. Cystic fibrosis pathophysiology involves a buildup of dehydrated mucus in the airways that leads to obstruction and poor oxygenation. The viscous mucus also blocks pancreatic secretions, which impairs the ability to absorb fats and fat-soluble vitamins appropriately. Extrapulmonary complications of CF include liver disease, CF-related diabetes, chronic sinusitis, malnutrition, problems with fertility, and psychological processes associated with management of a chronic disease. Modern-day therapies have allowed up to 80% of CF patients to reach adulthood.[1] The CF Foundation estimates that of the people currently living with CF, more than half are now older than 18 years. With this improved life expectancy, new manifestations of the disease are increasingly noted.[2]

Gastrointestinal (GI) comorbidities encountered by CF patients later in the course of their disease include chronic constipation and distal intestinal obstruction syndrome (DIOS).[2] Increased viscosity of intestinal mucus and an inherently prolonged transit time associated with CF are thought to contribute to its intestinal complications.[2] Other contributing factors include loss of CFTR function in the intestine, leading to improperly regulated chloride, bicarbonate, and sodium transport.[3] Unfortunately, studies are lacking to guide therapy recommendations in the management of CF-related GI complications, especially DIOS. *N*-acetylcysteine (NAC) is commonly used for treatment of DIOS despite lack of guidelines regarding its use. The purpose of this review article is to discuss currently available evidence regarding off-label use of NAC for management of this CF-related comorbidity.

## Distal Intestinal Obstruction Syndrome

CFTR mutations in the intestine can cause abnormally low volumes of fluid to be secreted into the lumen, leading to a dehydrated intraluminal state with electrolyte abnormalities.[4] Risk factors for GI complications in CF include pancreatic insufficiency, dehydration, fat malabsorption, organ transplant, and CF-related diabetes.[5] The dehydrated intraluminal state easily allows obstruction in the intestines to occur with a mixture of mucus and fecal-type matter combined with undigested materials and a high bacterial burden.[4] Many CF patients experience low-grade obstructions that manifest as chronic constipation.[4] In DIOS, this mixture accumulates in the final part of the small intestine (terminal ileum) and adheres strongly to the mucosal surface.[3,4] When it attaches to the bowel wall via the intestinal villi, removal becomes very difficult.[3]

Obstructions can present with differing levels of severity and at different times in a CF patient's life. Meconium ileus (MI) is a complete intestinal obstruction caused by inspissated meconium in the neonatal period.[2] It occurs in 15% of CF patients and can be the first clinical manifestation of their disease.[6] DIOS, formerly known as "meconium ileus equivalent," occurs after the neonatal period when a complete or incomplete intestinal obstruction of fecal accumulation forms in the terminal ileum and proximal colon.[2] The European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) CF Working Group defines complete DIOS as the combination of complete intestinal obstruction, as evidenced by vomiting of bilious material and/or fluid levels in small intestine on abdominal radiography, with a fecal mass in the ileo-cecum and abdominal pain or distention or both.[7] Conversely, incomplete or impending DIOS is defined as a short history (days) of abdominal pain or distension, or both, and a fecal mass in the ileo-cecum but without signs of complete obstruction.[7] In both types, the fecal mass can be palpable on physical examination.[2]

## Current Practice

Treatment of DIOS is still largely empirical owing to a lack of randomized controlled trials to guide therapy.[5] Historically, DIOS was treated with a surgical approach.[6] With the emergence of aggressive medical therapies, surgery is infrequently used to relieve obstructions in DIOS.[2] In 1969, the first non-surgical approach was attempted. Hyperosmolar methylglucamine diatrizoate, a contrast agent typically used for imaging, was introduced into the bowel via enema with the intent of drawing fluid into the intestine to allow the meconium to be flushed out.[4,6] Although successful, the procedure was associated with numerous adverse effects secondary to the massive osmotic fluid flux into the lumen that resulted in uncontrolled distention of the bowel and third-space fluid loss (e.g., hypovolemic shock, colonic mucosal inflammation, intestinal perforation, and ischemic enterocolitis).[6]

More recently, DIOS has been treated successfully with laxative therapy (oral and/or enema preparations) with a focus on rehydration.[2] More severe episodes often require intestinal lavage with a balanced electrolyte osmotic solution given orally or via nasogastric (NG) tube.[2] Several available formulations contain water and electrolyte concentrations that are isoosmotic to prevent large fluid shifts following administration.[5] Literature has reported on numerous other proposed medical therapies to treat refractory DIOS but data have been inconclusive. *N*-acetylcysteine is one of the proposed medical therapies that have been considered for treatment of DIOS before pursuing surgery.

*N*-acetylcysteine is indicated for acetaminophen poisoning and for adjuvant therapy in respiratory conditions in pediatric patients. It exhibits a mucolytic action through its free sulfhydryl group, which opens up the disulfide bonds in mucoproteins to lower mucous viscosity.[8] Available dosage forms include an intravenous (IV) preparation and a solution for inhalation or oral administration. For treatment of MI or DIOS, NAC can be given enterally by mouth or by feeding tube.[3] Thirty to 60 mL of the solution can be diluted 1:1 in a sweet drink (orange juice or cola) to mask the strong and bitter taste of the drug.[3] The solution can be manipulated to obtain different concentrations for administration; some examples of this are discussed in the literature review below. When administered orally, NAC has been associated with minimal adverse effects (nausea, vomiting, diarrhea, dyspepsia, and skin rashes).[9] Rectal administration can also be considered when using NAC for this indication (5–300 mL based on the desired concentration). Occasionally, NAC will be given both orally and rectally for treatment of DIOS.

## Clinical Studies: Efficacy and Adverse Effects

Available literature regarding use of NAC for DIOS is limited to *in vitro*/*in vivo* studies and case reports; no randomized controlled trials were found in the literature search (Table 1). A comprehensive study done by Burke and colleagues[6] in 2002 investigated *in vitro* and *in vivo* NAC studies. In the *in vivo* study, investigators quantitated stool output after administration of numerous enema solutions into the intestines of constipated mice with the aim of discovering new non-operative strategies for management of MI. Study agents included normal saline, liquefying agents (diatrizoate meglumine and diatrizoate sodium solution, polyethylene glycol–electrolyte solution, DNase, 4% NAC, and pancrelipase), and surface tension–reducing agents (perfluorocarbon liquid, surfactant, and 10% polysorbate 80). Mice were given subcutaneous morphine injections to induce constipation. Thirty minutes following morphine administration, each mouse received a study agent administered rectally that was left to dwell in the

**Table 1.** Clinical Experience of *N*-acetylcysteine for Distal Intestinal Obstruction Syndrome

| Reference | Population | NAC Formulation, % | Goal of NAC Therapy | Outcome | Adverse Effects |
|---|---|---|---|---|---|
| Burke[6] | *In vivo*: mice | 4 | To quantitate the dry weight of stool and measure toxicity | 4% NAC resulted in less stool output than controls | Minor intestinal mucosal changes |
| | *In vivo*: meconium from term, healthy, human newborns | | To assess the ability of the test solution to break down meconium | 69% decrease in meconium viscosity immediately, over 99% viscosity reduction at 6 hours | N/A |
| Parrish[12] | 25-yr-old F with CF | 4 | To relieve intestinal obstruction | 120 mL evacuated | None reported |
| | | 4 | To prevent recurrence of intestinal obstruction | Discharged on postoperative day 15 without further GI complications | |
| Khaitov[1] | 19-yr-old F with CF | Not reported | Resolution of ileus | Not successful for initial disimpaction | None reported |
| Lillibridge[13] | 26-yr-old M with CF | Not reported | Prevention of intestinal obstruction | Complete resolution of abdominal symptoms | None reported |
| | | | Treatment of intestinal obstruction followed by a weekly enema for obstruction prevention | Successfully treated | |
| Mabogunje[14] | 2 neonates with radiologically confirmed MI | Not reported | To relieve intestinal obstruction | Unsuccessful in both patients | None reported |
| Garza-Cox[15] | 8 premature (VLBW infants) | 20 | To relieve intestinal obstruction | Successful in 2/8 patients | None reported |
| Shaw[11] | 48 puppies 3 days to 3 mo | 2–20 | To assess the effects of varying concentrations and volumes of NAC on fluid volumes in the bowel, changes in hematocrit, and microscopic tissue analysis | Not assessed | 20% NAC caused extensive fluid shifts, hyperemia, and multiple hemorrhages; effects were more severe in younger puppies |
| Bailey[9] | 3-yr-old M with CF | 4 | To relieve intestinal obstruction | Progression to a diatrizoate meglumine and diatrizoate sodium enema for disimpaction | Liver biopsy confirmed drug-induced liver injury |
| Cooke[16] | Neonate born at 38-wk gestational age with CF | 0.2 | To relieve intestinal obstruction | Successful response | Dramatic increase in transaminases and bilirubin following NAC administration |
| Langer[8] | Premature infant, 30-wk gestational age with MI | 5 | To relieve intestinal obstruction | Successful response | Hypernatremia; returned to normal within 24 hours after discontinuation |

*CF, cystic fibrosis; F, female; GI, gastrointestinal; M, male; MI, meconium ileus; N/A, not applicable; NAC,* N-*acetylcysteine; VLBW, very low birth weight*

bowel for 15 minutes. Following administration of the study agent, stool output was quantitated at 30, 60, 90, and 120 minutes. Diatrizoate meglumine and diatrizoate sodium enema was found to be the most effective agent in relieving constipation. Mice who received diatrizoate meglumine and diatrizoate sodium enemas excreted 41% more stool after 120 minutes than control mice ($p < 0.01$). Normal saline and surfactant groups had slightly better stool output than controls (11% and 5%, $p > 0.05$). Many other agents, including 4% NAC, were not effective in relieving constipation and resulted in less stool output after 120 minutes than control mice. The only adverse effects reported were minor intestinal mucosal changes when the intestines were later viewed under the microscope.

An *in vitro* portion took place where meconium from term, healthy, human newborns was collected and the ability of each test solution to dissolve the meconium was assessed. Viscosity measurements were performed immediately after administration and at 2 and 6 hours post study-drug administration. Normal saline produced an 84% reduction in meconium viscosity immediately after administration. Many agents were found to be more effective than normal saline at immediately reducing meconium viscosity. Although 4% NAC only produced a 69% decrease in meconium viscosity immediately following administration, at 6 hours of incubation the viscosity reduction was over 99%. The findings of the *in vitro* experiment suggest that NAC needs prolonged contact time in order to obtain optimal efficacy. This idea of an increased NAC enema dwell time dates back to 1964 when Meeker and Kincannon[10] found that NAC that was instilled and retained in the bowel lumen for 30 to 50 minutes led to considerable liquefaction with no adverse events reported. This perhaps explains why NAC was not as efficacious in the *in vivo* portion where it was only instilled in the mice bowels for 15 minutes.

Although external validity is questionable regarding how morphine-induced constipation in mice represents the true pathology of obstruction in CF patients, this study provided promising preliminary results regarding NAC's ability to break down stool. The investigators ultimately recommended diatrizoate meglumine and diatrizoate sodium enemas as first-line therapy in uncomplicated MI but suggested that NAC could perhaps be more effective if instilled for a longer period.[11] Clinicians should be aware of the difficulty of retaining enema solutions in the bowel for prolonged periods in clinical practice, especially in pediatric patients who may have decreased compliance secondary to associated anxiety or anal aversion.

There have been several case reports and series published describing use of NAC for DIOS with variable results. In 2012, Parrish and colleagues[12] described a case report where NAC was successful in combination with surgical treatment in a 25-year-old female with CF who was found to have radiologically confirmed DIOS following a sinus surgery. The etiology of the patient's intestinal obstruction was likely due to the administration of postoperative opioids for pain management combined with withholding pancreatic enzymes before surgery. Conservative treatment with laxatives, bowel rest, and IV fluids failed. Intraoperative techniques aimed at resolving the obstruction resulted in an inadvertent serosal tear proximal to the obstruction. Clinicians decided to use the tear to introduce 10 mL of 4% NAC into the bowel lumen. The obstruction was immediately softened and much of the burden was milked distally toward the terminal ileum with catheter assistance; 120 mL of the mixture was evacuated but unfortunately did not result in complete obstruction resolution. She ultimately required an enterotomy at the serosal tear to manually remove the obstruction. The patient had a successful postoperative recovery with no reported complaints other than pain that was effectively managed in addition to ensuring adequate hydration and nutrition. Following the procedure, the patient was given 10 mL of 10% NAC via NG tube every 6 hours to prevent recurrence of the obstruction (total duration unspecified). She was discharged on postoperative day 15 without further complications. No adverse effects were reported during the treatment course. The authors of this case report concluded that intraoperative NAC might be useful for patients when conservative therapy for treatment of DIOS fails.

Conversely, Khaitov and colleagues[1] describe a case report where use of NAC for DIOS was unsuccessful in the initial treatment. A 19-year-old female presented with severe abdominal pain and distension, tachycardia, and hypoactive bowel sounds. DIOS with complete obstruction was confirmed radiologically. Initial failed treatment attempts included fluid resuscitation, NG and rectal diatrizoate meglumine and diatrizoate sodium, and NG NAC. Exploratory laparotomy revealed a 40-cm segment of distal small bowel inspissated with obstructive material. A manual disimpaction was performed and the obstruction was pushed into the cecum with warm saline and mineral oil administered via NG. Following the operation, the patient was maintained on oral NAC with an unknown dose and frequency for 5 additional days to ensure the obstruction had completely resolved. The patient was discharged on postoperative day 10 with increased pancreatic enzyme supplementation to prevent recurrence. No adverse effects were reported during the treatment course. While NAC failed in the initial management, the dose was not reported, and it may have helped provide adjunctive postoperative therapy.

Although not individually successful in relieving the obstructions, these 2 case reports describe the use of NAC for prevention of DIOS recurrence following relief of the initial obstruction. Similarly, an older case report by Lillibridge and colleagues[13] reports on the use of

**Table 2.** Case Report: Drug-Induced Liver Injury[9]

| Type and Timing of Labs | 2 mo Before NAC | 4 Days After NAC* Initiation | 1 wk After D/C of NAC | 4 mo Later |
|---|---|---|---|---|
| AST (IU/L) | 46 | 4850 | 143 | 38 |
| ALT (IU/L) | 64 | 4820 | 965 | 52 |
| Alkaline phosphatase (IU/L) | Not provided | 495 | 867 | 473 |
| Total bilirubin (mg/dL) | Not provided | 0.8 | Not provided | 0.4 |
| Albumin (g/dL) | Not provided | 3.0 | Not provided | Not provided |
| Total protein (g/dL) | Not provided | 4.6 | Not provided | Not provided |

*ALT, alanine aminotransferase; AST,* aspartate aminotransferase*; D/C, discontinuation; NAC,* N-*acetylcysteine; NG, nasogastric; every 6 hr*
Doses of NAC administered: 50 mL 4% NAC via NG tube every 6 hr; 150 mL 4% NAC via rectal enema every 6 hr for a total dose of 106 g over 3 days.

oral NAC for prophylaxis of DIOS in a 26-year-old male diagnosed at 4 years of age in 1946. The patient had frequent abdominal pain managed with stool softeners, enemas, high doses of pancreatic enzymes, and narcotics. At age 24 years, the patient was initiated on oral NAC 30 mL given 3 times a day. Subsequently, the patient's symptoms resolved with associated weight gain and return to normal bowel function. Four months following initiation of NAC, the patient experienced 1 episode of transient abdominal pain, which was thought to be associated with obstruction, and was successfully treated with a NAC enema in addition to his oral doses. He had no additional complications in 16 months of follow-up on oral NAC daily and rectal NAC weekly. No adverse effects were reported during the treatment course.

A previous episode of DIOS is a risk factor for recurrence. It is common to use maintenance laxative therapy for prophylaxis against an obstruction recurrence.[5] Avoidance of dehydration and frequent assessment of pancreatic enzyme dosage is also recommended.[5] Polyethylene glycol is an effective laxative and is associated with less flatulence and abdominal cramps than other agents such as lactulose.[2] It is currently recommended in CF care guidelines to consider oral polyethylene glycol at a dose of 0.5 to 1 g/kg/day with a maximum dose of 40 g/day orally for 6 to 12 months for maintenance laxative therapy.[5] Although its palatability is less favorable, oral NAC demonstrated dramatic improvement in the aforementioned patient's symptoms and could perhaps be considered an alternative option for management and prevention of DIOS following an initial episode, pending further investigation. Until future trials are performed with larger groups of patients, this intervention cannot be routinely recommended.

Although the bulk of literature describing efficacy of NAC in DIOS is from older patients, 2 case series in younger patients are available. A study by Mabogunje and colleagues[14] looked at 17 neonates with uncomplicated MI who were given therapeutic enemas. Two neonates received NAC enemas with pancreatin at an unspecified dose and neither of them had successful relief of their intestinal obstructions.[14] Poor success rates were also reported in a study by Garza-Cox and colleagues[15] where NAC was given to relieve MI in 8 premature infants. Only 2 of 8 infants experienced relief of the obstruction following an enema of 20% NAC solution. No adverse effects were reported during the course of treatment in either of these studies.

In contrast, a study by Shaw[11] in 1968 showed that NAC was used in varying strengths to successfully evacuate "plugs" from 5 of 6 newborns with no adverse events reported. Shaw[11] also reports positive results in using NAC in 48 puppies ranging in age from 3 days to 3 months. Various NAC strengths (2%–20%) were tested and compared to normal saline. Extensive fluid shifts with hyperemia and multiple hemorrhages of the bowel mucosa were found after exposure to 20% NAC. These changes were noted shortly after NAC administration and correlated with time of exposure. The degree of injury varied inversely with the age and size of the puppy. The severity of the mucosal injury was less with lower concentrations and there were no adverse events reported with the 4% solution, leading authors to conclude that 4% NAC seems to be an effective adjunct to aid relief of intestinal obstructions in MI and meconium plugs.

While preliminary success has been shown, use of NAC for DIOS may have potential associated risks. A case report from 1987 describes use of NAC for DIOS in a 3-year-old male with CF who was treated with oral and rectal NAC and experienced significant elevations in his liver enzymes 4 days after initiation (Table 2).[9] The elevated enzymes normalized 1 week after discontinuation of NAC. Unfortunately, 2 months later the patient again developed DIOS. This time the patient was given NAC enemas as monotherapy and again experienced significant elevations in his liver enzymes (Table 3). Following the repeated drug-induced liver injury (DILI), NAC was discontinued and a diatrizoate sodium enema was used to achieve disimpaction. The temporal relationship in enzyme elevation strongly correlated with administration of NAC on both occasions. Liver biopsy findings were suggestive of DILI but could have possibly been confounded by the typical hepatobiliary changes that occur in CF patients. However,

**Table 3.** Case Report: Repeated Drug-Induced Liver Injury[9]

| Type and Timing of Labs | 5 Days After NAC* Initiation | 1 wk After D/C of NAC | 4 mo Later |
|---|---|---|---|
| ALT (IU/L) | 2700 | 193 | 49 |
| AST (IU/L) | 6440 | 1080 | 109 |
| Alkaline phosphatase (IU/L) | 692 | 780 | 407 |
| Total bilirubin (mg/dL) | 1.1 | 0.5 | 0.3 |
| Prothrombin time (sec) | 14.3 | 11.7 | Not provided |

*ALT, alanine aminotransferase; AST,* aspartate aminotransferase*; D/C, discontinuation; NAC,* N-*acetylcysteine; every 4–6 hr*
Doses of NAC administered: 200 mL 5% NAC every 4–6 hr, received 25 enemas in 4 days for a total dose of 250 g.

the marked elevation of serum transaminases following NAC administration was thought to be greater than the mild to moderately elevated levels usually seen in CF.

Another case report by Cooke and colleagues[16] demonstrates similar hepatic derangements following NAC administration. This case involved a neonate born at 38 weeks' gestational age who was diagnosed with CF and found to have marked abdominal distension shortly after birth. The patient was diagnosed with uncomplicated MI and was treated with two 0.2% NAC enemas (60–80 mL). Suspicion for ileal atresia was raised when the proximal dilated loops could not be opacified with contrast. Meconium peritonitis and ileal atresia were found on laparotomy. A double barrel ileostomy was performed and the atretic segment was resected. The patient was maintained on total parenteral nutrition and pancreatic enzymes postoperatively. Ileostomies were closed at 6 weeks via an end-to-end anastomosis after which the infant developed severe fecal impaction. *N*-acetylcysteine enemas were administered with resolution of the impaction and resumption of full enteral feeds. On postoperative day 10, laboratory evaluation revealed a dramatic increase in transaminases and bilirubin. This rise was thought to be disproportionally high to be associated with the known liver manifestations of CF or total parenteral nutrition–induced cholestasis. The liver enzyme elevation resolved rapidly after discontinuation of NAC.

Hypernatremia associated with NAC was reported in a premature infant born at 30 weeks gestational age with MI complicated by volvulus, *in utero* perforation, and meconium peritonitis.[8] A 5% NAC solution was instilled into the distal ileum at a rate of 2.2 mL/hr. Serum sodium rose significantly in the following 48 hours from 135 to 163 mmol/L. Dehydration, absorption of sodium from the water-soluble contrast medium, and incorrect administration of sodium-containing parenteral solutions were excluded as possible causes of hypernatremia. Upon further investigation, it was discovered that 33.5 mmol/kg/day of sodium content from the drug had been administered to the patient. At this time therapy was immediately discontinued, and the patient's sodium normalized in 24 hours. The patient had successful outcomes overall and was transferred to a secondary care nursery 40 days postoperatively.

A 4% NAC solution was the formulation that was used most frequently in the cases included in this review. A lower concentration of 0.2% was used in the case report involving DILI in the neonate born at 38 weeks. It is important to note that differing NAC products will have varying levels of sodium content and patient tolerance may differ. Perhaps it is reasonable to attempt conservative use of NAC in the younger or premature neonate population that may have lower tolerance for a large sodium load, especially considering that use of NAC enemas in the neonatal population has historically had controversial efficacy as described by Mabogunje et al[14] and Garza-Cox et al.[15]

## Place in Therapy

At present state, available data describing use of NAC for DIOS are largely based on case reports, and the sample size of patients who have received NAC for this indication is small. Some of the published reports do not elaborate on the NAC formulations that were used. The available reports also do not describe the duration of dwell time in the bowel when given rectally, which is important in establishing appropriate administration guidelines. While these case reports detail the short-term effects of NAC for DIOS, little is known about its long-term effects. In the setting of these limitations, it is difficult to draw conclusions regarding the safety and efficacy of NAC and its overall role in the treatment of DIOS.

According to the results of the *in vitro* study by Burke and colleagues[6] and by Meeker and Kincannon,[10] it seems that NAC needs prolonged contact time to obtain optimal efficacy. Although this trend has consistently been noted, it is important to understand the clinical application of keeping enema solutions in the bowel for prolonged periods. Rectally administered medication in pediatric patients may not be as well tolerated as other available routes.

Another consideration is that NAC alone has often been unsuccessful in resolving MI and DIOS, based on the case reports available, especially for complete obstructions that are refractory to multiple medications and will likely require surgical intervention. In the case report by Parrish and colleagues,[12] NAC showed

success in softening the obstruction after the patient had already experienced failure with laxatives, bowel rest, and IV fluids. On the other hand, Khaitov and colleagues[1] describe a case where the obstruction was refractory to fluid resuscitation, NG and rectal diatrizoate meglumine and diatrizoate sodium, and NG NAC. It is possible, however, that an intestinal obstruction that is refractory to diatrizoate meglumine will likely not respond to any form of medical management, as this is the agent with the most proven efficacy in reducing viscosity and relieving obstructions.[4,6,9] In both of these cases, oral NAC was used after initial obstruction disimpaction, suggesting that NAC could be used in the clearance of any remaining fecal material and prevent recurrence of obstruction. Similarly, the case by Lillibridge and colleagues[13] describes successful use of NAC for prophylaxis in a 26-year-old patient with CF and frequent abdominal attacks who experienced significant relief after initiation of 3 times a day NAC with a weekly NAC enema. Although the evidence is promising, NAC cannot routinely be recommended for prophylaxis against repeated obstruction at this time. Polyethylene glycol remains a first-line treatment recommendation in current clinical guidelines.

Based on the limited existing literature of case reports and series, NAC may be better tolerated in older patients. In the case report by Lillibridge and colleagues,[13] a 26-year-old male took NAC 3 times a day and there were no reported adverse events throughout 16 months of follow-up. In the report by Parrish et al,[12] a 25-year-old patient tolerated 10 mL 10% NAC via NG tube every 6 hours and there were no reported electrolyte abnormalities or further postoperative complications noted. On the other hand, case reports by Bailey et al[9] and Cooke and colleagues[16] demonstrate DILI in a 3-year-old and a neonate born at 38 weeks, and Langer and colleagues[8] reported hypernatremia in a premature infant after exposure to NAC. Owing to mixed reports of efficacy and concerns for adverse effects in this younger population, perhaps NAC should be reserved for older patients, although there is limited evidence to suggest an appropriate minimum age for use. Owing to reports of controversial efficacy in the neonatal population, perhaps NAC should be avoided in this population altogether until further reports are available that demonstrate better outcomes. If NAC is to be used, these case reports suggest that serum sodium levels and hepatic panels should be monitored routinely.

Many of the abovementioned hypotheses can be validated with the early findings of Shaw,[11] published in the *Journal of Pediatric Surgery* in 1969. Extensive fluid shifts with hyperemia and multiple hemorrhages of the bowel mucosa were found following exposure to 20% NAC. The degree of injury varied inversely with the age and size of the puppy, suggesting that NAC should potentially be limited to older patients in order to avoid serious toxicities. The severity of the mucosal injury was also less with lower concentrations, and no adverse events were reported with the 4% solution. Given that lower concentrations have shown similar efficacy to higher concentrations, lower concentrations and dosages should likely be recommended when using NAC for GI indications.

## Conclusions

When used appropriately, NAC may have a role in management of DIOS. *N*-acetylcysteine could be recommended as first- or second-line therapy in older individuals owing to its demonstrated efficacy and fewer reported risks associated with its use in this age group. It may be more effective in relieving incomplete obstructions than complete obstructions. For younger patients, the limited case reports suggest that clinicians should use NAC cautiously. The lowest effective concentration should be used and awareness of the possibility for DILI or hypernatremia is important. In conclusion, additional research is needed to better define the role of NAC in DIOS, including safety and efficacy, recommended dosing, proper administration technique, and suggested monitoring parameters.

## ARTICLE INFORMATION

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