Meconium ileus in Cystic Fibrosis

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Abstract

Meconium ileus (MI) is often the first manifestation of cystic fibrosis (CF) and occurs in approximately 20% of patients diagnosed with CF. This article reviews the pathophysiology of MI and its clinical presentation. It focuses on the medical and surgical management emphasizing the importance of nutrition and a multidisciplinary approach to improve both short-term and long-term outcomes for CF patients with MI.

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1. Background

Meconium ileus (MI) is often the first manifestation of cystic fibrosis (CF) and occurs in approximately 20% of patients diagnosed with CF. It can present in two forms, simple MI and complex MI. In simple MI, viscid meconium physically obstructs the terminal ileum and the small intestine proximal to the obstruction, then becomes dilated with additional meconium, gas, and fluid [1]. In complex MI, the meconium-distended segments of ileum can give way to complications like prenatal volvulus, ischemic necrosis, intestinal atresia, or perforation and extrusion of the meconium into the peritoneum. The timing of perforation may contribute to the outcome. If perforation occurs earlier in utero, there is the possibility of reabsorption of some meconium in the peritoneum before delivery, leaving only a small number of calcifications. If necrosis and perforation occur close to delivery, meconium peritonitis is more likely to be seen. Meconium may also become (partly) encapsulated: giant cystic meconium peritonitis (GCMP) [2–3]. This condition may present with a palpable mass on exam in a patient with MI or meconium peritonitis [1]. Both simple and complex MI occur with similar frequency in patients with CF.

Understanding the pathophysiology of MI has been greatly advanced by the development of mouse models as well as the cystic fibrosis transmembrane conductance regulator (CFTR) knock out ferret and pig, which have 100% penetration of MI. Within the small intestine, CFTR is responsible for both Cl− and HCO3− excretion. It is the HCO3− that plays an integral role in chelating Ca2+ associated with the tight matrix of normally exocytosed mucins within the gut lumen to form normal, loose well-hydrated mucus [4]. Abnormal CFTR results in abnormal HCO3− excretion, thus decreasing luminal pH. This creates an acidic and dehydrated environment in which the tight matrix of exocytosed mucins are not disrupted appropriately resulting in thick, dehydrated mucus [4]. The abnormally acidic luminal environment also promotes the presence of elevated levels of stool albumin, increased mineral content, and protein-bound carbohydrates. These combine with the dense mucus to form viscid meconium that eventually leads to physical obstruction of the terminal ileum (TI) [1,4–6]. This process might result in the two outcomes described above, either simple or complex MI.

MI is most commonly associated with class I-III CFTR mutations. Specifically, MI is associated with F508del, G542X, W1282X, R553X, and G551D [7]. Based on the United States CF
Patient Registry 2010 database, a patient with two copies of the most common F508del mutation has a 24.9% risk of presenting with MI [7]. A patient with a F508del paired with another mutation has a 16.9% risk of presenting with MI [7]. The risk of a patient with two other CFTR mutations presenting with MI is 12.5% [7]. Evaluation for risk of MI in CF monozygotic and dizygotic twins also found an increased concordance in monozygotic twins [8]. In addition, it has been noted that in families where there is a history of an infant with MI, the chance that a subsequent child with CF will develop MI is greater than expected [9–10]. These findings point to the involvement of modifier genes in the development of MI. However, although multiple modifier genes that enhance or reduce the risk of MI have been identified in single studies, the ability to replicate these results has been limited [8–13].

With better understanding of CF and earlier recognition of MI, there have been significant improvements in the morbidity and mortality associated with MI. Mortality rates, as high as 33% in the 1960s for both simple and complex MI, have significantly improved [14]. Today, early and late survival rates for both simple and complex MI are consistently reported over 80% [1–2].

The first significant improvement came in 1948 when Hiatt and Wilson described a method for intraoperative disimpaction of MI with saline [15]. This was followed in 1969 with Noblett’s description of using hyperosmolar Gastrografin enemas in the management of simple MI [16]. At the time, this novel technique aided in the minimization of small bowel and colonic resection in simple MI. In addition, the development of a comprehensive multidisciplinary approach to the care of CF infants by pediatric surgeons, neonatologists, pulmonologists, respiratory therapists, gastroenterologists, and dieticians has not only led to further improvements in short-term morbidity, but has also allowed for negligible long-term differences in regards to nutritional status, pulmonary function, and infection status for CF patients with history of both simple and complex MI [17–19].

2. Clinical presentation and differential diagnosis

In the modern era of highly sensitive medical technology, MI and meconium peritonitis are often detected prenatally by the presence of hyperechoic bowel or peritoneal calcifications on ultrasound (US) [20]. However, hyperechoic bowel can also be seen in many other disease processes [20]. A 16 year review of US experience in Brittany, France from 1992 to 2007 found that only 7.6% of 289 patients who had abnormal bowel detected by prenatal US actually had CF. Nevertheless, if hyperechoic bowel is detected, it is imperative to assess the fetus’s risk of CF [20].

If not identified prenatally, the most common clinical presentation of MI is intestinal obstruction, which is often seen within hours of birth. When feedings are initiated, bilious emesis occurs with or without abdominal distention. The infant with meconium peritonitis often presents with additional signs of abdominal tenderness, fever, and shock [1]. Other infants may only display concern for MI with the delayed passage of meconium. In all of these cases, the differential diagnosis includes not only CF with MI, but also other conditions including meconium plug (hard stool covered with mucous that is difficult to pass), Hirschsprung’s disease, jejunoileal atresia, volvulus, and bowel perforation.

3. Diagnostic workup

In the case of an abnormal prenatal US, screening for CF should be offered by assessing the carrier state of the parents, either through a common mutation panel or through sequencing of the whole CFTR gene, understanding the limitations of both. If both parents are noted to be carriers of CF, then appropriate genetic counseling should be offered to discuss the risks of having an infant with CF and future implications. If one or both parents are noted not to be carriers, genetic counseling should still be offered to discuss the limitations of testing as well as other disease processes associated with hyperechoic bowel. (Fig. 1) Once a hyperechoic bowel has been seen on US, the fetus should be followed with US every 6 weeks or less [4]. In addition, referral to a perinatologist should be made so that delivery can be planned at a tertiary care center with an experienced neonatal intensive care unit (NICU) and a multidisciplinary team, including a pediatric surgeon.

Initial workup of any infant with bilious emesis, with or without abdominal distention, requires initial stabilization of the patient including prescribing nothing per os (NPO), establishing intravenous (IV) access, and assuring adequate hydration to maintain good perfusion. Laboratory evaluation, including electrolytes, white blood cell count (WBC), hemoglobin, and lactate, is also useful in determining the clinical status of the infant. If fever is present or WBC is elevated it may be appropriate to obtain blood and urine cultures and consider initiation of antibiotic therapy. Often a nasogastric tube (NGT) is placed to allow for decompression of the stomach and proximal small bowel, as well as to prevent further bilious emesis and decrease risk of aspiration. If the infant is not already in a NICU under the care of a multidisciplinary team including pediatric surgeons, neonatologists, and gastroenterologists, transfer should be arranged immediately.

In an infant that presents with bilious emesis, the assumption is that there is a small bowel obstruction (SBO). Evaluation for its etiology begins with basic abdominal films. Usually both flat and upright films are needed. In MI, abdominal films often show dilated loops of bowel with or without air-fluid levels. Air may not be present in the rectum if there is a complete obstruction. Abdominal calcifications may be present if there has been a contained or now closed intestinal perforation. The classic “soap-bubble” sign seen when meconium mixes with swallowed air may also be appreciated in the distal small intestine (Fig. 2) [21]. If abdomen is distended and peritoneal signs are present on physical exam or if the infant is hemodynamically unstable, assumption of complex MI will be made and the infant will be taken emergently to the operating room (OR). In a stable infant, a diagnostic contrast enema may be beneficial in detecting a microcolon due to proximal obstruction in the TI and disuse below the obstruction, as well as malrotation by localizing the position of the cecum. If malrotation is suspected based on results of the contrast enema, an upper gastrointestinal series (UGI) needs to be done to confirm diagnosis of malrotation and to better
evaluate for midgut volvulus. Findings on contrast studies will determine the next course of action for the multidisciplinary team. MI will need to be further defined as simple versus complex in order to decide whether to attempt a therapeutic contrast enema or to proceed directly to the OR. Malrotation with or without presence of volvulus requires surgical attention; however, the presence of volvulus is considered a surgical emergency.

Although MI can be associated with other etiologies, it is most often associated with CF, making it imperative to screen neonates with MI for CF [22]. This starts by confirming that newborn screening has been sent. The newborn screen is based on abnormally elevated levels of immunoreactive trypsinogen (IRT) detected in a dried blood spot on the Guthrie card [23]. IRT is a pancreatic enzyme precursor that is released into the bloodstream in the presence of pancreatic damage and is utilized as the selected biomarker suggestive of CF for newborn screening. However, falsely normal IRT blood levels have been reported in patients with MI [24–25]. This validates that
confirmation of the diagnosis of CF must be made using the gold standard sweat test or genetics [24–25]. A sweat chloride test can be done as early as 48 h after delivery if the infant is not edematous and is well hydrated, otherwise, genetic testing can be sought. However, most infants with MI are too small, malnourished, edematous, or critically ill for immediate sweat testing and will need to have primary genetic testing.

4. Routine management

Medical management of simple MI has been developed around the use of hyperosmolar enemas given under fluoroscopic guidance to ensure that the solution refluxes into/reaches the TI [16]. This technique was first described in 1969 by Noblett utilizing Gastrografin, which contains diatrizoate meglumine, 0.1% polysorbate 80 (Twee 80), and 37% organically bound iodine amounting to a solution with 1940 mOsm/L. [16] The mechanism of action is to act as a direct solvent and shift fluid into the bowel lumen instead of competing with the intracellular space surrounding the mucosa [26]. When utilizing such a hyperosmolar agent, adequate hydration (150 mL/kg/day minimum) via an IV line is imperative to avoid hypovolemia that can lead to shock and end-organ damage including necrotizing enterocolitis [1,4,27]. Presence of an IV line is also essential to respond appropriately to complications such as need for emergent surgical intervention. Most commonly with Gastrografin, a ¼–½ dilution with water is infused under low hydrostatic pressure through a catheter under fluoroscopy through the rectum until the terminal ileum is reached [4]. Perforation risk has been described as low as 2.7% and as high as 23% [28–30]. If hyperosmolar enema is unsuccessful, then surgical intervention is pursued (Fig. 3).

The primary surgical intervention is disimpaction of the meconium by irrigating the obstructed TI with warm saline or Gastrografin in the OR [15,27]. The subsequent creation of a continuous enterostomy such as the Bishop-Koop is preferred to allow for ongoing irrigation, if necessary, of the TI post-operatively. It also reduces the risk of postoperative complications of a primary enterostomy which can be as high as 30% [33–34]. Risks of creating an enterostomy include high output losses, especially of sodium. Bowel resection is reserved for more complex cases and is dependent on the extent of bowel injury. It can vary from simple resection with primary anastomosis to simple enterostomy with anastomosis several months later requiring minimal resection of small bowel (<10 cm) to more extensive bowel resection, involving both small bowel and colon, or removal of a meconium cyst.

In the case of simple MI, after the successful disimpaction of MI with the use of a hyperosmolar enema, Noblett recommended using 5 mL of 10% N-acetyl cysteine (NAC) via NGT every 6 h to dissolve meconium proximal to TI [16]. However, due to the potential risk of aspiration and chemical pneumonia from instilling NAC via NGT, currently it is more common to recommend the use of warm saline rectally every 12–24 h for several days to encourage further evacuation of meconium. This is often done in conjunction with serial abdominal films to evaluate for the presence of remaining meconium.

Although many different solutions have been used through time clinically and studied in animal models, Gastrografin continues to have the most efficacious outcomes of success both in man and mice [27]. Despite this evidence, Omnipaque (240–350 mOsm/kg water) and Cysto-contray II (400 mOsm/kg water), which are much less toxic and less hyperosmolar than Gastrografin, are currently the more commonly utilized agents, at least in the United States [1,27]. Rate of success of contrast enemas ranges widely from approximately 30–80% [1–2,31–32]. Our own anecdotal experience is similar, ranging from 30 to 50%.

Often infants with MI, especially those with complex MI requiring surgical intervention, will initially require TPN and lipids to support their growth. If possible, the lipid choice should favor an anti-inflammatory profile, including medium chain triglycerides (MCT) and fish oil to minimize risk of cholestasis. In Europe, SMOF lipid, which meets these criteria, is readily available and used routinely in these infants.

As soon as possible after resolution of MI, the GI tract should be utilized for enteral nutrition and feeds should be advanced as tolerated. Often in the presence of complex MI, due to poor perfusion of the intestine and necrosis during the initial period of small bowel obstruction, peritonitis, and potential surgical complications, infants benefit from amino acid-based or protein hydrolysate formulas rich in MCT oil (ideally 50%). Amino acid-based and protein hydrolysate formulas allow for easier digestion of proteins, while medium chain triglycerides (MCT) are directly absorbed into portal blood, bypassing the lymphatic system. As the infant continues to recover from the initial insult of MI, and GI tolerance improves, breastmilk or traditional formulas can be introduced.

Of note, in the presence of an enterostomy, excess intestinal sodium losses may result in total body sodium deficit [4]. Total body sodium deficit will often contribute to metabolic acidosis, poor weight gain, and will negatively impact growth [35–36]. It can be evaluated by checking spot urine sodium: creatinine ratio with goal for adequate growth being 17–52 mmol/mmol [35] or measuring sodium excretion in a spot urine. If either is low, treatment is supplementation of sodium until values are in the middle of the normal range. This can be done by increasing sodium in TPN or, if infant is tolerating enteral feeds, increasing sodium supplementation in enteral feeds.

The majority of infants with CF and MI, whether simple or complex, have pancreatic insufficiency (PI). Confirmation of PI is most efficiently and effectively done by obtaining a fecal elastase. However, the fecal elastase sample should be collected from rectally delivered, formed stools and not from an enterostomy. Watery stools from either an enterostomy or rectally delivered can result in falsely low fecal elastase values. Therefore, in infants with MI and an enterostomy, PI should be assumed and fecal elastase collected at a later date after the gastrointestinal tract is back in continuity and stools are at least of a pasty consistency to confirm diagnosis. Once the infant is able to take a minimal amount of formula or breastmilk by mouth or feeding tube, PERT should be initiated at 2000–4000 lipase units per 120 mL of formula [37]. PERT contains lipase to digest to lipids, amylase to digest carbohydrates, and protease to digest proteins. PERT dosing is based on lipase units per mL of formula or lipase units
Fig. 3. Algorithm for evaluation and management of suspected MI.

Bilious emesis +/- abdominal distension

Evaluation of vital signs and physical exam

Stabilize patient:
- Make infant NPO, establish IV access, and ensure adequate hydration
- Laboratory evaluation and correction of abnormalities +/- blood and urine cultures +/- antibiotics
- Place NGT to low intermittent wall suction (LIWS) and obtain basic abdominal films
- Obtain surgical and gastroenterology consults

*Ensure infant is in a NICU with an experienced multidisciplinary team*

Suspected Simple MI

Diagnostic Contrast Enema:
Evaluation of microcolon and malrotation
(Result of malrotation will require UGI for further evaluation of volvulus)

Clinical status of patient and imaging concerning for Complex MI

Surgical Intervention

Simple MI: Contrast Enema

*Confirm presence of IV line to ensure adequate hydration and to be prepared for potential complications*

Contrast enema under fluoroscopic guidance:
1. 1/4 - 1/5 dilution of hyperosmolar Gastrografin with water (~ 500 -1000 mOsm/L). Use ~ 10 mL/kg.
2. Full strength Omnipaque or Cysto-contray II (~ 250-400 mOsm/L). Use ~ 10 mL/kg.

Resolution of MI

Persistent MI

Consider use of warm saline enemas (~ 10 mL/kg) for continued evacuation of retained meconium every 12-24 hours.

*Sreevaluate with serial abdominal films looking for retained meconium every 12-24 hours*
per kilogram per meal. Infants require that PERT capsules be opened and enteric-coated beads be mixed in baby applesauce or other acidic baby fruit and delivered by mouth prior to each feed for bolus feeds or every 4 h for continuous feeds. This allows the enteric coating to be protected until it reaches the basic pH of the proximal duodenum, where the enteric coating dissolves and PERT is released to facilitate the digestion of nutrients. In addition to PERT, fat-soluble vitamin supplementation should be initiated as soon as possible after the infant is tolerating an appropriate amount of breastmilk or formula.

Gastric hypersecretion is common in patients with CF.[38] Combined with the lack of HCO3− secretion by the pancreas, this often precludes the basic environment in the proximal duodenum that is necessary for the activation of PERT. In vivo, PERT works effectively at a pH of 6–6.5[39–42]. One study evaluating duodenal pH in CF patients over a 24-hour period showed pH was <5 between 15 and 90% of the time and that there was a decrease in duodenal pH with each subsequent meal[43]. In a subset of patients in this same study, treating with acid suppressing medication showed significant improvement in weight gain and decrease in fat-malabsorption[43]. Another study showed that acid suppression improved the efficacy of PERT by decreasing the excretion of fecal fat significantly[44]. Both of these studies support the practice of utilizing acid suppressing medications, such as histamine blockers or proton-pump inhibitors (PPIs), to increase the pH of gastric and proximal duodenal fluid to optimize the efficacy of PERT[43,44].

5. Complications and their management

In the neonatal period, the most common complication of MI, especially for those with complex MI requiring surgical intervention, is elevated liver enzymes and cholestasis. This is secondary to the mixed pathophysiology of exposure to TPN and lipids, NPO status promoting biliary sludge, CFTR dysfunction within biliary ducts, and intestinal obstruction. Neonatal cholestasis seen in these patients will most often resolve completely within 3 months with weaning from TPN and lipids, introduction and advancement of enteral feedings, and the short-term use of polyethylene glycol could potentially prevent episodes of DIOS, thereby decreasing morbidity due to hospitalization and possible surgical intervention.

Another common complication of simple and complex MI, as well as CF in general, is the occurrence of small bowel bacterial overgrowth (SIBO). Patients with a history of MI are often at higher risk for delayed small bowel transit time due to history of injured bowel or surgical intervention. In addition, in the presence of surgical adhesions, these patients are at risk for intermittent partial SBO. These factors, combined with risk factors for SIBO common to all CF patients, including frequent use of antibiotics, prolonged use of acid suppression, PI, intestinal inflammation, and high rates of constipation, increase the risk of these patients developing SIBO even further[52]. Symptoms of SIBO often include abdominal pain, bloating, flatulence, and increase in malabsorptive, foul smelling, greasy stools. When symptomatic, SIBO can be treated with a monthly cycled short-course (5–7 days) of antibiotics including metronizadole (most commonly used), amoxicillin/clavulanic acid, or rifaximin. Probiotics have also been utilized, although the results in the literature vary significantly in terms of evaluating effectiveness.

6. Future directions

Although there has been evidence that modifier genes play a role in the development of MI, multiple studies have failed to replicate the same results. However, it is important to understand this relationship in order to identify fetuses at risk for the development of MI and develop novel interventions to decrease this risk. One potential intervention to consider is treatment of mothers with CFTR correctors and potentiators to act on abnormal CFTR in the fetus. Theoretically, if started early enough, it is possible that these medications could alter the natural progression of MI. Another potential prenatal intervention would be in utero surgical decompression of SBO or correction of MI to prevent development of microcolon or other complications. There have already been significant advancements in the field of in utero surgery as it relates to neurologic and urologic conditions.

It would also be interesting to see if modifier genes play a role in the risk of DIOS. For CF patients identified as high risk for the development of DIOS, prophylactic management with polyethylene glycol could potentially prevent episodes of DIOS, thereby decreasing morbidity due to hospitalization and possible surgical intervention.

A final area to explore would be the studying the microbiome of SIBO in CF with MI and developing therapeutic protocols for management of SIBO in these patients with specific pre and probiotics.

7. Clinical practice points

- It is imperative to evaluate every infant with MI for CF, as early diagnosis and management by a multidisciplinary team has shown to improve both short-term and long-term outcomes for these patients.
Newborn screening, which is based on IRT, can be falsely normal in MI and CF; therefore, patients with suspected MI should have further evaluation with sweat test and/or genetics to confirm the diagnosis of CF.

Infants with MI and an enterostomy should be presumed to have PI and PERT should be initiated as soon as volume of feeds is adequate.

Fecal elastase should be utilized to confirm the presence of PI once the gastrointestinal tract is in continuity and pasty stool is present. Watery stool from an enterostomy or rectally delivered can result in a falsely low fecal elastase.

Especially in the presence of an enterostomy, total body sodium deficit may contribute to poor weight gain and overall growth. It is imperative for this to be evaluated and corrected to achieve an optimal nutritional status.

Even with MI, overall prognosis with respect to lung function is identical to other CF patients. However, the risk for developing DIOS is much higher.

8. Summary

In conclusion, it is important to recognize that MI can be the 1st manifestation of CF. CF should therefore be high in the differential diagnosis of any infant who presents with MI, regardless of newborn screening results or ethnicity. A combination of factors, including early diagnosis of both MI and CF, an overall improvement in the multidisciplinary approach to the care of CF patients, and specific improvements in medical and surgical management of MI (use of contrast enemas to treat MI, better surgical techniques, and early implementation of nutritional support) has resulted in a prognosis for CF patients with MI that is comparable to those CF patients without MI. The advancement of science and ongoing quality improvement in clinical care continues to make the future for our CF patients more promising by positively impacting the morbidity and mortality of CF’s many manifestations.

Conflict of interest

Authors declare no conflict of interest.

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