A review of pathophysiology and management of fetuses and neonates with meconium ileus for the pediatric surgeon

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Abstract

\textbf{Purpose:} Meconium ileus (MI) is the earliest clinical manifestation of cystic fibrosis (CF), occurring in up to 20% of patients with CF. Our aim was to review and integrate current knowledge about the diagnosis and management of fetuses and neonates with MI that may aid the pediatric surgeon in caring for these patients.

\textbf{Methods:} We identified areas of interest including pathophysiology, prenatal diagnosis, nonoperative and operative management, postoperative management, and prognosis. We performed a Medline search using the search term \textit{meconium ileus} for English language articles published in the last 20 years. We reviewed reference lists to identify other articles of historical significance.

\textbf{Results:} Meconium ileus is primarily associated with CF transmembrane (conductance) regulator mutations F508del, G542X, W1282X, R553X, and G551D, and modifier genes have been found to explain approximately 17% of the phenotypic variability. Mouse, pig, and ferret models for CF demonstrate neonatal bowel obstruction mimicking MI. Sonographic findings of hyperechoic masses and dilated bowel in a high-risk fetus are suggestive of MI. Less than 7% of low-risk fetuses with hyperechoic bowel will have MI. Contemporary series of noninvasive management with Gastrografin enema report success rates of 36% to 39%, significantly lower than historical values. The optimal surgical technique remains controversial, although primary anastomosis results in surgical complication rates between 21\% and 31\%, higher than those noted with delayed anastomosis. Pulmonary function for patients with CF and MI at 15 and 25 years old is similar to those without MI, although height and weight percentiles may be lower.

\textbf{Conclusions:} This review for pediatric surgeons presents an examination of the literature and synthesizes current information about the pathophysiology, prenatal diagnosis, nonoperative and operative management, postoperative management, and prognosis of the patient with CF and MI.

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Although cystic fibrosis (CF) remains a life-shortening disease, primarily as a result of respiratory complications, the gastrointestinal tract is the first system affected...
clinically. Meconium ileus (MI) is the earliest manifestation of CF, occurring in up to 20% of patients with CF. Meconium ileus is characterized by thick, adhesive, desiccated meconium in the bowel lumen and a failure to pass meconium rectally. The natural course of untreated MI is uniformly poor. Recent studies show that long-term nutritional, pulmonary, and mortality outcomes of patients with CF and MI are no worse than outcomes of patients with CF without MI [1-3].

1. Pathophysiology of MI: insights from patients with CF and animal models

Cystic fibrosis is an autosomal recessive disease with a heterozygote frequency estimated to be as frequent as 1 in 25 non-Hispanic whites, 1 in 58 in Hispanic whites, 1 in 61 in African Americans, and 1 in 94 in Asian Americans [4]. Each offspring of 2 heterozygote parents has a 1 in 4 chance of developing the illness. In families that already have at least 1 child with CF complicated by MI, there is a 39% recurrence rate for MI in subsequent children [5].

Cystic fibrosis results from mutations in the gene, which codes for a cell membrane protein termed the **CF transmembrane (conductance) regulator** (CFTR), localized through linkage analysis to the long arm of human chromosome 7, band q31 in 1989 [6]. This protein is an adenosine 3′,5′ cyclic phosphate–induced chloride channel, which also regulates the flow of HCO₃⁻ ions across the apical surface of epithelial cells. An abnormal CFTR protein results in altered electrolyte content in the environment external to the apical surface of epithelial membranes. This leads to desiccation and reduced clearance of secretions from tubular structures lined by affected epithelia. In the sweat gland, CFTR dysfunction leads to inadequate resorption of sodium, chloride, and potassium.

A total of 1900 CFTR mutations have been reported to the CF Genetic Consortium as of January 2012 [7]. The most common mutation of the CFTR gene is F508del, a 3-base pair deletion of a phenylalanine residue at amino acid position 508 of CFTR. By the new nomenclature, its protein name is p.Phe508del, and its complementary DNA name is 1521_1523delCTT; it was previously termed ΔF508. Globally, 66% of patients with CF have at least 1 F508del mutation; however, there is wide variability within different ethnic and geographic populations. In Denmark, F508del represents 87.5% of CF mutations, whereas in Tunisia, F508del only accounts for 17.9% of mutations [8]. Worldwide, the mutations not attributable to F508del are a heterogeneous group; less than 20 mutations occur at a frequency of greater than 0.1%. The most common genotypes in people with MI are F508del, G542X, W1282X, R553X, and G551D [9]. Patients with 2 copies of the F508del mutation have a 24.9% chance of presenting with MI; F508del plus any “other” CF mutation confers 16.9% chance, and 2 “other” CF mutations confer a 12.5% chance of MI [9].

In 1992, the first CF mouse model (Cftr−/− UNC) was engineered. Newborn mice were noted to have severe intestinal obstruction at birth with minimal pulmonary or pancreatic involvement. This suggested that the role of pancreatic insufficiency in the development of MI was minimal, despite previous speculation that lack of protease caused MI. Since the first mouse CFTR knockout in 1992, a total of 11 CF mouse models have been characterized including 2 of the most common mutations, F508del and G551D [10,11]. Recently, a ferret and pig model CFTR knockout were engineered. Of note, the pig model shows 100% penetrance for MI. Similar to humans, CF pig meconium was sticky and adherent to the intestinal wall, and the site of obstruction ranged from the distal jejunum to the proximal spiral colon (equivalent to the human ascending colon). Inflammation was seen only as a secondary feature near sites of perforation and necrosis [12]. Gastrointestinal histopathology of CFTR−/− ferret kits having MI demonstrated intestinal luminal mucus and mucous cell hyperplasia; half of these kits died of intestinal perforation at the level of the ileum or colon [13].

Mouse models have been available longer, and thus, most intervention studies have been done in CF mice. Mouse models have shown that CFTR affects HCO₃⁻ transport via 2 separate mechanisms [14]. Quintron and others [15-17] note that patients with CF likely have defective HCO₃⁻ excretion in addition to the traditionally understood Cl⁻ excretion defect. The defective secretion of HCO₃⁻ creates an altered luminal environment that is more acidic and dehydrated than seen within the normal intestine and may be a factor in the pathophysiology of MI. In the process of normal mucogenesis, mucins are excreted into the bowel lumen by exocytosis in a tight matrix formation around Ca²⁺ ions. By chelating the Ca²⁺ ions, HCO₃⁻ helps to expand these mucins from a tight matrix into the loose, well-hydrated form that comprises normal mucus. This compacted, dehydrated mucus likely contributes to MI [18,19]. Strategies to improve the hydration state of the gut in CF mice can prevent lethal obstruction of the distal small intestine [20]. The findings from animal models about the roles of bicarbonate and gut hydration in MI should generate hypotheses but have not yet been translated to therapeutic interventions in humans.

Non-CFTR genetic factors also influence MI. In a twin study, Blackman et al found that 82% of monozygotic twins showed concordance for MI, whereas only 22% of dizygotic and 24% of 2 affected siblings showed concordance, thus providing strong evidence for the role of modifier genes in the pathogenesis of MI. In CF, initially chromosome 19q13.2 plus others and more recently 12p13.3 (ADIPOR2 gene) have been identified as possible modifier genes for MI; chromosome 4q13.3, 20p1.1.22, and 21q22.3 may be modifier genes that are protective for MI [21-23]. Recent genome-wide association studies have been able to account for approximately 17% of the phenotypic variability [24]; clearly, there are more genetic modifiers to be identified.
2. Prenatal and perinatal diagnosis and management

As of 2011, the American College of Obstetrics and Gynecology recommends that, as a routine part of obstetric care and regardless of ethnicity, all women of reproductive age should be offered preconception and prenatal CF carrier screening [4]. Antenatal diagnosis of MI can be made in 2 different groups, a high-risk group and a low-risk group. In the low-risk group, the diagnosis is suspected when the sonographic features seen in MI are found on routine prenatal ultrasound in a mother with a negative CF carrier screening.

![Suggested algorithm for management of patients with prenatal ultrasound suspicious for MI](image)

**Fig. 1** Suggested algorithm for management of patients with prenatal ultrasound suspicious for MI. A, This algorithm excludes families with a child with CF or mothers with CF but could be adapted to those situations. B, Maternal carrier screening is strongly recommended if it was not previously performed, but the ultrasound is suspicious for MI. C, Cystic fibrosis is unlikely but families and care providers should be aware that negative carrier screening cannot definitively rule out CF.
Screen. Sonographic findings consistent with MI in a fetus with parents who are known CF carriers and all pregnancies subsequent to the birth of a CF-affected child are considered high risk. An algorithm can be used in decision making and management of the fetus suspected of having MI based on prenatal ultrasound findings (Fig. 1).

2.1. Sonographic evaluation

Sonographic characteristics associated with MI include hyperechoic masses (inspissated meconium in the terminal ileum), dilated bowel, and nonvisualization of the gallbladder on prenatal sonogram. Normal fetal meconium, when visualized in the second and third trimesters, is usually hypoechoic or isoechoic to adjacent abdominal structures. A hyperechoic mass has been variably defined as one with sonographic density greater than that of liver or bone. As a sonographic marker of MI (Fig. 2), this finding is plagued by difficulties such as the subjective assessment of echogenicity and the lengthy associated differential diagnosis. In addition to MI, hyperechoic bowel has been reported with Down syndrome, intrauterine growth retardation, prematurity, in utero cytomegalovirus infection, intestinal atresia, intestinal duplication, internal hernia, meconium plug syndrome, or Hirschsprung disease [28].

In addition to the findings of increased abdominal echogenicity and bowel dilation, inability to visualize the gallbladder on fetal ultrasound has been associated with CF. Combined with other sonographic features, nonvisualization of the gallbladder can be useful in the prenatal detection of the disease. However, caution should be exercised in the interpretation of a nonvisualizing gallbladder because the differential also includes biliary atresia, omphalocele, diaphragmatic hernia, chromosomal abnormalities, and normal pregnancy [29].

Sonographic characteristics of fetal bowel obstruction are neither sensitive nor specific for MI; thus, the interpretation must include consideration of the risk of the fetus of having CF.

The prenatal diagnosis of MI using the sonographic feature of hyperechoic bowel must take into account the a priori genetic risk of the couple. The positive predictive value of hyperechoic masses in a high-risk fetus is estimated to be 52%, whereas in the low-risk fetus, the estimate is only 6.4% [26]. In a large regional study encompassing 573,820 newborn screening sonograms, Scotet et al [25] found 289 fetal cases of hyperechoic bowel. Of these, 7.6% were found to have CF, 3.7% had chromosome abnormalities, and 3.7% had maternofetal infections, and a disorder of any sort was diagnosed in 32.2% of fetuses. It is crucial to note that hyperechoic bowel, in both the second and third trimesters, has been found to be a normal variant. As many as 65% of cases detected by sonogram will resolve upon subsequent sonographic evaluation [27]. Although an increase in risk of MI and CF has been associated with hyperechoic bowel, most fetuses with hyperechoic bowel do not have MI or CF and may be a normal variant even in a family with a child with CF.

The finding of dilated bowel on prenatal ultrasound has been reported less frequently in association with CF than hyperechoic bowel [26]. In MI, bowel dilation is caused by obstruction by meconium but mimics similar findings with midgut volvulus, congenital bands, bowel atresia, intestinal duplication, internal hernia, meconium plug syndrome, or Hirschsprung disease [28].

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Fig. 2 Echogenic bowel with meconium pseudocyst in anterior right abdomen. Courtesy of Dr Mark Johnson (Children’s Hospital of Philadelphia) and Dr Beverly Coleman (University of Pennsylvania).

Fig. 3 Pathognomonic “soap bubble” sign owing to MI. Courtesy of Dr Dean Yacobucci (Women and Children’s Hospital of Buffalo).
2.2. Prenatal testing for CF

*CF transmembrane (conductance) regulator* analysis can be accomplished using a technique for recovering DNA from cells obtained from the parents by buccal brushing or directly by sampling blood. With this technique, the carrier status of parents suspected of having a fetus with CF based on sonographic findings of MI can be determined. Many region- and ethnic-specific commercial screening panels have been developed to reflect the mutations present in a specific population. The Technical Standards and Guidelines for CFTR Mutation Testing published by the American College of Medical Genetics recommends a panethnic panel that includes 23 common mutations. This panel identifies 94% of mutations found in Ashkenazi Jews, 88% in whites, 64% in African Americans, 72% in Hispanics, and 49% in Asian Americans [30]. Thus, negative tests must still be interpreted with some caution. Even complete gene sequencing along with evaluation for duplications and deletions is not 100% accurate in finding all CFTR mutations. For example, mutations in the promoter region cannot be identified. In addition, it is critical to understand that not all CFTR mutations cause CF. Thus, results of genetic testing need to be evaluated by someone with experience, preferably a genetic counselor.

If both parents have identified CF-causing mutations, subsequent evaluation of the fetus can be made by chorionic villus sampling or amniocentesis. If the results predict CF in the fetus, the mother should be followed up at a tertiary care facility for discussion of the diagnosis and further management.

3. Postnatal management

Meconium ileus is either simple or complicated. Each occurs with a frequency of approximately 50%. In the simple form, thickened meconium begins to form in utero, and because it obstructs the midileum, proximal dilatation, bowel wall thickening, and congestion occur (Fig. 3). Up to 26% of neonates may have abdominal calcifications, although only half are visible on plain radiograph [31]. In complicated MI, thickened meconium and obstruction lead to complications such as segmental volvulus, atresia, necrosis, perforation, meconium peritonitis (generalized), and giant meconium pseudocyst formation.

After birth, both simple and complicated MI should be managed as a newborn intestinal obstruction. Resuscitative measures including mechanical respiratory support, if necessary, and intravenous hydration are initiated along with gastric decompression, evaluation, and correction of any coagulation disorders and with empiric antibiotic coverage.

3.1. Nonoperative management

Helen Noblett [32] is credited with the first use of Gastrografin enemas in treating 4 infants with MI. Gastrografin is meglumine diatrizoate, a hyperosmolar, water-soluble, radiopaque solution containing 0.1% polysorbate 80 (Tween 80) and 37% organically bound iodine. The osmolarity of the solution is 1900 mOsm/L. Upon instillation, fluid is drawn into the intestinal lumen, hydrating and softening the meconium mass. Transient osmotic diarrhea and diuresis follow. Dr Noblett’s recognition of the need to hydrate the intestinal lumen presages our recent insights from CF mouse animal models.

Under fluoroscopic control, a 25% to 50% solution of Gastrografin is infused slowly at low hydrostatic pressure through a catheter inserted into the rectum. Escobar et al [33] found that 48% of neonates with CF and MI demonstrated microcolon on barium enema; “rabbit pellets” (scybala) of meconium may be seen (Fig. 4). Upon completion, the catheter is withdrawn, and an abdominal radiograph is obtained to rule out perforation. Upon return to the neonatal care unit, warm saline enemas containing 4% N-acetylcyesteine may be given to help complete the evacuation. Usually, there is rapid passage of semiliquid meconium, which continues in the ensuing 24 to 48 hours. Radiographs should be taken in 8 to 12 hours, or as clinically indicated, to confirm evacuation of the obstruction and to exclude late perforation. In the nonoperative management of MI, if evacuation is incomplete or if the first attempt at Gastrografin evacuation does not reflux contrast into dilated bowel, a second enema may be necessary. Reflux of the enema into the terminal ileum is critical for the bowel obstruction to be relieved [34]. Serial Gastrografin enemas can be performed at 12- to 24-hour intervals if necessary. Several other wetting agents have been investigated for use as therapeutic enema, but Gastrografin remains the most commonly used agent [35].

Fig. 4 “Microcolon of disuse” as seen on contrast enema and “rabbit pellets” or scybala of inspissated meconium. Courtesy of Dr Dean Yacobucci (Women and Children’s Hospital of Buffalo).
Historically, the addition of 1% N-acetylcysteine to the enema solution has been hypothesized to aid in dissolution of the inspissated meconium. Cystic fibrosis mice treated with N-acetylcysteine had 50% less mucus accumulation compared with control mice (measured histologically as dilation of the intestinal crypts) and 63% less small intestinal bacterial overgrowth (SIBO) but did not normalize small intestinal transit [36]. These findings in the CF mouse lend support to the clinical practice of use of adjunctive N-acetylcysteine.

Potential causes for late perforation include severe bowel distension by fluid osmotically drawn into the intestine or direct injury to the bowel mucosa by the contrast medium. Hypovolemic shock is a profound risk when delivering hypertonic enemas. The risk of rectal or colonic perforation can be avoided with careful placement of the catheter under fluoroscopic guidance and avoidance of inflating balloon-tipped catheters. Low pressure is important because Escobar et al found that 96% of neonates with CF and MI undergoing barium enema demonstrated a microcolon. An older study of 22 patients found a 23% perforation rate in patients when barium enema demonstrated a microcolon. An older study of et al found that 96% of neonates with CF and MI undergoing barium enema demonstrated a microcolon. An older study of 22 patients found a 23% perforation rate in patients when barium enema demonstrated a microcolon.

3.2. Operative management

The prognosis for infants with MI was uniformly poor despite surgical treatment before 1948, when Hiatt and Wilson [40] reported the first successful surgical management of 5 infants. They advocated intraoperative disimpaction of meconium with saline instilled into the bowel via a tube enterostomy [40]. Over the years, a number of surgical approaches in the treatment of uncomplicated MI have been proposed. The goals of operative management remain evacuation of meconium from the intestine, establishment of intestinal continuity, and preservation of maximal intestinal length.

The Mikulicz double-barreled enterostomy (Fig. 5A), first reported by Gross [41], is preferred by some because complete evacuation of inspissated meconium is not necessary and intra-abdominal anastomosis is avoided, thereby preventing the risk of anastomotic leakage. In addition, the bowel can be opened after complete closure of the abdominal wound, thereby reducing the risk of intraperitoneal contamination. A distal chimney enterostomy (Fig. 5B), described by Bishop and Koop [42] in 1957, involves resection with anastomosis between the end of the proximal segment and the side of the distal segment of bowel. The reverse of the Bishop-Koop enterostomy is the proximal enterostomy (Fig. 5C) described by Santulli and Blanc [43] in 1961. Like the distal chimney enterostomy, catheter access to the distal limb is placed, exiting through the stoma, thus providing means of irrigating the distal bowel. The apparent disadvantage with these techniques is the presence of a high output stoma and the inherent risk of dehydration. In 1970, O’Neill et al [44] described success with tube enterostomy (Fig. 5D) with and without resection. Harberg et al [45] described a similar procedure in which a T-tube enterostomy (Fig. 5E) is used. Fitzgerald and Conlon [46] later proposed performing appendectomy and inserting a cecostomy catheter through the appendiceal stump for instillation of irrigant and evacuation of impacted meconium.

Resection with primary anastomosis, first suggested by Swenson in 1962, met with initial difficulty and complication with leakage from the anastomosis. Improved results were reported by later investigators that emphasized the necessity of adequate resection of compromised bowel, complete proximal and distal evacuation of meconium, and preservation of adequate blood supply to the anastomosis [47,48]. In a recent study, Karimi et al [39] reviewed 41 patients with MI and compared resection with primary anastomosis to resection with enterostomy. They found that 21% of the primary anastomosis group developed peritonitis, whereas none of the resection with enterostomy group did. Jawaheer et al [49] found a 31% surgical complication rate in a report of MI treated with primary anastomosis. Del Pin et al [50], however, found no difference in morbidity with primary anastomosis vs resection with enterostomy. Thus far, studies have not been large enough to indisputably identify best practices for the surgical treatment of MI.

3.3. Postoperative care

Initial postoperative management involves ongoing resuscitation. The fluid losses from preoperative diuresis and diarrhea, if Gastrografin enema has been attempted, and from surgical losses must be carefully replaced. Ongoing maintenance fluids and replacement of insensible fluids as well as gastrointestinal losses (nasogastric suction and ileostomy) must be adjusted accordingly. Anecdotally, instillation of 4% N-acetylcysteine via a nasogastric tube or via ileostomy may help solubilize residual meconium, and findings from CF mouse models noted above lend support to this practice. Stomas placed in the course of surgical management should be closed as soon as possible (6-12 weeks) to help avoid prolonged problems with fluid, electrolyte, and nutritional losses.
3.3.1. Postnatal diagnosis of CF

In the patient with fetal or neonatal bowel obstruction, CF must be suspected, and diagnostic tests should be performed as soon as possible. Patients should have the diagnosis of CF confirmed or refuted by a sweat test performed using a technique, which meets all the Clinical and Laboratory Standards Institute standards (formerly National Committee on Clinical Laboratory Standards). Sweat tests may be performed any time after the first 48 hours of life, providing that the patient is not edematous. The test involves a transdermal application of pilocarpine to promote sweat gland secretion. To assure that the sweat glands have been maximally stimulated either 75 mg or 15 $\mu$L of sweat needs to be collected, depending on the technique used. Sweat quantity is more likely to be decreased if infants are African American, less than 36 weeks postmenstrual age, or less than 2000 g [51]. A result of 60 mmol/L or higher is considered diagnostic for CF, whereas results from 30 to 59 mmol/L are intermediate, and 29 mmol/L or less is a negative result in a neonate [52]. Patients with intermediate sweat test results on repeat examination and MI should be followed up in a CF center. Mutation analysis, performed on buccal or blood cells, is useful in diagnosis if it yields 2 known CF-causing mutations. Patients with confirmed CF should be referred to the regional CF center or affiliate center for counseling and education. A listing of accredited centers can be obtained by calling 1-800-FIGHT CF or from the Internet at www.cff.org.

Although MI is almost always associated with pancreatic insufficiency in patients with CF, a definitive test of pancreatic function should be performed [53]. In practice, the fecal elastase (FE) test has mostly replaced the classic coefficient of fat absorption test based on a timed stool
collection and measurement of fat intake [54]. Fecal elastase can be done on a small quantity of stool from a single specimen passed per rectum. Thus, patients with complex MI and an ostomy may not be able to have FE performed. Patients with CF and MI should be presumed to have pancreatic insufficiency, and treatment with pancreatic enzyme replacement therapy (PERT) should not be withheld while awaiting definitive evidence of pancreatic insufficiency. However, FE should be performed once bowel continuity has been restored; results are reliable even in a patient taking PERT.

3.3.2. Nutritional management

Infants with uncomplicated MI and CF may be given breast milk or routine infant formula, PERT, and vitamins [53]. Those who have a complicated surgical course will require either continuous enteral feedings or total parenteral nutrition (TPN). Patients who have had complicated MI and/or sizeable bowel resection and are being fed enterally may tolerate continuous feedings better than bolus feedings. Because the bowel mucosa may or may not be damaged by stasis, feedings are begun with predigested, diluted, formula, usually one-half strength and at low volume (Alimentum; Abbott Nutrition, Columbus, OH, or Pregestimil; Mead Johnson, Glenview, IL). If this is well tolerated, strength may be increased and then the volume, while observing for signs of feeding intolerance (ie, abdominal distention, hemepositive stools, and/or increasing emesis). Once oral feedings are begun, PERT must be given orally (even with predigested formula) starting at the historical recommendation of 2000 to 5000 lipase units per 120 mL of full strength formula [53]. For example, a 2.5-kg infant receiving 4 mL/kg per hour formula could be given 3000 lipase units orally every 12 hours. New infant dosage strength PERTs were approved by the Food and Drug Administration in June 2011 and may make dosing easier (Creon 3000 capsules and Zenpep 3000 capsules; Pancreaze 4, with 4200 lipase units per capsule, is also available). Pancreatic enzyme replacement therapy products also contain protease and amylase, but dosing is based primarily upon lipase content. Although PERT has been available commercially for more than 50 years, the Food and Drug Administration recently required all manufacturers of PERT to demonstrate efficacy and safety of these products. Capsules containing enteric-coated microspheres can be opened, and the contents, mixed with applesauce. This is then given orally. The microcapsules should not be crushed because this will expose the enzymes to the acid of the stomach where they will be inactivated. Uncrushed pancreatic enzymes should be given even with medium-chain triglyceride oil–containing formulas [55]. Desitin ointment (zinc oxide) can be applied to perianal skin to prevent skin breakdown from unabsorbed bile acids.

Infants who have had significant bowel resection (greater than one-third) may be difficult to manage, especially if the ileocecal valve has been resected. In addition, the presence of an ileostomy may lead to excessive loss of fluid and sodium. Patients with CF and an enterostomy have the double burden of excessive sweat and intestinal sodium losses and may have a total body sodium deficit that will not be reflected by serum sodium. The spot urinary sodium:creatinine ratio has been proposed as a more sensitive measure of sodium status, with a goal of 17 to 52 mmol/mmol [56]. Ostomies should be taken down as soon as possible. In the interim, if access to the distal, defunctionalized bowel is feasible, ostomy-drip feeds of gluten-free-enriched formula may be given at low volumes to enhance bowel growth, to help prevent bacterial translocation, and to minimize TPN-associated hepatic injury [57]. Infants with MI are at risk for cholestasis, particularly if they have had or are receiving TPN. Although neonatal cholestasis and later CF-related liver disease are different entities, Colombo et al [58] found that 35% of patients with CF and MI had liver disease, whereas only 12% of patients with CF without MI had liver disease. Alkaline phosphatase, alanine aminotransferase, and bilirubin (total and direct) should be monitored weekly.

Gastric acid hypersecretion is seen in patients who have short bowel syndrome [59]. An acid intestinal environment inactivates pancreatic enzymes and prevents dissolution of enteric-coated microcapsules and, as noted above, may affect mucus rheology. Proton pump inhibitors or histamine 2 receptor blockers may be useful as an adjunct to pancreatic enzyme therapy in patients who have had significant bowel resections, although their use may contribute to SIBO. Management of SIBO leads to improved growth in CF mice [36,60] and improved fat absorption in older patients with CF [61] but has not been explored as a treatment modality in infants with CF and MI who fail to thrive.

3.3.3. Pulmonary management

Although clinical lung disease does not usually develop early, mucus plugging and atelectasis can be seen. Inhaled albuterol twice a day followed by chest physiotherapy is initiated immediately postoperatively. The head-down position should not be used because this may increase the risk of gastroesophageal reflux and aspiration [53]. A surveillance endotracheal tube or oropharyngeal culture should be obtained and processed as CF sputum. Prophylactic antibiotics are not necessary and antibiotic therapy is directed based on respiratory tract cultures if needed. If aminoglycosides are given, the dose is likely to be higher than in other patients [62].

4. Prognosis

Early series, subsequent to the report of Hiatt and Wilson of the first survivors with MI in 1948, showed discouraging mortality rates. With the advent of improved nonoperative and operative treatments, good nutritional support, and better treatment of bacterial infection, the prognosis for infants with both simple and complicated MI has improved dramatically. Survival rates approaching 100% have been reported [33,50,63]. Generally, once infants are discharged from the
hospital, they do well. Encouragingly, one of the best predictors of prognosis is birth cohort, with patients born in more recent years doing better than those born in previous decades [64].

Several recent studies indicate that the long-term health of patients with CF and MI is as good as those of patients with CF only. Researchers in Israel followed up patients for, on average, 24.9 years and reported no significant difference in pulmonary status (measured by pulmonary function tests) and nutritional status (measured by body mass index) in patients with MI and without MI. They also found no difference in pulmonary outcomes in patients treated surgically for MI and patients treated medically for MI [2]. Munck et al [1] found similar results in that there was no difference in nutritional status or pulmonary function at 15 years old. Johnson et al [3] did not find a difference in pulmonary status and nutritional health between these groups. In addition, there was no difference in the time to first pseudomonas colonization in patients with CF and MI and CF only [3]. There are some older studies that contradict these results, however. For instance, Lai et al [65] found that patients with CF and MI had lower length percentile (33 ± 6 vs 48 ± 4) and weight percentile (21 ± 4 vs 39 ± 4) than patients with CF only.

5. Conclusion

Progress in the perinatal diagnosis and management of MI and CF as well as our understanding of the CFTR protein has vastly improved the outlook of affected infants. Continued success in the management of these patients will depend upon prenatal diagnosis, multidisciplinary care, and innovative strategies in therapy. The goals for the future should thus include exploration of new ways to reduce perinatal complications, which add to morbidity, mortality, and the cost of medical care. With the ability to detect both MI and CF prenatally, we should begin to consider strategies that can prevent the progression of simple MI to complex MI. In addition, with the creation of mouse, ferret, and pig models for CF, we have a unique opportunity to study the basic pathophysiology of MI and improve care based on these insights. This review for pediatric surgeons presents an examination of the literature and synthesizes current information about the pathophysiology, prenatal diagnosis, nonoperative and operative management, postoperative management, and prognosis of the patient with CF and MI.

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