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Intestinal Obstruction Syndromes in Cystic Fibrosis: Meconium Ileus, Distal Intestinal Obstruction Syndrome, and Constipation

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Abstract Meconium ileus at birth, distal intestinal obstruction syndrome (DIOS), and constipation are an interrelated group of intestinal obstruction syndromes with a variable severity of obstruction that occurs in cystic fibrosis patients. Long-term follow-up studies show that today meconium ileus is not a risk factor for impaired nutritional status, pulmonary function, or survival. DIOS and constipation are frequently seen in cystic fibrosis patients, especially later in life; genetic, dietary, and other associations have been explored. Diagnosis of DIOS is based on suggestive symptoms, with a right lower quadrant mass confirmed on abdominal radiography, whereas symptoms of constipation are milder and of longer standing. In DIOS, early aggressive laxative treatment with oral laxatives (polyethylene glycol) or intestinal lavage with balanced osmotic electrolyte solution and rehydration is required, which now makes the need for surgical interventions rare. Constipation can generally be well controlled with polyethylene glycol maintenance treatment.

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Introduction

The survival of cystic fibrosis (CF) patients has dramatically improved because of centralized management of patients in specialized CF centers, more aggressive use of antibiotics, and intensive nutritional support [1]. Cystic fibrosis is mainly characterized by exocrine pancreatic insufficiency and progressive pulmonary disease, but with the improved life expectancy, less frequent and less severe manifestations of CF, such as the intestinal obstruction syndromes, are becoming clinically more relevant.

Meconium ileus (MI) at birth, distal intestinal obstruction syndrome (DIOS, formerly designated "meconium ileus equivalent"), and constipation are all consequences of the increased viscosity of intestinal mucus and the prolonged intestinal transit time in CF [2–5]. Meconium ileus is unique to CF and is characterized by complete intestinal obstruction in the neonatal period caused by accumulation of inspissated meconium. After the neonatal period, DIOS emerges, characterized by complete or incomplete intestinal obstruction of viscid fecal accumulation in the terminal ileum and proximal colon. Characteristically, DIOS patients have abdominal pain, distension, and vomiting in combination with a right lower quadrant mass, which is palpable and usually seen on plain abdominal radiography. An important

differential diagnosis of DIOS is constipation. However, in contrast to DIOS, symptoms are usually milder and of longer standing. Each condition is frequently seen in CF patients, with constipation in particular being greatly underdiagnosed in CF [6•]. This review describes the incidence, genetics, risk factors, diagnosis, and treatment of MI, DIOS, and constipation in CF.

Incidence and Prevalence

Meconium Ileus Occurs at Birth in 13% to 17% of All CF Patients [7–10]

Studies on the incidence and prevalence of DIOS and constipation are difficult to compare because of the different definitions used. The recent consensus guidelines issued by the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) CF Working Group define DIOS as an acute, complete or incomplete, fecal obstruction in the ileocecum, whereas constipation is defined as gradual fecal impaction of the total colon (Tables 1 and 2) [10]. Using these definitions, both the incidence (2.2–6.2 episodes per 1000 patient-years) and lifetime prevalence (7–8%) of DIOS in childhood is low [9, 11•, 12, 13]. Two studies report that DIOS incidence and lifetime prevalence increase as patients become older [12, 13]; indeed, incidence (23.3 episodes per 1000 patient-years) and lifetime prevalence (14–16%) are higher in adult patients [12–14]. Additionally, DIOS is recurrent medical issue, because 20% of all pediatric patients experienced more than one episode during a 5-year observation period [11•].

Reports on lifetime prevalence of constipation are scarce; only two studies for pediatric patients (published in 1986 and 2010) [9, 13] and one for adult patients (published in 1986) [13] are available. They show that constipation is very common in both pediatric (lifetime prevalence 26–47%) and adult (lifetime prevalence 42%) CF patients [9, 13]. In the pediatric population, the prevalence of constipation seems to have increased over time [9, 13]. However, this might be a false image, because the use of laxatives was a key component in establishing constipation in both reports, and laxatives probably are prescribed more readily now in CF patients suspected of constipation, especially because current laxatives are almost devoid of side effects [15].

Genetics

Meconium Ileus

Meconium ileus occurs in 13–17% of all CF patients at birth [7–10], and is clearly influenced by genetic factors, because a large twin study reports that monozygous twins show a greater concordance for MI than dizygous twins [10]. This variation can be partially explained by the *cystic fibrosis transmembrane regulator* (*CFTR)* genotype. For example, homozygosity for the delta F508 deletion, the most common *CFTR* mutation in CF patients, is strongly associated with the presence of MI [10]. However non-*CFTR* genes (ie, modifier genes) also influence the risk for developing MI [10, 16, 17]. Several genes and regions have been reported to be associated with MI [9, 10, 16–18], but a solid association between a causal modifier gene and MI has yet to be discovered. Rozmahel et al. [18] were the first to report a modifier locus for MI (*Cfm1*) on chromosome 7 in a murine CF model. Subsequently, several markers on human chromosome 19, the region syntenic to the mouse locus, showed significant linkage with the presence of MI in 185 CF sibling pairs [16]. However, in a genome-wide analysis in more than 1000 patients, this reported linkage between *CFM1* and MI could not be replicated [10]. Thus, a role of *CFM1* in the development of MI seems to be unlikely. The genome-wide analysis by Dorfman et al. [17] provided two new candidate modifier genes (*ADIPOR2* and *SLC4A4*), although the function of these genes and their relation to MI are unknown. In addition, we recently reported an association between a variant in the *CLCA1* gene and MI in European CF patients [9]. The *CLCA1* gene and its ortholog in mice, *Clca3*, encode a calcium-activated chloride channel. Recent studies show an important role for CLCA1/Clca3 in intestinal obstruction in CF; the expression of *Clca3* in the intestine of CF mice, which all die of intestinal obstruction, is decreased [19, 20], and up-regulation of *Clca3* in CF mice results in ameliorated intestinal disease and improved survival [20].

Table 1 European society for pediatric gastroenterology, hepatology, and nutrition CF working group definition for distal intestinal obstruction syndrome (DIOS) in cystic fibrosis

1	Complete intestinal obstruction as evidenced by vomiting of bilious material and/or fluid levels in small intestine on abdominal radiography
2	Fecal mass in ileocecum
3	Abdominal pain and/or distension

Complete DIOS: 1, 2, and 3

Incomplete/impending DIOS: 2 and 3, without 1

Table 2 European society for pediatric gastroenterology, hepatology, and nutrition CF working group definition for constipation in cystic fibrosis

1	Abdominal pain and/or distension
2a	Reduced frequency of bowel movements in the past few weeks or months
2b	Increased consistency of stools in the past few weeks or months
3	Symptoms 1 and 2 are relieved by the use of laxatives

Constipation: 1 or 2a or 2b and 3

DIOS and Constipation

Some studies report an increased frequency of severe *CFTR* genotypes in DIOS [14, 11•], whereas others report no differences [10], and a large twin study shows equally low concordance rates for DIOS in monozygous and dizygous twins [10]. Constipation in CF is not associated with a severe *CFTR* genotype [6•]. Therefore, genetic factors, both *CFTR* and non-*CFTR,* seem not to play an important role in DIOS or constipation in CF.

Risk Factors

Relationship with Diet

The relationship between pancreatic insufficiency, or poorly controlled steatorrhea, and constipation or DIOS is unclear; conflicting results have been published. In general, it is thought that constipation correlates with high doses of pancreatic supplements [21, 22]. However, this is not supported by Baker et al. [23], who report no correlation between constipation and the dosage of pancreatic supplements. We recently found that constipated patients had a lower total fat absorption than control patients, although both patient groups (with and without constipation) had adequate control of steatorrhea, with a mean total fat absorption of 86% and 90%, respectively [6•]. Koletzko et al. [24] also describe a higher fat excretion in DIOS patients compared to controls. Slow intestinal transit, as is frequently seen in CF [2, 3], could be aggravated by a high percentage of undigested food and may promote the accumulation of fecal material.

Furthermore, fiber and fluid intake are not correlated with constipation in CF [6•, 25], despite the general opinion that inadequate fluid and fiber intake is an etiological factor of constipation in CF [13].

Relationship with Other Gastrointestinal CF Manifestations

The relationship between MI and CF-related liver disease is unclear; some report a higher frequency of MI in patients with CF-related liver disease [26–28], but others report no differences [29–32, 33•]. One study even reports a significantly lower frequency of MI in patients with CF-related liver disease [34].

A relatively new research topic in CF is intestinal inflammation. In the majority of the general CF population, intestinal inflammation is present, as evidenced directly by capsule endoscopy or indirectly by elevated fecal calprotectin levels [35, 36]. More specifically, ileal biopsies from both MI and DIOS patients also show signs of intestinal inflammation, especially in the myenteric ganglion cells and myocytes [37•]. This intestinal inflammation may play a role in the development of intestinal obstruction in CF, either directly or indirectly, through delaying intestinal transit time.

We found a surprisingly high frequency of MI in patients with gastroesophageal reflux disease (42%) compared to controls (10%) [38]. Our findings are supported by a study reporting a higher number of reflux episodes in MI patients [39]. Furthermore, gastrointestinal motility disorders are frequently reported in CF. For example, CF patients with symptoms suggesting gastroesophageal reflux may have esophageal motility defects [40], and in the general CF population, prolonged intestinal transit time is described [2, 3]. Although the intestinal transit time in MI patients is unknown, the association between gastroesophageal reflux disease and MI suggests common defects in gastrointestinal motility.

After lung transplantation, DIOS is frequently seen; about 10% to 20% of CF lung transplant patients develop at least one DIOS episode early in the post-transplant period [41]. The transplantation period is characterized by dehydration, immobility, and opiate use, and in combination with predisposing factors (eg, MI or abdominal surgery), could promote fecal impaction in the ileocecum, eventually leading to complete intestinal obstruction in selected patients. As in the general CF population [10], DIOS occurs mainly in patients with a history of MI or laparotomy [41]. Therefore, starting preventive laxative treatment in these high-risk patients after lung transplantation could be considered.

Diagnostic Investigations

Constipation is a clinical diagnosis based on a careful history and physical examination. The recent definition of constipation includes 1) abdominal pain and/or distension, or 2a) a reduced frequency of bowel movements in the past few weeks, and/or 2b) increased consistency of stools in the past few weeks, while 3) the symptoms are relieved by the use of laxatives [11•]. Additionally, complete DIOS is defined as the combination of 1) complete intestinal obstruction, as evidenced by vomiting of bilious material and/or fluid levels in the small intestine on an abdominal radiography, with 2) a fecal mass in the ileocecum, and 3) abdominal pain and/or

distension. Incomplete or impending DIOS is defined as a short history (days) of abdominal pain and/or distension and a fecal mass in the ileocecum, but without signs of complete intestinal obstruction [11•]. Despite these strict definitions, diagnosing constipation or DIOS can be a real challenge. Abdominal radiography in CF patients, using the Barr and Leech scoring systems, has both a poor value for diagnosing constipation and poor inter- and intraobserver variability [6•]. Consequently, abdominal radiography is not recommended as a standard diagnostic tool in the regular gastrointestinal follow-up of CF patients. However, abdominal radiography is useful to differentiate between constipation and DIOS in CF patients with acute abdominal pain, because DIOS patients have a fecal mass in the ileocecum with or without fluid levels in the small intestine, whereas constipation patients have a distribution of fecal material throughout the colon [11•]. Therefore, plain abdominal radiography is recommended in CF patients with acute abdominal pain.

Treatment and Long-Term Effects

Meconium Ileus

Survival in patients with MI has improved dramatically; Kerem et al. [7] report that survival through the first year of life increased from 55% in CF patients born between 1958 and 1972 to 96% in those born between 1973 and 1987. More recent articles even report no differences in survival between MI and non-MI patients [33•, 42•]. Nutritional status follows the same trend as survival; an older study showed worse long-term nutritional outcomes in MI patients [7], but more recent reports show no differences between MI and non-MI patients [33•, 42•, 43–45]. In contrast, the long-term outcome of pulmonary function in MI patients is less uniform between the MI and non-MI groups. Although the majority of papers report no differences between patients with or without MI [8, 33•, 42•, 43], two other studies report a worse pulmonary function in MI patients. These ambiguities could be explained by the control groups used; the first studies used controls who were diagnosed based on suggestive symptoms of CF [8, 33•, 42•, 43], whereas the last two studies used matched controls diagnosed in infancy through a newborn screening program [45, 46]. Consequently, this suggests that MI patients have a worse pulmonary phenotype, when corrections for the advantage of early detection and treatment were made.

DIOS and Constipation

Most DIOS episodes can be treated conservatively with intensive laxative treatment (oral laxatives and/or enema or polyethylene glycol lavage), and most large studies report low numbers of surgical interventions [11•, 13, 14]. Nevertheless, the frequency of surgery varies widely among studies (0–11%) [11•, 12–14, 41].

For treatment of constipation, we prefer polyethylene glycol, because it is more effective and does not have the adverse events inherent to lactulose (flatulence and abdominal cramps) [15]. For DIOS patients, treatment is still largely empiric because there are no reported trials. It is generally recommended to start with an oral laxative (polyethylene glycol), with or without an enema, and restoration of adequate hydration, in patients with impending DIOS and in those with complete DIOS, at least in patients who do not vomit [47]. When this treatment is not effective, or in more severe DIOS episodes, intestinal polyethylene glycol lavage with a balanced electrolyte osmotic solution is started orally or via nasogastric tube. In rare cases, the retrograde use of meglumine diatrizoate (Gastrografin; Schering AG, Berlin, Germany) can be considered, although this intervention might have serious complications, such as fluid shift from the circulation to the bowel leading to shock, perforation, and necrotizing enterocolitis [47]. Surgery should be used if conservative treatment is not successful; however, with early aggressive medical management, surgery is seldom required.

Because most DIOS patients have more than one episode, continuation of the laxative treatment (polyethylene glycol) after the first DIOS episode can be considered and seems logical, although no published evidence for this approach is available. Furthermore, dehydration and fat malabsorption (coefficient of fat absorption < 85%) should be avoided to prevent recurrence. Finally, in transplantation patients, pre-transplant bowel preparation with polyethylene glycol and early postoperative start of enteral feeding seem appropriate, as does adequate use of pancreatic enzymes and polyethylene glycol [41].

Conclusions

Intestinal obstruction syndromes are significant issues for CF patients. Long-term outcomes for MI have improved dramatically, and today no differences are seen between MI and non-MI patients. Later in life, DIOS becomes an issue, with a lifetime prevalence of 8% in pediatric CF patients and 16% in adult CF patients. In DIOS, early aggressive laxative treatment with oral laxatives (polyethylene glycol) or intestinal lavage with balanced osmotic electrolyte solution is almost always effective, making surgical interventions rare. With adequate use of polyethylene glycol, constipation, which is frequently seen in CF, can generally be well controlled.

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References

Papers of particular interest, published recently, have been highlighted as:
• Of importance

1. Slieker MG, Uiterwaal CS, Sinaasappel M, et al. Birth prevalence and survival in cystic fibrosis: a national cohort study in the Netherlands. Chest. 2005;128:2309–15.
2. Bali A, Stableforth DE, Asquith P. Prolonged small-intestinal transit time in cystic fibrosis. Br Med J. 1983;287:1011–3.
3. Escobar H, Perdomo M, Vasconez F, et al. Intestinal permeability to 51Cr-EDTA and orocecal transit time in cystic fibrosis. J Pediatr Gastroenterol Nutr. 1992;14:204–7.
4. Sinaasappel M. Relationship between intestinal function and chloride secretion in patients with cystic fibrosis. Neth J Med. 1992;41:110–4.
5. Mall M, Kreda SM, Mengos A, et al. The DeltaF508 mutation results in loss of CFTR function and mature protein in native human colon. Gastroenterology. 2004;126:32–41.
6. • van der Doef HP, Kokke FT, Beek FJ, et al. Constipation in pediatric cystic fibrosis patients: an underestimated medical condition. J Cyst Fibros 2010;9:59–63. *This is the most recent overview article of constipation in CF, reporting prevalence, diagnosis, risk factors, and treatment of constipation at our center.*
7. Kerem E, Corey M, Kerem B, et al. Clinical and genetic comparisons of patients with cystic fibrosis, with or without meconium ileus. J Pediatr. 1989;114:767–73.
8. Kappler M, Feilcke M, Schröter C, et al. Long-term pulmonary outcome after meconium ileus in cystic fibrosis. Pediatr Pulmonol. 2009;44:1201–6.
9. van der Doef HP, Slieker MG, Staab D, et al. Association of the CLCA1 p.S357N variant with meconium ileus in European patients with cystic fibrosis. J Pediatr Gastroenterol Nutr. 2010;50:347–9.
10. Blackman SM, Deering-Brose R, McWilliams R, et al. Relative contribution of genetic and nongenetic modifiers to intestinal obstruction in cystic fibrosis. Gastroenterology. 2006;131:1030–9.
11. • Houwen RH, van der Doef HP, Sermet I, et al. Defining DIOS and constipation in Cystic Fibrosis with a multicenter study on the incidence, characteristics and treatment of DIOS. J Pediatr Gastroenterol Nutr 2010;50:38–42. *This report of the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition CF Working Group defining DIOS and constipation in CF makes a clear distinction between these conditions*.
12. Andersen HO, Hjelt K, Waever E, et al. The age-related incidence of meconium ileus equivalent in a cystic fibrosis population: the impact of high-energy intake. J Pediatr Gastroenterol Nutr. 1990;11:356–60.
13. Rubinstein S, Moss R, Lewiston N. Constipation and meconium ileus equivalent in patients with cystic fibrosis. Pediatrics. 1986;78:473–9.
14. Dray X, Bienvenu T, Desmazes-Dufeu N, et al. Distal intestinal obstruction syndrome in adults with cystic fibrosis. Clin Gastroenterol Hepatol. 2004;2:498–503.
15. Lee-Robichaud H, Thomas K, Morgan J, Nelson RL. Lactulose versus polyethylene glycol for chronic constipation. Cochrane Database Syst Rev. 2010;7:CD007570.
16. Zielenski J, Corey M, Rozmahel R, et al. Detection of a cystic fibrosis modifier locus for meconium ileus on human chromosome 19q13. Nat Genet. 1999;22:128–9.
17. Dorfman R, Li W, Sun L, et al. Modifier gene study of meconium ileus in cystic fibrosis: statistical considerations and gene mapping results. Hum Genet 2009; [Epub ahead of print]
18. Rozmahel R, Wilschanski M, Matin A, et al. Modulation of disease severity in cystic fibrosis transmembrane conductance regulator deficient mice by a secondary genetic factor. Nat Genet. 1996;12:280–7.
19. Brouillard F, Bensalem N, Hinzpeter A, et al. Blue native/SDS-PAGE analysis reveals reduced expression of the mClCA3 protein in cystic fibrosis knock-out mice. Mol Cell Proteomics. 2005;4:1762–75.
20. Young FD, Newbigging S, Choi C, et al. Amelioration of cystic fibrosis intestinal mucous disease in mice by restoration of mCLCA3. Gastroenterology. 2007;133:1928–37.
21. Littlewood JM, Wolfe SP, Conway SP. Diagnosis and treatment of intestinal malabsorption in cystic fibrosis. Pediatr Pulmonol. 2006;41:35–49.
22. Sinaasappel M, Stern M, Littlewood J, et al. Nutrition in patients with cystic fibrosis: a European Consensus. J Cyst Fibros. 2002;1:51–75.
23. Baker SS, Borowitz D, Duffy L, et al. Pancreatic enzyme therapy and clinical outcomes in patients with cystic fibrosis. J Pediatr. 2005;146:189–93.
24. Koletzko S, Corey M, Ellis L, et al. Effects of cisapride in patients with cystic fibrosis and distal intestinal obstruction syndrome. J Pediatr. 1990;117:815–22.
25. Proesmans M, De Boeck K. Evaluation of dietary fiber intake in Belgian children with cystic fibrosis: is there a link with gastrointestinal complaints? J Pediatr Gastroenterol Nutr. 2002;35:610–4.
26. Colombo C, Battezzati PM, Crosignani A, et al. Liver disease in cystic fibrosis: a prospective study on incidence, risk factors, and outcome. Hepatology. 2002;36:1374–82.
27. Minicucci L, Lorini R, Giannattasio A, et al. Liver disease as risk factor for cystic fibrosis-related diabetes development. Acta Paediatr. 2007;96:736–9.
28. Lamireau T, Monnereau S, Martin S, et al. Epidemiology of liver disease in cystic fibrosis: a longitudinal study. J Hepatol. 2004;41:920–5.
29. Lindblad A, Glaumann H, Strandvik B. A two-year prospective study of the effect of ursodeoxycholic acid on urinary bile acid excretion and liver morphology in cystic fibrosis-associated liver disease. Hepatology. 1998;27:166–74.
30. Wilschanski M, Rivlin J, Cohen S, et al. Clinical and genetic risk factors for cystic fibrosis-related liver disease. Pediatrics. 1999;103:52–7.
31. Slieker MG, Deckers-Kocken JM, Uiterwaal CS, et al. Risk factors for the development of cystic fibrosis related liver disease. Hepatology. 2003;38:775–6.
32. Ling SC, Wilkinson JD, Hollman AS, et al. The evolution of liver disease in cystic fibrosis. Arch Dis Child. 1999;81:129–32.
33. • Efrati O, Nir J, Fraser D, et al. Meconium ileus in patients with cystic fibrosis is not a risk factor for clinical deterioration and survival: the Israeli Multicenter Study. J Pediatr Gastroenterol Nutr 2010;50:173–8. *Efrati et al. (together with the paper by Johnson et al. [42•]) give a complete overview of the improved nutritional status, pulmonary function, and survival of meconium ileus patients today.*
34. Corbett K, Kelleher S, Rowland M, et al. Cystic fibrosis-associated liver disease: a population-based study. J Pediatr. 2004;145:327–32.

35. Bruzzese E, Raia V, Gaudiello G, et al. Intestinal inflammation is a frequent feature of cystic fibrosis and is reduced by probiotic administration. Aliment Pharmacol Ther. 2004;20:813–9.
36. Werlin SL, Benuri-Silbiger I, Kerem E, et al. Evidence of intestinal inflammation in patients with cystic fibrosis. J Pediatr Gastroenterol Nutr. 2010;51:304–8.
37. • Smith VV, Schäppi MG, Bisset WM, et al. Lymphocytic leiomyositis and myenteric ganglionitis are intrinsic features of cystic fibrosis: studies in distal intestinal obstruction syndrome and meconium ileus. J Pediatr Gastroenterol Nutr 2009;49:42–51. *This is the first report of intestinal inflammation in ileal biopsies of patients with DIOS and meconium ileus*.
38. van der Doef HP, Arets HG, Froeling SP, et al. Gastric acid inhibition for fat malabsorption or gastroesophageal reflux disease in cystic fibrosis: longitudinal effect on bacterial colonization and pulmonary function. J Pediatr. 2009;155:629–33.
39. Heine RG, Button BM, Olinsky A, et al. Gastro-oesophageal reflux in infants under 6 months with cystic fibrosis. Arch Dis Child. 1998;78:44–8.
40. Cucchiara S, Santamaria F, Andreotti MR, et al. Mechanisms of gastro-oesophageal reflux in cystic fibrosis. Arch Dis Child. 1991;66:617–22.
41. Gilljam M, Chaparro C, Tullis E, et al. GI complications after lung transplantation in patients with cystic fibrosis. Chest. 2003;123:37–41.
42. • Johnson JA, Bush A, Buchdahl R. Does presenting with meconium ileus affect the prognosis of children with cystic fibrosis? Pediatr Pulmonol 2010;45:951–8. *Johnson et al. (together with the paper by Efrati et al. [33•]) give a complete overview of the improved nutritional status, pulmonary function, and survival of patients with meconium ileus today.*
43. Munck A, Gérardin M, Alberti C, et al. Clinical outcome of cystic fibrosis presenting with or without meconium ileus: a matched cohort study. J Pediatr Surg. 2006;41:1556–60.
44. Fuchs JR, Langer JC. Long-term outcome after neonatal meconium obstruction. Pediatrics. 1998;101:E7.
45. Evans AK, Fitzgerald DA, McKay KO. The impact of meconium ileus on the clinical course of children with cystic fibrosis. Eur Respir J. 2001;18:784–9.
46. Li Z, Lai HJ, Kosorok MR, et al. Longitudinal pulmonary status of cystic fibrosis children with meconium ileus. Pediatr Pulmonol. 2004;38:277–84.
47. Colombo C, Ellemunter H, Houwen R, et al. Guidelines for the diagnosis and management of distal intestinal obstruction syndrome in cystic fibrosis patients. J Cyst Fibros. In press.