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Original Article

International prospective study of distal intestinal obstruction syndrome in cystic fibrosis: Associated factors and outcome☆

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Abstract

Background: Distal intestinal obstruction syndrome (DIOS) is a specific complication of cystic fibrosis.
Methods: A study was performed in 10 countries to prospectively evaluate the incidence, associated factors, and treatment modalities in children and adults.

Abbreviations: CF, Cystic fibrosis; CFRD, CF-related diabetes; DIOS, Distal intestinal obstruction syndrome; I DIOS, Incomplete distal intestinal obstruction syndrome; C DIOS, Complete distal intestinal obstruction syndrome; EPI, Exocrine pancreatic insufficiency; FEV1, Forced expiratory volume in 1 s; MI, Meconium ileus

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Results: 102 patients presented 112 episodes. The incidence of DIOS was similar in children and adults. Medical treatment failed only in cases of complete DIOS (11%). Children with meconium ileus had a higher rate of surgery for DIOS (15% *vs.* 2%, p = 0.02). Complete DIOS entailed longer hospitalisation (4 [3; 7] days *vs.* 3 [1; 4], p = 0.002). Delayed arrival at hospital and prior weight loss had a significant impact on the time needed for DIOS resolution. Associated CF co-morbidities for DIOS included meconium ileus (40% *vs.* 18%, p < 0.0001), exocrine pancreatic insufficiency (92% *vs.* 84%, p = 0.03), liver disease (22% *vs.* 12%, p = 0.004), diabetes mellitus (49% *vs.* 25%, p = 0.0003), and Pseudomonas *aeruginosa* (68% *vs.* 52%, p = 0.01); low fibre intake and insufficient hydration were frequently observed. Female gender was associated with recurrent DIOS (75% *vs.* 52%, p = 0.04), constipation with incomplete episodes (39% *vs.* 11%, p = 0.03), and poor patient compliance in taking pancreatic enzyme therapy during complete episodes (25% vs. 3%, p = 0.02).
Conclusion: DIOS is a multifactorial condition having a similar incidence in children and adults. We show that delayed arrival at hospital after the initial symptoms causes significant morbidity. Early recognition and treatment would improve the prognosis.

Keywords: Cystic fibrosis; Abdominal pain; Distal intestinal obstruction syndrome; Incidence

1. Introduction

Distal intestinal obstruction syndrome (DIOS) is a distinct gastrointestinal complication occurring in persons with cystic fibrosis (CF). It is characterised by accumulation of viscous faecal material, combined with sticky mucous secretions located in the distal ileum and caecum that adhere to the intestinal wall. Since symptoms are subjective, previous reports of DIOS without a clear definition may have included constipation with an overestimated DIOS incidence. Recently, the European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) CF/Pancreas Working Group defined a consensus document establishing a definition of DIOS and its spectrum of severity, with a clear distinction between incomplete and complete episodes [1].Onset of both entities is fairly acute compared to constipation, which is usually a chronic condition with distal gradual colonic faecal impaction. Complete DIOS (C DIOS) was defined as a combination of 1) complete intestinal obstruction, as evidenced by vomiting of bilious material and/or fluid levels in the small intestine on abdominal radiography; 2) a faecal mass in the ileo-caecum; and 3) abdominal pain and/or distension. Incomplete or impending DIOS (I DIOS) was defined as 1) a short history (days) of abdominal pain and/or distension; and 2) a faecal mass in ileo-caecum, but without signs of complete obstruction. The new definition of DIOS prompted a multinational prospective study in order to evaluate its incidence in children and adults, with the objective of evaluating management of DIOS episodes and factors associated with occurrence, recurrence and resolution of DIOS.

2. Patients and methods

A prospective observational longitudinal study at 27 university hospitals housing paediatric and /or adult CF centres was conducted between August 2009 and October 2012 in 9 European countries and Israel. Individuals with CF (defined based on clinical symptoms associated with a sweat test ≥ 60 mmol/L and /or 2 CFTR causing mutations according to the CFTR2 Project (www.cftr2.org list July 22nd 2013) [2–4] regularly followed at a CF centre were included when a new DIOS episode occurred. The study was approved by the ethical committee IRB APHP, no. 00006477, University Bichat Claude Bernard, and by each participating country. Written information was given to adult patients or to parents of children at enrolment. The following data were collected: demographic data, CFTR genotype, exocrine pancreatic status based on a biological definition (exocrine pancreatic insufficiency (EPI) if faecal elastase <200 μg/g), previous history of DIOS episodes, CF co-morbidity factors (meconium ileus, (MI), CF-liver disease as defined by Debray et al. [5], CF-related diabetes mellitus (CFRD) defined as an abnormal oral glucose tolerance test requiring insulin or hypoglycaemic prescription), patient's weight and height for calculating body mass index (BMI), z-score in children (<18 years of age) and absolute values in adults [6], most recent data on lung function (forced expiratory volume in 1 s (FEV_1)) using published reference ranges in children and adults [7,8], chronic *Pseudomonas aeruginosa* colonisation [9], and prior organ transplantation. Rates of CF co-morbidity factors observed in the DIOS cohort were compared with data extraction rates in the ECFS patient registry (ECFSPR) 2009; detailed information on definitions is provided in the annual report www.ecfs.eu/projects/ecfs-patient-registry/annualreports. Data were collected to classify severity of DIOS episodes [1] and included delay in arrival at hospital (days from onset of symptoms to presentation at the CF centre), duration of hospitalization, treatment, history of constipation, environmental factors at the onset of the DIOS episode with the highest daytime outdoor temperature, recent intensive sports activity, general anaesthesia, pancreatic enzyme replacement therapy dosage and compliance reported by the patient (as poor or good), dietetic modifications and current daily fibre [10] and fat intakes (low, normal, high), via a face-to-face non-standardized interview with a dietician to evaluate dietary intake over the 3 days prior to the episode and the beverage intake for persons over 2 years of age (then using the standard recommended intake [11] and the assumption of a 20% increment for correct hydration for the CF population, we defined an insufficient beverage intake when it was <80% coverage). DIOS resolution was defined as the time needed to resume normal eating habits with respect starting from the initial symptoms. Recurrent DIOS episodes were defined as a

previous history of a DIOS episode or a second episode during the study period. The incidence of DIOS episodes could not be calculated at centres that did not record data on all patients with DIOS episodes during the study period, since some patients had been admitted to other hospitals. All this information was reported via an electronic database hosted by the European Cystic Fibrosis Society website.

2.1. Statistical analysis

Qualitative variables are described as numbers and percentages and quantitative variables as medians [Q1–Q3]. Incidence rates are given with their 95% confidence interval (CI). For comparing groups, Chi-square and Fisher exact tests were used for qualitative variables and the Wilcoxon test for quantitative variables. Factors that could impact the delay in DIOS resolution were examined by quantile regression in bivariate and multivariable models. Variables significant at the 0.20 level in bivariate analysis were entered into the multivariable model and were retained if they remained significant at the 0.05 level. Analysis of associated factors for DIOS episodes was performed by comparison with the ECFS patient registry for CF co-morbidity factors using the chi-square goodness-of-fit test. Factors associated with recurrent DIOS episodes compared to isolated episodes were studied by linear or logistic regression depending on the nature of the variable (quantitative or qualitative) adjusted for age at the last episode. For statistical analysis, all DIOS episodes were considered as independent, since results were not modified after considering only the first episode or all episodes. All tests were bilateral and the level of significance (p-value) was set at 5%. Statistical analyses were performed using SAS 9.4 (Cary, NC) software for a PC computer.

3. Results

3.1. Study population

A total of 102 patients (61 males (60%) and 41 females) were recruited (Table 1), including 61 children and 41 adults. Median age at entry into the study was 14.7 [6.3–23.8] years. Median follow-up duration was 1.6 [1.1; 1.9] years and no deaths were reported during the study period. Recurrence of DIOS episodes occurred in 9 patients (10 episodes) during the study, resulting in a total of 112 episodes. DIOS episodes were subsequently and completely collected in 18/27 (67%) CF centres, enabling calculation of the incidence, in children, of 7.67 episodes per 1000 patient-years (95% confidence interval, 7.64; 7.7) and, in adults, of 7.80 episodes per 1000 patient-years (95% confidence interval, 7.76; 7.84) (Table 1). Table 2 shows the median age at CF diagnosis, age distribution of patients at entry into the study, genotype, nutritional status, and lung function. We compared rates of co-morbidity factors between our cohort and the ECFS registry database 2009 and found a significantly higher percentage of MI, EPI, CF-liver disease, CFRD, and *Pseudomonas aeruginosa* colonisation in adults.

3.2. Presentation of DIOS episodes

Table 3 shows the clinical presentation and investigation for the 112 DIOS episodes. A plain abdominal film was performed in most patients, while remaining patients underwent other imaging modalities (ultrasonography or computed tomography). Comparison of environmental factors showed no difference between I DIOS and C DIOS, but a higher rate of constipation in I DIOS (49% *vs.* 31%, p = 0.05).

Table 1
Distribution of DIOS cases at CF centres and incidence.

CF CENTRES	DIOS episode/patient	CF cohort	Patient-years	DIOS incidence (IC95%) (episodes/1000 patient-years)
France: Limoges, Lyon, Marseille, Paris Robert Debré, Roscoff, Toulouse, Versailles.	36/33	1062	2896.1	11.05 (10.98; 11.12)
[1]Clermont-Ferrand, Lyon paediatric, Nantes, Paris Necker, Saint Denis.	17/14	921		
Italy: Brescia, Florence, Milan, Roma.	22/19	1285	3688.1	5.15 (5.1; 5.19)
[1]Messina	2/2	196		
Israel: Jerusalem	14/14	400	1244.1	11.25 (11.09; 11.42)
Russia: Moscow	6/5	250	664.7	7.52 (7.27; 7.78)
Austria: Innsbruck	4/4	150	397.3	10.07 (9.57; 10.56)
Greece: Thessaloniki	3/3	130	346.0	8.67 (8.14; 9.20)
Belgium: Ghent	2/2	161	477.1	4.19 (3.93; 4.46)
[1]Brussels	1/1	158		
[1]Leuven	1/1	127		
The Netherlands: [1]Utrecht	2/2	221		
Germany: Tubingen	1/1	130	348.2	2.87 (2.57; 3.17)
United Kingdom: Newcastle	1/1	160	428.1	2.34 (2.11; 2.56)
Total < 18 years	52/47[+]	2166	6128.8	7.67 (7.64; 7.70) *
Total ≥ 18 years	36/34	1562	4361.1	7.80 (7.76; 7.84) *

DIOS = distal intestinal obstruction syndrome; [1]Incidence was not calculated in these centres because during the study period, not all subsequent patients with DIOS were recorded completely; [+]one adult followed at a paediatric CF centre was excluded for incidence calculation.
* Poisson regression analysis p = 0.94.

Table 2
Demographic and clinical characteristics of the study population and data provided by the ECFS Patient Registry 2009.

	DIOS cohort N = 102	ECFSPR[#] N = 26 374	p-value[*]
Age at CF diagnosis, weeks[1]	5 [1;26 years]	–	
Age distribution at entry into the study, N (%)			
0–4 years	19 (19)		
5–9 years	15(15)		
10–14 years	18 (18)		
15–19 years	14 (14)		
20–24 years	13 (13)		
≥25 years	23 (23)		
Genotype, N (%)			
Severe	96/102 (94)	–	
508/508	33/96 (34)	–	
Undetermined	6/102 (12)		
[+]*BMI, mean ± SD*			
<18 years (*z-score*)	0.53 (1.16)	–	
≥ 18 years	20.1 (2.2)	–	
FEV_1 [++] %, median [25–75]	80 [64;91]		
Meconium ileus, N (%)	40/101 (40)	3624/19,924 (18)	<0.0001
Pancreatic insufficiency, N (%)	94/102 (92)	20,943/24,864 (84)	0.03
CF-liver disease, N (%)	22/101 (22)	2308/18,646 (12)	0.004
CF-related diabetes mellitus, *≥18 years*, N (%)	20/41 (49)	2996/12,228 (24)	0.0003
PA [+++] colonisation, *≥18 years*, N (%)	28/41 (68)	4880/9313 (52)	0.04

[+] Body mass index (BMI) is weight in kilograms divided by square of height in metres.
[++] Forced vital capacity in 1 s expressed in percentage of predicted value (FEV_1).
[+++] *Pseudomonas aeruginosa* (PA).
[#] European Cystic Fibrosis Society Patient Registry (ECFSPR) 2009.
[1] Median [Q1–Q3].
* Chi-square goodness-of-fit test.

3.3. Treatment of DIOS episodes

Treatment modalities are summarized in Table 4. Hospitalization at a CF centre was required for 85% of I DIOS and 96% of C DIOS patients (two adult patients were sufficiently stable and received treatment in the emergency room only). Medical symptomatic management was significantly different between I DIOS and C DIOS episodes. Medical curative treatment for I DIOS consisted of oral osmotic laxatives (i.e. macrogol), osmotic laxative lavage containing polyethylene glycol and, in some cases (7/60, 12%), sodium meglumine diatrizoate enema (Gastrografin; Shering AG, Berlin, Germany); medical treatment was successful for all I DIOS episodes. Most patients with C DIOS were treated with a meglumine diatrizoate enema (repeated a maximum of 10 times (median number: 2 [1–3])) alone or in combination with polyethylene glycol (PEG) lavage. Six centres used N-acetyl cysteine in I DIOS or C DIOS (n = 8/112, 7%). Medical failure involved only C DIOS episodes (6/52; 12%). For these cases, colonoscopy with local instillation of meglumine diatrizoate in the caecum was successful in treating 2 cases. Surgery was required in 4 children within 1–2 days after arrival at hospital; the surgical procedure was a laparotomy with gut lavage, without temporary ileostomy, while one patient had secondary intestinal resection; home discharge time ranged from 20 to 26 days. Tolerance for usual feeding starting from initial symptoms, which was the definition of DIOS resolution, was similar in both cohorts (4 [3; 7] days *vs.* 4 [3; 7] days, p = 0.82). However, duration of hospitalisation was significantly longer for C DIOS (4 [3; 7] days *vs.* 3 [1; 4] days, p = 0.002), with a shorter proportion of time for arrival at hospital compared to time to DIOS resolution (33% [11; 50] *vs.* 50% [25; 67], p = 0.03). Long-term maintenance therapy was prescribed for 86% of all patients. It consisted mainly of an oral osmotic laxative (i.e. macrogol or lactulose) and in 20% of cases, N-acetyl cysteine, or lubricant laxative (i.e. mineral oil) combined with dietary advice.

3.4. Description of patients with isolated or recurrent DIOS episodes and either C DIOS or I DIOS

Over half of the patients (58/101, 58%) experienced at least two DIOS episodes prior to or during the study period, with the number of episodes ranging from 2 to 11. We compared CF co-morbidity and environmental factors in patients with isolated or recurrent DIOS episodes and in patients with either C DIOS or I DIOS, at centres that recorded all patients with DIOS episodes (Table 5). We showed that only female gender was significantly associated with recurrent episodes (24 out of 32 females and 26 out of 50 males) (75% versus 52%, p = 0.04 logistic regression adjusted for age at the last episode), constipation (39% *vs.* 11%, p = 0.03) with I DIOS and poor PERT compliance (25% *vs.* 3%, p = 0.02) in C DIOS. A history of meconium ileus was more frequent in C DIOS (53% *vs.* 28%, p = 0.07).

Table 3
Presentation of DIOS episodes and associated environmental factors.

	All DIOS n = 112	I DIOS[+] n = 60	C DIOS[++] n = 52	p-value*
Clinical presentation				
Anorexia, N (%)	70/110 (64)	31/60 (52)	39/50 (78)	0.004
Abdominal pain, N (%)	105/111 (95)	55/60 (92)	50/51 (98)	0.22[F]
Faecal ileocaecal mass, N (%)	90/104 (87)	50/57 (88)	40/47 (85)	0.70
Weight loss N, (%)	58/109 (53)	30/57 (53)	28/52 (54)	0.90
Abdominal X-ray (n = 90)				
Fluid levels in small intestine, N (%)	40/100 (40)	0	40/49 (82)	–
Increased stool content, N (%)	90/100 (90)	43/51 (84)	47/49 (96)	0.09[F]
Vomiting and/or fluid levels, N (%)	51/111 (46)	0	51/51 (100)	-
Ultrasonography (n = 47)				
Small bowel dilatation, N (%)	24/44 (55)	5/22 (23)	19/22(86)	<0.0001
Increased stool content, N (%)	35/44 (80)	13/22 (59)	22/22 (100)	0.001[F]
Computed tomography (n = 17)				
Small-bowel dilatation	13/17 (76)	Not performed	13/17 (76)	–
Inspissated faecal mass in ileum	7/17 (41)	Not performed	7/17 (41)	–
Environmental factors				
Daytime outdoor temperature				
≤20 °C N, (%)	61 (54)	33 (55)	28 (54)	0.90
>20 °C N, (%)	51 (46)	27 (45)	24 (46)	
Intensive sport activity, N (%)	9 (8)	4(7)	5 (10)	0.57
General anaesthesia, N (%)	4 (4)	2 (3)	2 (4)	>0.99[F]
Dietetic modification, N (%)	16/111 (14)	9/60 (15)	7/51 (14)	0.85
Fibres low, high, N (%)	41/107 (38); 2 (2)	24/59 (41); 1 (2)	17/48 (35); 1 (2)	0.58
Fat low, high, N (%)	15/109 (14);11 (10)	6/59 (10); 2 (3)	9/50 (18); 9 (18)	0.24
Insufficient beverage intake, N (%)	47/94 (50)	24/53 (45)	23/41(56)	0.30
Constipation, N %	44/109 (40)	28/57 (49)	16/52 (31)	0.05
Lipase dosage[1] UI per kg and day	5188[2992;8013]	5600[4310;8013]	4858[2587;8223]	0.11
Lipase ≥10,000 UI per kg and day N,%	15/106 (14)	7/56 (13)	8/50(16)	0.5
Poor PERT[+++] compliance, N (%)	10/98 (10)	4/52 (8)	6/46 (13)	0.51[F]

[+] Incomplete distal intestinal obstruction syndrome (I DIOS).
[++] Complete distal intestinal obstruction syndrome (C DIOS).
[+++] Pancreatic enzyme replacement therapy (PERT).
[1] Median [Q1–Q3].
* Chi-square or [F]Fisher exact test, Wilcoxon test.

3.5. Factors in DIOS resolution

Table 6 shows that the delay in arrival at hospital, time needed for arrival at hospital compared to time to DIOS resolution (%), and the percentage of relative weight loss compared to usual weight were pivotal factors in the time span needed for DIOS resolution.

3.6. Discussion

This is the first prospective longitudinal international study performed on DIOS in children and adults with CF. It reveals that the spectrum of DIOS severity based on ESPGHAN criteria shows significant clinical differences between complete and incomplete DIOS [1]. We found similar incidences between paediatric and adult patients and an increased incidence of recurrent episodes in females. Meconium ileus is a significant risk factor. Delay in receiving medical assistance causes significant morbidity. Similar delays in DIOS resolution between I DIOS and C DIOS were found, but with longer hospitalisation in C DIOS. For the first time, factors that might impact the time needed for DIOS resolution were analysed; we found that, in multivariate analysis, delay in arrival at hospital and prior weight loss had a significant impact. Our study indicates that DIOS is as frequent in adults as in children. This is in contrast to current assumptions based on two retrospective studies in adults, published over 10 years ago by Anderson et al., who found an incidence of 35.5/1000 patient-years [12], and by Dray et al. reporting a prevalence of 15.8 (95% CI, 10.3–21.3) [13], possibly related to an overestimated incidence due to inclusion of severe constipation episodes. A paediatric retrospective analysis across Europe using the ESPGHAN definition [1] found a slightly lower incidence of 6.2 episodes per 1000 patients (95% CI, 4.5–7.9). Our descriptive study found unexplainable variations in incidences among countries. One hypothesis might be the impact of factors apart from the CFTR gene, i.e. modifier genes or differences in nutritional management, but these would require further investigation. We showed that children with meconium ileus had a higher rate of surgery for DIOS prior to or during the study (6/40, (15%) vs. 1/60 (2%), p = 0.02). The high incidence of meconium ileus is in agreement with other studies showing rates ranging from 8.8% [13,14] to 44% [1]. The high proportion of pancreatic-insufficient patients correlates well with the low

Table 4
Treatment management and delay in DIOS resolution in I DIOS and C DIOS episodes.

	All DIOS n = 112	I DIOS[+] n = 60	C DIOS[++] n = 52	p-value *
Hospitalisation rates, N (%)	101/112 (90)	51/60 (85)	55/52 (96)	0.05
Symptomatic treatment, N (%)				
IV hydration	76/109 (70)	32/57 (56)	44/52 (85)	0.001
Fasting	81/109 (74)	34/57 (60)	47/52 (90)	0.002
Nasogastric aspiration	27/109 (25)	6/57 (11)	21/52 (40)	0.0003
Pain relief, non-opioid	74/112 (66)	32/60 (53)	42/52 (81)	0.002
Pain relief, opioid	9/112 (8)	1/60(2)	8/52(15)	0.01[F]
Curative treatment, N (%)				
Gastrografin enema, N (%)	36/108 (33)	7/52 (13)	29/50 (58)	<0.001
Gastrografin enema + PEG lavage, N (%)	11/108 (10)	1/58 (2)	10/50 (20)	0.002
PEG lavage, N (%)	52/110 (47)	28/59 (47)	24/51 (47)	0.97
N-acetyl cysteine, N (%)	8/110 (7)	2/59 (3)	6/51 (12)	0.20
Oral osmotic laxative, N (%)	73/106 (69)	44/58 (76)	29/48 (60)	0.09
Colonoscopy, N (%)	2/112 (2)	0	2/52 (4)	NA
Surgery, N (%)	4/112(4)	0	4/52(8)	NA
Maintenance therapy, N (%)	95/111 (86)	50/60 (83)	45/51 (88)	0.46
Oral osmotic laxative, N (%)	84/95 (88)	42/60 (70)	42/45 (93)	0.16
N-acetyl cysteine, N (%)	12/95 (13)	5/50 (10)	7/45 (16)	0.42
Lubricant laxative, N (%)	5/95 (5)	3/50 (6)	2/45 (4)	>0.99[F]
Delay in DIOS resolution[#], days	4[3;7]	4 [3;7]	4 [3;7]	0.82
Delay in arrival at hospital[1], days	1[1;3]	2 [1;4]	1 [1;2]	0.14
Duration of hospitalization[1], days	3[2;5]	3 [1;4]	4 [3;7]	0.002
Proportion of time for arrival at hospital /time to DIOS resolution[1] (%)	45[15;63]	50 [25;67]	33 [11;50]	0.03

[+] Incomplete distal intestinal obstruction syndrome (I DIOS); [++]Complete distal intestinal obstruction syndrome (C DIOS).
[#] Delay in DIOS resolution was defined as resumption of prior feeding practice starting from initial symptoms.
[1] Median [Q1–Q3].
* Chi-square or [F]Fisher exact test, Wilcoxon test.

frequency of mild genotype [1,13,15] and emphasises the role of severely impaired CFTR-mediated intestinal secretion in the physiopathology of DIOS, although this is not the only pathogenic factor, since patients with mild genotypes may still develop DIOS. As both MI and DIOS share clinical and pathologic similarities, a common cause was suggested, involving a defective intestinal secretion flow and slow intestinal transit, leading to sticky mucus overproduction and further development of intestinal obstruction. Nevertheless, this hypothesis is not supported by Blackman SM et al. [16] who found high concordance rates of MI in monozygotic twins, but low concordance rates in monozygotic persons and high rates in dizygotic twins and sibling pairs for DIOS, thus indicating that genetic factors play a major role in MI, but not in DIOS. An increased incidence of DIOS in individuals presenting CF-liver disease and CFRD has been suggested [13,17,18] and we report the first comparison between a DIOS cohort and registry data. In animal CF mouse models, it has been shown that intestinal dysbiosis, which increases the risk of translocation of potentially pathogenic bacteria through the intestinal mucosa barrier, is a condition that has been associated with strong risk of diabetes and liver disease [19,20]; these data must be interpreted with caution because of significant differences in gastrointestinal pathology between the CF mouse model and humans in terms of pancreatic function.

In DIOS, small intestinal bacterial overgrowth can be enhanced by obstruction, thus playing a possible role in the pathogenesis of these co-morbidities by creating a vicious cycle. Medical treatment adapted to DIOS spectrum severity [21] using a stepwise approach, failed only in complete DIOS (11%). Discrepancies in curative treatment among different countries or CF centres were related to the availability of osmotic laxative preparations. None of the patients who received gastrografin presented with complications linked to fluid or ion shifts, as previously reported [22,23]. Colonoscopy resolved complete obstruction in 2 cases. Three patients out of 4 who required surgery were from one CF centre that recruited 5 patients; thus, we cannot eliminate possible bias in surgery indication. Successful colonoscopy case reports have been published [24,25], justifying this approach in specific cases that were discussed by gastroenterology and surgical teams. To avoid the high morbidity of laparotomy, an innovative procedure was recently reported in an adult based on a hand-assisted laparoscopic exploration, followed by antegrade enemas, leading to early home discharge [26]. The higher rate of surgery for DIOS in children was in agreement with recent publications [15,16,27].

During the study, we described higher frequency of recurrent episodes in females, which was not reported previously. In those with a history of DIOS prior to entry into the study (5/48, 10.4%) *vs.* no previous DIOS episodes (2/34 (5.9%), results were in agreement with other reports [1,13], but did not reach significance (p = 0.42). Unexpectedly, upon recurrence, over half of the episodes were C DIOS, since milder bowel obstruction presentations may have occurred with earlier recognition of symptoms. We compared CF co-morbidities between our cohort and the ECFS registry database, and found, in our study, a strong association between DIOS and MI, EPI,

Table 5
Characteristics of patients with isolated or recurrent DIOS episodes and those with C DIOS or I DIOS episodes in centres that recorded all patients with DIOS episodes.

	Isolated DIOS n = 32	Recurrent DIOS n = 50	p-value *	C DIOS n = 19	I DIOS n = 37	p-value **
Age at entry into the study [1], (y)	12.8[5.7; 28.5]	16.4 [10.2; 23]	0.11	11.6[4.0; 28.2]	14.9[9.0; 20.3]	0.46
Meconium ileus, N (%)	14/31 (45)	19/50 (38)	0.70	10/19 (53)	10/36 (28)	0.07
Pancreatic insufficiency, N (%)	28/32 (88)	17/49 (94)	0.25	18/19 (95)	31/37(84)	0.40
CF-liver disease, N (%)	9/32 (28)	11/50 (22)	0.50	4/19 (21)	8/43 (19)	0.72
CF-related diabetes, ≥ *18 y*, N (%)	7/13 (54)	11/22 (50)	0.88	2/6 (33)	8/14 (57)	0.63
PA $^{+++}$ colonisation, ≥ 18 y, N (%)	8/13 (62)	17/22 (77)	0.16	4/6 (67)	8/14 (57)	>0.99
Constipation	7/31 (23)	17/49 (35)	0.25	2/19 (11)	14/36 (39)	0.03
Daytime outdoor temperature, >20 °C, N (%)	17/32 (53)	24/50 (48)	0.61	10/19 (53)	18/37 (49)	0.78
Low fibre intake, N (%)	11/31(35)	16/47(34)	0.97	4/18 (22)	13/36 (36)	0.30
High fat intake, N (%)	3/31(10)	5/49 (10)	0.91	3/18 (17)	1/36 (3)	0.10
Insufficient beverage intake, N (%)	12/26 (46)	22/44 (50)	0.28	7/13 (54)	15/33 (46)	0.61
Lipase dosage [1] (UI per kg and day)	4583[2632; 7212]	5188[3087; 7916]	0.75	5971[4444; 9542]	4182[2500; 8535]	0.20 > 0.99
Lipase ≥ 10,000 UI per kg and day, N (%)	3/29 (10)	5/48 (10)	0.61	2/18 (11)	4/34 (12)	
Poor PERT^{+} compliance, N (%)	4/26 (15)	4/44 (9)	0.46	4/16 (25)	1/30 (3)	0.02
FEV_1 $^{++}$ %, ≥ *18 years*, N	84[65; 100], 24	75[55; 90], 41	0.10	78[66; 85], 8	81[69; 91], 15	0.78
Organ transplantation, N (%)	2/32 (6)	5/50 (10)	0.41	2/19 (11)	2/37 (5)	0.60

$^{++}$ Forced vital capacity in 1 s expressed in percentage of predicted value (FEV_1).
[1] Median [Q1–Q3].
* Linear or logistic regression adjusted on age at last episode
** Chi-square or Fisher exact test, Wilcoxon test.

CF-liver disease, diabetes mellitus, and chronic *Pseudomonas aeruginosa* infection in adults.

Environmental factors were previously considered to have a major impact on the incidence of DIOS. The present study does not support a predisposing dehydration role for either hot weather, as suggested in the literature [13,21] or intense sports activities. The strength of our study lies in the fact that we provided the exact maximum daytime temperature at the onset of initial symptoms in countries with highly variable temperatures, from Russia to Israel. Dehydration may also be a consequence of insufficient beverage intake, especially in CF patients, and it was found in half of the cohort, with increasing rates with age (from 13% in toddlers to 64% in adolescents and 55% in adults). Nutritional advice on maintaining adequate hydration should be part of an educational program for maintenance therapy. Low fibre intake was found in 38% of our cohort, a relatively high percentage. This is in agreement with diets reported in CF patients with abdominal complaints compared to CF controls [17]. It is possible that low fibre intake may compromise colon function, as it is an important factor in the pathogenesis of gastrointestinal symptoms; however, clinical trials demonstrating the benefit of increasing fibre intake are lacking. Conversely, Proesmans et al. [28] identified higher fibre intake in children with DIOS compared to children with CF without DIOS, but high fibre intake was advocated in all patients with constipation, thereby creating a bias. Dietary modifications at the onset of a DIOS episode identified rather anecdotic changes: increased calorie intake (n = 6), increased consumption of potato chips (n = 2), cauliflower, chocolate, tomatoes, popcorn, and acute alcohol consumption. Until now, no specific food had been identified as playing a role in DIOS, except for one case report showing a potential role of potato chips [29]. We found that pancreatic enzyme replacement therapy (PERT) dosage was within recommended ranges [30], thus contradicting the widely supported hypothesis that insufficient supplementation [12,24,28] is a predisposing factor

Table 6
Factors in delay of DIOS resolution for the 112 DIOS episodes.

	Bivariate analysis		Multivariate analysis	
Variables	β Coefficient [95%CI]	p-value *	β Coefficient [95%CI]	p-value *
Age at entry into the study [1]	0.00 (−0.05; 0.05)	>0.99		
Meconium ileus at birth	−1.00 (−2.24; 0.24)	0.11		
CF-related diabetes mellitus	1.00 (−0.90; 2.90)	0.30		
Daytime maximal outdoor temperature	0.00 (−0.06; 0.06)	>0.99		
Beverage intake	0.00 (−1.42; 1.42)	>0.99		
Poor enzyme compliance	0.300 (−1.34; 1.34)	>0.99		
Delay in arrival at hospital starting from initial symptoms	1.05 (0.96; 1.13)	<0.001	1.10 (0.92; 1.29)	<0.001
Proportion of time needed for arrival at hospital /time to DIOS resolution (%)	0.03 (0.00; 0.05)	0.08	−0.03 (−0.05; −0.02)	<0.0001
Percentage of relative weight loss [2]	0.53 (0.20; 0.85)	0.002	0.24 (0.09; 0.39)	0.002

[1] Median [Q1–Q3].
[2] Defined as weight at arrival: prior weight.
* Quantile regression.

for DIOS. This could be a consequence of increased unabsorbed fat in the distal ileum, a slowdown in gastric emptying and delayed intestinal transit. In our study, poor enzyme compliance was associated with C DIOS (53% *vs.* 28%, p = 0.07; 25% *vs.* 3%, p = 0.02); however, compliance often is overestimated. In the recent study of Declercq et al. [31], 3-day dietary information at the time of the first DIOS episode compared to the previous year and to a matched control CF cohort showed similar pancreatic enzyme dosage, calories, fat, fibre, and liquid intake, thus also not supporting a role for pancreatic enzyme dosage or nutritional factors in occurrence of DIOS.

Several limitations of our study should be pointed out. Our cohort with classical CF may not resemble patients recruited from registries that could include milder phenotypes. Definitions used for CF co-morbidities (www.ecfs.eu/projects/ecfs-patients-registry/annual-reports) differed; however, those of our cohort were more accurate, adding power to the increased percentages we found. Another weakness of our study was the lack of a 3-day nutrition and beverage record and of a control-matched CF cohort; however, organising this type of study at so many centres would have been unrealistic.

In conclusion, this first prospective observational study on DIOS shows that incidences were similar in children and adults, that medical treatment adapted to DIOS spectrum severity failed only in C DIOS, and that children with meconium ileus had a higher surgery rate for DIOS. Delay in DIOS resolution was similar for incomplete and complete episodes, but with longer hospitalization in complete DIOS. Factors having an impact on delay in DIOS resolution included the delay in receiving medical assistance, and weight loss. Poor compliance with PERT was not a predisposing factor. CF teams should be encouraged to include DIOS in educational programs, leading to earlier recognition and care. Associated CF co-morbidity factors for DIOS were meconium ileus, exocrine pancreatic insufficiency, CF-liver disease, and CFRD; low fibre intake and insufficient beverage intake were frequently observed. We emphasise here the complexity of factors contributing to DIOS. Our study will help gastroenterologists in understanding of this complication.

Contributors' statements

AM, CA, CC, NK, HE, MF, RH, ER, and MW contributed to the study concept and design and interpretation of the data. AM, CC, NK, HE, MF, RH, ER, and MW were study coordinators. CA and PB contributed to analysis and interpretation of the data. PR, JL, VL, GT, NDD, RP, IDB, PF, SR, RNJ, EM, GV, LD, MB, AH, BH, and IS were study investigators. All authors contributed to critical revision of the manuscript and approved the submitted version. AM and MW supervised the study.

Disclosures

None of the authors declare a conflict of interest.

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