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Risk factors for complications in patients with Hirschsprung disease while awaiting surgery: Beware of bowel perforation

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ABSTRACT

Background: Patients with Hirschsprung disease (HD) mostly undergo surgery around the age of three to six months. While awaiting surgery, therapy to treat the obstruction such as transanal irrigation (TAI) or laxatives is applied. The aim of this study was to gain insight in the prevalence and severity of complications occurring while awaiting surgery and to identify patient characteristics associated with the development of these complications.

Methods: This study retrospectively analyzed data of patients with HD operated in our center between 2000 and 2021. Complications emerging while awaiting surgery were graded using Clavien-Dindo (CD). Patient characteristics as predictor of a complication were tested using logistic regression analysis.

Results: Twenty-two of 132 (17%) included patients (preoperative treatment: 94% TAI; 2% laxatives; 2% other therapy) developed 45 complications while awaiting surgery, including predominantly major complications (91%). Bowel perforation occurred most frequently (n = 9, 7%) wherefrom six caused by TAI (5%), including three patients with total colon aganglionosis (TCA) (2%) counting one life-threatening and one lethal perforation. The other perforations were caused by meconium ileus (n = 2) and Hirschsprung associated enterocolitis (HAEC) (n = 1). Other frequent complications were: sepsis (5%), ileus (4%) and persistent obstruction (4%). Predictive factor for developing complication was TCA (OR 9.905, CI 2.994–32.772, p < 0.001).

Conclusion: We found a complication rate of 17% in patients while awaiting surgery, reporting bowel perforation most frequently. We found this complication in patients with TCA being highly dangerous causing one life-threatening and one lethal perforation. Therefore, we advise in patients with (suspected) TCA to limit the time awaiting surgery.

Level of evidence: level III.

1. Introduction

Hirschsprung disease (HD) is a congenital disorder characterized by absent or impaired neural innervation of the distal segment of the bowel. This results in obstructive symptoms, which are often present in the first week after birth [1]. Definitive treatment of the obstruction warrants resection of the diseased bowel in one or two stages. One-staged surgery includes direct resection of the bowel and two-staged surgery includes the placement of a stoma before definitive resection. There is ongoing debate about the ideal timing of performing definitive treatment. Surgery at neonatal age may prevent inadequate bowel decompression, which occurs in 25% of the preoperative patients possibly causing persistent colorectal obstruction with associated episodes of Hirschsprung associated enterocolitis (HAEC) [2–4]. On the contrary, a retrospective multi institutional study has shown that surgery at non neonatal age decreases the risk of postoperative HAEC and also decreases the risk of postoperative fecal incontinence [5]. Moreover, surgery at non-neonatal age has the benefits of a more mature anal canal and sphincter complex [6–8]. Hence, most surgeons strive to per-

Abbreviations: HD, Hirschsprung disease; CD, Clavien-Dindo; TAI, Transanal irrigation; HAEC, Hirschsprung related enterocolitis; TCA, Total colon aganglionosis.

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form surgery at the age of three to six months. Consequently, bridging time while awaiting surgery with substitute therapy is necessary to prevent complications from severe obstipation [8].

The standard therapy bridging the time to surgery is transanal irrigation (TAI) which is performed in 77% of patients with HD [7,9]. Performing preoperative TAI has the aim to evacuate the rectum and thereby preoperatively prevents both excessive colon dilatation and HAEC, thereby reducing the risk of postoperative complications [10,11]. In addition, the need for a colostomy before definitive surgery can be prevented by performing TAI, which leads to less anesthesia exposure and a potential decrease in health care resource utilization [12]. Because of this, surgery at a non-neonatal age combined with preoperative TAI is seen as the standard treatment for most children/neonates with HD [7]. However, no study has been performed assessing the complications that occur while awaiting surgery. Therefore, the current retrospective cohort study aims to chart the prevalence and severity of complications in patients with HD while awaiting all types of bowel surgery. Severity of complications was assessed using the Clavien-Dino (CD) classification, a grading system designed for scoring the severity of surgical complications [13]. Furthermore, it was examined whether patient characteristics are related to an increased risk of developing complications while awaiting surgery.

2. Methods

2.1. Patient population

All patients over a 21-year period (May 2000 until May 2021) who were preoperatively and surgically treated for HD in one of the two academic tertiary hospitals of the Amsterdam university medical centers (Academic Medical Center and VU Medical Center), were included in this retrospective cohort study. Exclusion criteria were: patients receiving preoperative care in another hospital, patients operated in another hospital, patients receiving surgery before the suspicion HD was made, patients in whom no medical report or no histopathological confirmation of HD was available, patients who died preoperatively owing to a cause that was unrelated to HD, patients not receiving surgery for HD because of conservative treatment, patients diagnosed after the age of six months, and patients that did not provide informed consent. The length of follow-up for all included patients was equal to the total length of preoperative period. The preoperative period was defined as the period between birth and the point in time where each kind of bowel surgery was performed (excluding biopsies under general anesthesia) or patients died as a consequence of HD. If a complication required surgery, the follow-up period was extended with 30-days to monitor occurrence of additional postoperative complications. None of the patients was lost to follow-up.

2.2. Clinical procedure

TAI started at time of suspicion of HD and was started in the hospital in order to train caregivers and monitor their compliance with the procedure. The local protocol for TAI included using an Unomedical catheter® with size Ch.18, 20 or 22, irrigating with NaCl 0.9%, applying 25 ml per kilogram body weight per day. Patients were discharged when caregivers could independently perform TAI with good fecal results. If caregivers were not able to independently irrigate, home support was provided. Diagnosis of HD was based on histopathological findings, in which acetylcholinesterase staining was used until the end of 2011 and calretinin staining thereafter [14,15]. Patients were followed up at the outpatient clinic or contacted every 4–8 weeks. Surgery was scheduled around the age of three months. Patients with a suspected long segment disease or TCA were operated in two stages whereby initially stoma was created combined with perioperative colon mapping to determine the length of resection for the secondary definitive surgery.

2.3. Data extraction

Medical records of all eligible patient were reviewed by multiple authors (HL and LB) and stored in a Castor database. Data validation was done by checking 10% of the entered records of each author by the other author. In case there were inconsistencies, the complete record was checked by the other author. Inconsistencies were found in less than 5% of the checked records. Percentage of data missing was less than 10% for all variables taken form the medical records except for the APGAR-score (38% missing).

2.4. Measurements and definitions

We retrospectively calculated the overall prevalence of complications while awaiting surgery, as the proportion of all patients that had a history of at least one minor or major complication according to CD. CD grades 1 and 2 were considered as minor complications and CD grades 3, 4, and 5 were considered as major complications. In case of CD1 no interventions took place, with CD2 pharmacological interventions took place, with CD3 radiological or surgical interventions took place. In case of CD4 and CD5, the details about the treatment are given in the results section [16]. The CD classification fulfilled all requirement to be used as a tool to rate preoperative complications, despite only being validated for scoring postoperative complications in adults. We did not make a distinction between grades 3a and 3b because this distinction has been found clinically irrelevant in pediatric surgery [17].

For each complication, the following patient details were extracted from the medical files: severity of complication graded by CD, age at presentation of complication (weeks), location where complication occurred (home/hospital), length of diseased bowel (short-segment was defined as aganglionosis extending to the rectosigmoid, long-segment as aganglionosis extending to the proximal colon or total colon aganglionosis (TCA)) and type of preoperative therapy (TAI, laxatives, no therapy or other therapy). No therapy was registered in case of a complication occurred immediately after the suspicion HD was made with surgery being required. The process we used determining the length of disease was performed in a standardized manner, using the verdict of the pathological report first, the surgical report second and the radiological report third. Sepsis was diagnosed by using the systemic inflammatory response syndrome (SIRS) criteria for pediatrics [18]. Sepsis was coded present, if at least two of the following criteria were met including criterion 1 and/or 4: (1) temperature >38.5 °C or <36 °C (2) age-dependent tachycardia or bradycardia (3) tachypnea or need for mechanical ventilation (4) abnormal white blood cell count or $>10\%$ bands counts [18]. Line sepsis was diagnosed using the criteria developed by Maki et al. the presence of intravascular device combined with a sepsis as defined by Goldstein et al. without an identifiable local infection and with a bloodstream infection being refractory to antimicrobial therapy [18,19]. HAEC was diagnosed using the criteria of Roorda et al. presence of clinical signs of bowel inflammation, that required treatment with intravenous antibiotics and admittance to the hospital during at least two days [20]. We used the characteristics of Waldhausen et al. to define meconium ileus: inspissated meconium impacted in the distal ileum leading to a distended abdomen, bilious vomiting and failure to pass meconium within 48 h and radiography showing multiple loops of bowel of various sizes with ground glass appearance without the presence of air-fluid levels [21]. Gastroenteritis was diagnosed when the following symptoms were present:

presence of clinical sings of bowel inflammation without previous bowel obstruction, not requiring intravenous antibiotics [22]. Persistent obstruction was defined as decreased fecal production for more than four days despite repeatedly performing TAI. In patients not receiving TAI with decreased fecal production, TAI was started and if obstruction lasted for more than two days, persistent obstruction was noted.

2.5. Factor associated with developing a complication while awaiting surgery

Possible predictors that were tested for developing a complication while awaiting surgery were: sex, gestational age (weeks), low birth weight (<2500 g), comorbidity present (yes/no), syndrome present (Down/other/no), age at diagnosis (weeks), and length of disease (short-segment, long segment or TCA).

2.6. Statistical analysis

Statistical analysis used IBM SPSS Statistics for Windows, version 26 (IBM Corp., Armonk, N.Y., USA). Logistic regression analysis was performed to identify risk factors for developing a complication while awaiting surgery. *P*-values of <0.05 were considered statistically significant. For significant predictors of postoperative complications, odd ratios with 95% confidence interval (CI) were calculated as estimates of relative risk.

2.7. Ethics

The Institutional Board of Review approved this study (W18_160#18.198). All procedures were in accordance with the Helsinki declaration and its later amendments.

3. Results

3.1. Population characteristics

We analyzed 200 patients of whom 68 were excluded: In 32 patients preoperative care was performed outside the Amsterdam UMC, in nine patients preoperative documentation was missing, three patients died prior to definitive surgery of a HD unrelated cause, three patients underwent surgery before the suspicion of HD, 16 patients were diagnosed after the age of six months and five caretakers did not provide informed consent to participate in the study. Subsequently, 132 patients were included in the study of whom 102 (77%) were male with a mean age at diagnosis of four weeks ranging from 0 to 6 months and a mean follow-up duration of 11 weeks ranging from 0 to 1069 weeks. Off all patients awaiting surgery, 124 patients received TAI (94%), three patients took laxatives only (2%), one patient received anal dilatation (1%) and one patient received rectal cannulation (1%). Three patients did not receive preoperative treatment (2%) because a complication immediately occurred after the suspicion HD, warranting surgery. Ninety-nine patients had a short-segment disease (75%), 18 a long segment disease (14%), 14 a TCA (11%) and in the one remaining patient (1%), the exact extent of the aganglionosis could not be retrieved from data in the medical record. Thirty patients (23%) received a stoma before definitive surgery took place. Indication for the stoma placement was a suspected long segment disease or TCA in 14 patients (11%), a preoperative complication in 15 patients (11%) and a cecal atresia in one patient (1%). Definitive surgery did not took place in two patients owing to previous death. From the 130 patients undergoing definitive surgery, 92 patients received pull-through technique (70%) and 38 patients Duhamel technique (29%). Baseline characteristics of the included patients are described in Table 1.

Table 1
Patient characteristics from all patients awaiting surgery (n = 132 patients).

Sex, *n* (%)	
Male	102 (77)
Female	30 (23)
Gestational age in weeks, median (range)	40 (28–42)
Gestational age, *n* (%)	
Preterm (<37 weeks)	22 (17)
Term (≥37 weeks)	108 (81)
Missing	2 (2)
Birthweight in grams, mean (SD)	3212 (688)
Birthweight, *n* (%)	
Low birthweight (<2500 g)	20 (15)
Normal birthweight (≥2500 g)	112 (85)
Missing	0 (0)
APGAR score, median (range)	
1 min	9 (1-10)
5 min	10 (5-10)
Missing	50 (38)
Comorbidity present, *n* (%)	
Yes	39 (30)
No	93 (71)
Syndrome, *n* (%) [1]	15 (11)
Downs syndrome	12 (9)
Other syndrome*	3 (2)
No syndrome	177 (89)
Meconium passage, *n* (%)	
<24 h	30 (23)
24–48 h	17 (13)
>48 h	77 (58)
Missing	8 (6)
Age at diagnosis in weeks, mean (SD)	4 (7)
Preoperative therapy, *n* (%)	
TAI	124 (94)
Laxatives	3 (2)
No therapy	3 (2)
Other**	2 (2)
Missing	0 (0)
Length of disease, *n* (%)	
Short segment disease	99 (75)
Long segment disease	18 (14)
TCA	14 (11)
Missing	1 (1)
Stoma before definitive surgery, *n* (%)	30 (23)
Technique definitive surgery, *n* (%) [2]	
Pull-through	92 (70)
Duhamel	38 (29)
Missing	0 (0)

[1] Genetic testing was done in 71 patients, in case of clinical suspicion of a syndrome.
[2] Two patients did not underwent definitive surgery owing to previous death.
* Other syndromes were MEN2A (n = 1), Mowat-wilson (n = 1) and diGeorge syndrome (n = 1).
** Other preoperative therapy includes anal dilatation and rectal cannulation.

3.2. Prevalence of complications

Twenty-two patients (17%) had 45 complication while awaiting surgery, including 20 patients with at least one major complication (91%) and two with only minor complications (9%) (Table 2). Thirteen patients developed one, five patients developed two, two patients developed four, one patient developed six and one patient developed eight complications. The most prevalent complication was bowel perforation (n = 9, 7%) including six caused by TAI (5%), one caused by HAEC (1%) and two caused by meconium ileus (1%). The second most prevalent complication was sepsis (n = 6, 5%) including two central venous line sepsis (1%) and four caused by bowel perforation (3%). The third most prevalent complications were both ileus (n = 5, 4%) and persistent obstruction (n = 5, 4%). Of all patients with a complication, eight patients developed a complication at home (36%) and in 14 patients the complication occurred in the hospital (64%) at a mean age at presentation of four weeks (range 0–25 weeks) with 10 patients having a short-segment disease (45%) three a long segment disease (14%) and nine a TCA (41%).

Table 2
Prevalence and severity of different type of complications while awaiting surgery.

	Total	CD gr I	CD gr II	CD gr III	CD gr IV	CD gr V
Perforation	9	–	–	6	2	1
Caused by TAI	*6*	–	–	4	1	1
Caused by HAEC	*1*	–	–	–	1	–
Caused by meconium blow-out	*2*	–	–	2	–	–
Sepsis	6	–	1	–	4	1
Ileus	5	–	1	4	–	–
HAEC	3	–	1	2	–	–
Enterocutaneous fistula stoma	2	2	–	–	–	–
Persistent obstruction	5	–	–	5	–	–
Gastroenteritis	2	–	2	–	–	–
Anemia	3	–	3	–	–	–
Other*	10	1	2	5	2	–
Total		13			32	

* Other complications included: hypertonic dehydration, peritonitis, hyponatremia, sigmoid volvulus, organ failure, watershed cerebral infarction, and fecaloma.HAEC: Hirschsprung associated enterocolitis.

3.3. Patients with perforation in detail

Bowel perforation is a poorly reported complication in patients with HD awaiting surgery. Therefore we here describe the patients with a life-threatening (CD=4) and lethal (CD=5) perforation in detail Table 3. provides an overview of all patients with a perforation. Case 7 was born preterm (33 weeks) without comorbidities with a positive family history of HD. TAI was started one day after birth. Rectal suction biopsies taken 34 days after birth showed HD. The patient was discharged 42 days after birth awaiting surgery at the age of three months. Six weeks after birth, despite good fecal results on TAI, the patient started vomiting and became lethargic whereafter the caregivers immediately went to the hospital. The patient had a temperature of 36 °Celsius and was respiratory and hemodynamically instable. Because of good fecal results, no HAEC was expected and a sepsis workup was started. X-ray and ultrasound showed large amounts of free abdominal air suggestive for perforation. Because of persistent respiratory problems, the patient was intubated which caused cardiac arrest needing short reanimation. Lactate acidosis developed just before surgery. Laparotomy showed ample amounts of abdominal turbid liquid. Owing to the instable situation of the patient, it was not possible to search for the perforation, and it was decided to create a split ileostomy proximal to the suspected perforation. No ascites was taken for investigation. After surgery, circulatory decline was seen with multi organ failure and it was decided to discontinue therapy. The patient died on the same day as presenting in the hospital at an age of six weeks. Autopsy was performed, showing a bacterial peritonitis and progressive organ ischemia as a result of multi organ failure, with the plausible primary cause being bowel perforation at the splenic flexure. Because of the perforation's location, TAI is unlikely to have caused the perforation, making inadequate bowel decompression the most likely cause. Case 9 had not produced meconium and showed bilious vomiting two days after birth wherefore TAI was started. Rectal suction biopsies taken four days after birth showed HD. Eight days after birth, catheter advancement beyond sigmoid was not possible. Twelve hours later the patient developed tachycardia and a painful and distended abdomen. X-ray showed free abdominal air warranting surgery that revealed a sigmoid perforation and peritonitis whereafter the patient developed disseminated intravascular coagulation, leading to severe multi organ failure, watershed infarct and anemia starting extracorporeal membrane oxygenation. Fortunately, the patient survived despite the life-threatening situation, with the primary cause being a perforation caused by TAI and/or by inadequate bowel decompression.

3.4. Predictors of complications

Table 4 shows patient characteristics tested as predictors for complications in patients with HD awaiting surgery. Univariable logistic regression showed a significantly increased risk for patients with a TCA (OR 9.905, CI 2.994–32.772, $p < 0.001$) compared to patients with a short-segment disease to develop a complication.

4. Discussion

This retrospective cohort study is the first to examine the prevalence and severity of complications in patients with HD while awaiting surgery, graded with CD classification. We found 17% of all patients in await of surgery having at least one complication, which were predominantly patients with a major complication (91%). Most frequent complications were: bowel perforation (7%), sepsis (5%), ileus (4%) and persistent obstruction (4%).

Regarding bowel perforation, five of nine perforations were caused by TAI, all five being major complications (CD≥3) including one patient that deceased. One patient developed a perforation at the splenic flexure after TAI was performed and because of the location of perforation, an iatrogenic perforation was less likely. Therefore, we assume that inadequate decompression was the most likely cause for this perforation. The remaining three perforations were twice caused by meconium ileus at the caecum and the sigmoid and once by HAEC. Thus, from all patients awaiting surgery 7% developed a perforation. This possible lethal complication has not been described before in patients with HD while awaiting surgery and therefore no direct comparison can be made. However, Mosiello et al. has studied the relation of TAI and the occurrence of a bowel perforation in children with different types of congenital bowel obstructions and reports a lower prevalence of perforations in children receiving TAI of 0.0002% having a bowel perforation [23]. The difference in the prevalence rate of bowel perforations may be explained in two ways. One explanation is that Mosiello et al. studied patients with all kinds of congenital obstructions mainly including patients with neurogenic bowel dysfunctions ($n = 686$, 66%), anorectal malformations ($n = 167$, 16%) and functional constipation/fecal incontinence ($n = 155$, 15%), and only included 16 patients with HD (2%). The limited number of patients with HD, combined with the evidence that in patients with HD the perforation occurs in the aganglionair part of the bowel, suggests that patients with HD have higher risk of developing a perforation compared to patients without an aganglionair bowel [23,24]. The second explanation is that the higher prevalence rate observed in our current study is related to the lower mean age

Table 3
Patients with a perforation and other related complication occurring while awaiting surgery ($n = 9$).

Case no.	Perforation and related complications	CD	Location occurrence complication	Preoperative treatment	Age perforation (weeks)	Meconium production (days after birth)	Side perforation	Length of disease	Presentation perforation
1	Perforation	3	Home	No**	0	No***	Caecal	Short segment	Persistent bilious vomiting and distended abdomen combined with E. Coli blood cultures.
2	Perforation	3	Home	No**	0	No***	Sigmoid	Short segment	Bilious vomiting. Contrast enema showed extravasation.
3	Iatrogen perforation*	3	Hospital	TAI	0	2 on TAI	Sigmoid	TCA	Rectal blood loss and distended and painful abdomen.
4	HAEC Perforation Sepsis Gastroenteritis	2 4 4 2	Hospital	TAI	1	2 on TAI	Ileal	TCA	Bilious vomiting and tachycardia (suspecting HAEC). Clinical deterioration. Surgery revealed ileal ischemia including perforation.
5	Iatrogenic perforation *	3	Home	TAI	1	4 on TAI	Sigmoid	Short segment	Distended abdomen. X-ray showing free intra abdominal air.
6	Iatrogenic perforation * Sepsis	3 4	Hospital	TAI	0	1 on TAI	Sigmoid	Short segment	Tachycardia and distended abdomen. X-ray showing free abdominal air.
7	Iatrogenic perforation * Sepsis	5 5	Home	TAI	6	1 on TAI	Splenic flexure	TCA	Vomiting, lethargy, respiratory and hemodynamically instable. X-ray showing free abdominal air.
8	Iatrogenic perforation * Suspected ileus	3 2	Home	TAI	6	1	Sigmoid	Short segment	Fever. X-ray showing free abdominal air.
9	Perforation Sepsis Organ failure Watershed cerebral infarction Anemia Enterocutaneous fistula stoma	3 4 4 4 2 1	Hospital	TAI	1	2 on TAI	Sigmoid	TCA	Tachycardia and painful and distended abdomen.

* Iatrogenic perforation was registered when the perforation was most plausibly caused by TAI, based on location of perforation and previous performed TAI.
** No therapy was performed when direct after the suspicion HD was made, a complication occurred, so therapy was not started yet.
*** No meconium was registered when surgical intervention took place before the production of meconium.CD: Clavien-Dindo; HAEC: Hirschsprung associated enterocolitis; TAI: transanal irrigation, TCA: total colonic aganglionosis.

Table 4
Odds Ratio (OR) of development of complication while awaiting surgery.

	Patients awaiting surgery (n = 132)		Univariable analysis		
	Without complication (n = 110)	With complication (n = 22)	OR	95% CI	P value
Male sex, *n (%)*	84 (76)	18 (82)	1.393	0.433–4.485	0.579
Gestational age in weeks, *median (IQR)*	39 (3)	39 (6)	0.988	0.807–1.210	0.908
Low birth weight, *n (%)*	17 (15)	3 (3)	1.158	0.0308–4.346	0.828
Comorbidity present, *n (%)*	31 (28)	8 (7)	1.456	0.556–3.814	0.444
Syndrome, *n (%)*	14 (13)	1 (1)	0.327	0.041–2.621	0.292
Down's syndrome	11 (10)	1 (1)	0.429	0.052–3.052	0.429
Age at diagnosis in weeks, *mean (SD)*	5 (6)	4 (7)	0.968	0.885–1.057	0.466
Length of disease, *n (%)*					
Short segment disease	89 (81)	10 (45)	-	-	-
Long segment disease	14 (13)	4 (18)	1.524	0.450–5.161	0.499
TCA	6 (5)	8 (36)	9.905	2.994–32.772	<0.001**

*$p < 0.05$.
** $p < 0.01$.

at diagnosis of included patients compared to patients included in the study of Mosiello et al. (0 weeks vs. 8.5 years). Indeed, younger patients have been found more vulnerable for a bowel perforation than older patients [25,26]. From all nine perforations in our study, four patients had a TCA, including one patient who died because of the perforation. This mortality rate is line with Wildhaber et al. describing a mortality rate of 13% in patients with a TCA while awaiting surgery [27].

In patients not receiving TAI we found three perforations, accounting for 38% of all patients not receiving TAI. One perforation was caused by HAEC and two by meconium ileus. Both patients with a meconium ileus developed the perforation soon after birth as a result of which therapy had not started yet. Therefore, we need to conclude that having a perforation based on a meconium ileus is part of the natural course of HD. Tan et al. studied the occurrence of spontaneous gastrointestinal perforation in neonates, showing that HD is the underlying cause in 46% of all small bowel perforations and in 10% of all colon perforations. The mean age at presentation of this complication was 5.5 days and 4.9 days, respectively, which is comparable to our study [28]. Therefore, we firstly advice to consider HD in the case of a neonate presenting with perforation based on a meconium ileus, as this can be part of the natural course of the disease. Secondly, we suggest surgeons to be extra watchful for a meconium ileus in patients with HD not receiving TAI in the first week after birth. This underlines the importance of early detection of HD, facilitating the immediate start of TAI after birth in patients without a TCA, aimed at preventing a perforation caused by meconium ileus [11].

We found that in patients receiving TAI, five patients had persistent obstruction (4%). Our findings are in accordance with Mosiello et al. reporting TAI to be effective in 53–95% of obstructed patients with different etiologies [23]. Once persistent obstructions are found, we showed that this may cause other complications such as failure to thrive, ileus and peritonitis [11]. Therefore, acting appropriately when persistent obstruction is present is vital, substantiating the importance of good information for caregivers if they are sent home with their neonate on TAI.

In our study, only 29% of all complication caused by TAI occurred at home. This is in line with Lu et al. showing that postoperative TAI is safely performed at home [11]. We found that, most of all complications occurring in the hospital developed soon after start of TAI, when still performed by experienced healthcare workers. Hence, we expect that in the majority of the cases, it is not the technique of performing TAI to blame, but the presence of certain risk factors might place a patient at higher risk of developing a complication.

We also found that the majority of the complications developed soon after birth, at a mean age at presentation of four weeks. Based on this finding, the advice would be to operate HD patients at neonatal age. However, other factors influencing the development of the child should also be taken into account for the ideal timing of surgery in children with HD. Concerning the neurodevelopment, the review of McCan and Soriano shows that there is no consensus about the possible higher risk from receiving anesthesia at a younger age [29]. Regarding the functional postoperative outcomes, we do know that older age at time of endorectal pull-through is a risk factor for developing postoperative complications [30]. However, we do not know how age at surgery influences the functional postoperative outcomes, owing to lacking consensus [31–36]. By taking all the information into account, we need to conclude that with the recent knowledge, no advice can be given about the optimal surgical timing in children with HD.

The second aim of the current study was to identify patients that are at risk of developing a complication while awaiting surgery. We found patients with TCA, compared to patients with short-segment disease, to have a significantly higher chance of developing a complication. This finding might be explained by the observation that, as mentioned before, perforations predominantly occur in the aganglionair bowel. Thus, patients with TCA having a longer aganglionair bowel are expected to be at higher risk to develop a perforation, than those with a shorter aganglionair bowel [26,27]. Another explanation lies in the assumption that patients with TCA have more severe distended small bowel loops. This in turn might limit abdominal space and results in more severe obstructive symptoms and hence more complications either with or without TAI [11,25,37]. We also found that a TAI-induced perforation in patients with a TCA can be highly dangerous, as we found one perforation to degenerate into a life-threatening situation and another to result in lethal outcome. Therefore, we advise patients with a (suspected) TCA, neither to await surgery nor to treat with TAI. Hence, we recommend that when the suspicion HD is made and a TCA is suspected, surgery takes place soon after diagnosis to prevent possible lethal complications as bowel perforation.

4.1. Limitations

There are some limitations to our study, which are mainly related to the retrospective study design. Because of this design, there was missing data. However, the amount of missing data was limited with only data on APGAR-scores missing in more than 10% of subjects. Hence, missing data is not expected to bias our findings. In addition, owing to the retrospective character of our study,

we might have missed cases with mild complications as mild complications might nog have been noted in the medical files [38]. On the other hand, we did include both surgical and non surgical complications, which may in turn lead to an overestimation of the prevalence of complications compared to studies only including surgical complications. Furthermore, some complications had overlapping characteristics, making it hard to retrospectively distinguish the different complications. However, we used strict diagnostic criteria to prevent this potential misidentification. We also need to emphasize that the use of CD for pediatric patients and preoperative complications is not validated, therefore possibly being less accurate for grading the complications in our study. Finally, we employed strict inclusion criteria to prevent heterogeneity in the group. This might have led to a smaller study cohort, subsequently decreasing the power to detect risk factors with a small predictive value.

4.2. Future perspectives

Our findings suggest surgeons should beware of complications and especially a bowel perforation in patients with HD awaiting surgery either with or without TAI. This suggests that future study should focus on the ideal timing of surgery in HD patients. Therefore, more information is needed on the short- and long-term functional and neurocognitive outcomes of performing surgery at neonatal and non neonatal ages in patients with HD. Next to this, we found that patients with a TCA have a higher risk of developing a complication. However, distinguishing patients with a TCA at a young age is challenging with the existing techniques [39]. Chen et al. shows that in patients with a long segment disease, including TCA, the radiological findings have a lower predictive value in estimating the correct length of disease. Therefore, we advise to be precautious to radiological predict which patients suffer from TCA. Hence, we advise future studies to focus on the development of a more reliable technique to determine the correct length of disease in neonates. Lastly, a validated pre and postoperative grading system for surgical complications in pediatric patients is required to allow the results of studies to be compared and generalize findings.

4.3. Conclusion

In conclusion, this is the first study to describe the prevalence and CD-graded severity of complications in patients with HD developed while awaiting surgery. Most frequently prevalent complication was bowel perforation. This complication can be highly dangerous in patients with a TCA as we found one perforation to degenerate into a life-threatening situation and another to results in lethal outcome. Substantiated by our finding that patients with a TCA have significantly higher risk of complications, we advise in patients with (suspected) TCA to limit the time they wait for surgery.

Declaration of Competing Interest

None of the authors have any conflicts-of-interest to disclose.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jpedsurg.2022.02.022.

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