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# Ernica Clinical Consensus Statements on Total Colonic and Intestinal Aganglionosis

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## ABSTRACT

*Background:* Hirschsprung disease is a congenital intestinal motility disorder characterized by an absence of enteric ganglion cells. Total colonic aganglionosis and near total or total intestinal aganglionosis, defined as absence of ganglion cells in the entire colon and with variable length of small bowel involved, are life-threatening conditions which affect less than 10 % of all patients with Hirschsprung disease. The aim of this project was to develop clinical consensus statements within ERNICA, the European Reference Network for rare congenital digestive diseases, on four major topics: Surgical treatment of total colonic aganglionosis, surgical treatment of total intestinal aganglionosis, management of poor bowel function in total colonic and/or intestinal aganglionosis and long-term management in total colonic and or intestinal aganglionosis.

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Surgical treatment
Long-term management

*Methods:* A multidisciplinary panel of representatives from ERNICA centers was invited to participate. Literature was searched, using specified search terms, in Medline (ALL), Embase and Google Scholar. Abstracts were screened and full text publications were selected. The panel was divided in four groups that extracted data from the full text publications and suggested draft statements for each of the major topics. A modified Delphi process was used to refine and agree on the statements.
*Results:* The consensus statement was conducted by a multidisciplinary panel of 24 participants from 10 European countries, 45 statements reached consensus after 3 Delphi-rounds. The availability of high-quality clinical evidence was limited, and most statements were based on expert opinion. Another 25 statements did not reach consensus.
*Conclusions:* Total colonic and total intestinal aganglionosis are rare variants of Hirschsprung disease, with very limited availability of high-quality clinical evidence. This consensus statement provides statements on the surgical treatment, management of poor bowel function and long-term management for these rare patients. The expert panel agreed that patients benefit from multidisciplinary and personalized care, preferably in an expert center.
*Type of Study:* Clinical consensus statement.
*Level of Evidence:* 3a.


## 1. Background

Hirschsprung disease (HSCR) is a congenital intestinal motility disorder characterized by an absence of enteric ganglion cells. It is a developmental defect of the enteric nervous system caused by incomplete migration, proliferation, differentiation, and survival of enteric nervous system progenitors. The birth prevalence is 1 in 5000 living newborns [1]. Total colonic aganglionosis (TCA) affects less than 10 % of all patients with HSCR and is defined as the absence of ganglion cells in the entire colon extending into the distal ileum up to 50 cm from the ileocaecal valve [2,3]. The most severe form of aganglionosis is near total, with aganglionosis extending up to 50–100 cm from the ileo-caecal valve or total intestinal aganglionosis (TIA) with less than 50 cm of ganglionic segment from the Treitz ligament [4,5]. TCA is a life-threatening condition with an overall mortality rate of 2–20 % due to Hirschsprung-associated enterocolitis (HAEC), intestinal failure, or associated genetic syndromes [2,3,6]. TCA remains a challenging surgical condition despite recent advances in surgical techniques and pre- and post-operative care.

To address healthcare inequalities and ensure delivery of high-quality care for patients with rare and complex diseases, the European Union (EU) initiated European Reference Networks (ERNs) [7]. ERNICA is the ERN for rare inherited and congenital digestive disorders, including HSCR.

ERNICA guidelines for management of rectosigmoid HSCR were recently published [8]. However, TCA and TIA require a different approach in various aspects of care as compared to HSCR and specific TCA and TIA clinical decision support is missing. For TCA and TIA, there is a lack of high-level evidence. Therefore, the aim of this paper was to develop clinical consensus statements on four major topics: Surgical treatment of TCA, surgical treatment of TIA, management of poor bowel function in TCA or TIA and long-term management in TCA or TIA.

A clinical consensus statement reflects opinions, drafted by content experts, for which consensus is sought using explicit methodology to identify areas of agreement and disagreement. In contrast to clinical practice guidelines, which are based primarily on high-level evidence, clinical consensus statements are more applicable to situations where evidence is limited or lacking, yet there are still opportunities to reduce uncertainty and improve quality of care.

## 2. Materials and methods

### 2.1. Panel

For this consensus statement, a multidisciplinary panel was sought amongst ERNICA members of the intestinal diseases working group. In total, 24 participants originating from 10 European countries participated in the consensus panel. Amongst the 24 panel members were three pediatric gastroenterologists, three patient representatives (one of whom is also a microbiologist) and 17 pediatric surgeons. The panel was supported by a methodologist throughout the entire project.

### 2.2. Literature search and selection

At the start of the project, a literature search was conducted by a professional information specialist. The aim of the search was identification of relevant literature on the (surgical) treatment and follow up of children with TCA or TIA published between 2006 and January 2022. Initially the main search terms were ‘total colonic aganglionosis’, ‘hirschsprung’ and related terms and combinations, later on ‘intestinal aganglionosis’ was added. The search was conducted in databased Medline (ALL), Embase and Google Scholar. After removal of duplicates all publications (n = 1004) were screened for title and abstract. The first screening was done by a pediatric surgeon (ALG) and a methodologist (WI). Both screened all results based on title and abstract using the systematic review app Rayyan© and identified useful publications according to the inclusion criteria displayed in Table 1.

After completing the screening of all titles and abstracts decision discrepancies were discussed. After the first screening round, two pediatric surgeons (ALG, AHT) screened the included publications and categorized them to the four major topics: Surgical treatment of TCA, surgical treatment of TIA, investigation and management of poor bowel function in TCA or TIA and long-term follow up in TCA or TIA, including organization of care. Some publications could be categorized to more than one topic. Any results that did not match

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**Table 1**
Inclusion criteria of publications on treatment and follow up of children with TCA or TIA prior to the Delphi process of this consensus statement.

| Patients | Patients with TCA or TIA |
|---|---|
| Intervention | Any surgical, non-surgical or pharmacological treatment |
| Comparison | Any comparison |
| Outcome | Any outcome |
| Study design | • Randomized controlled trials<br>• Cohort studies<br>• Case-control studies<br>• Case series<br>• Meta-analyses<br>• Guidelines<br>• Reviews |
| Timeline | 2006–2022 |
| Language | English |

one of these preselected topics were excluded in the second screening round. Prisma table over the literature search is shown in Fig. 1.

### 2.3. Data extraction

The panel was divided into four subgroups, each covering one of the four topics. Each group received electronic full-text versions of each article that was included for their topic. Panel members used spreadsheets to summarize the included literature for their topic and registered study design, study aim and intervention, type of patients, summary of the outcomes, the level of evidence and a suggestion for a statement to enter the Delphi process based on the publication's conclusion [9].

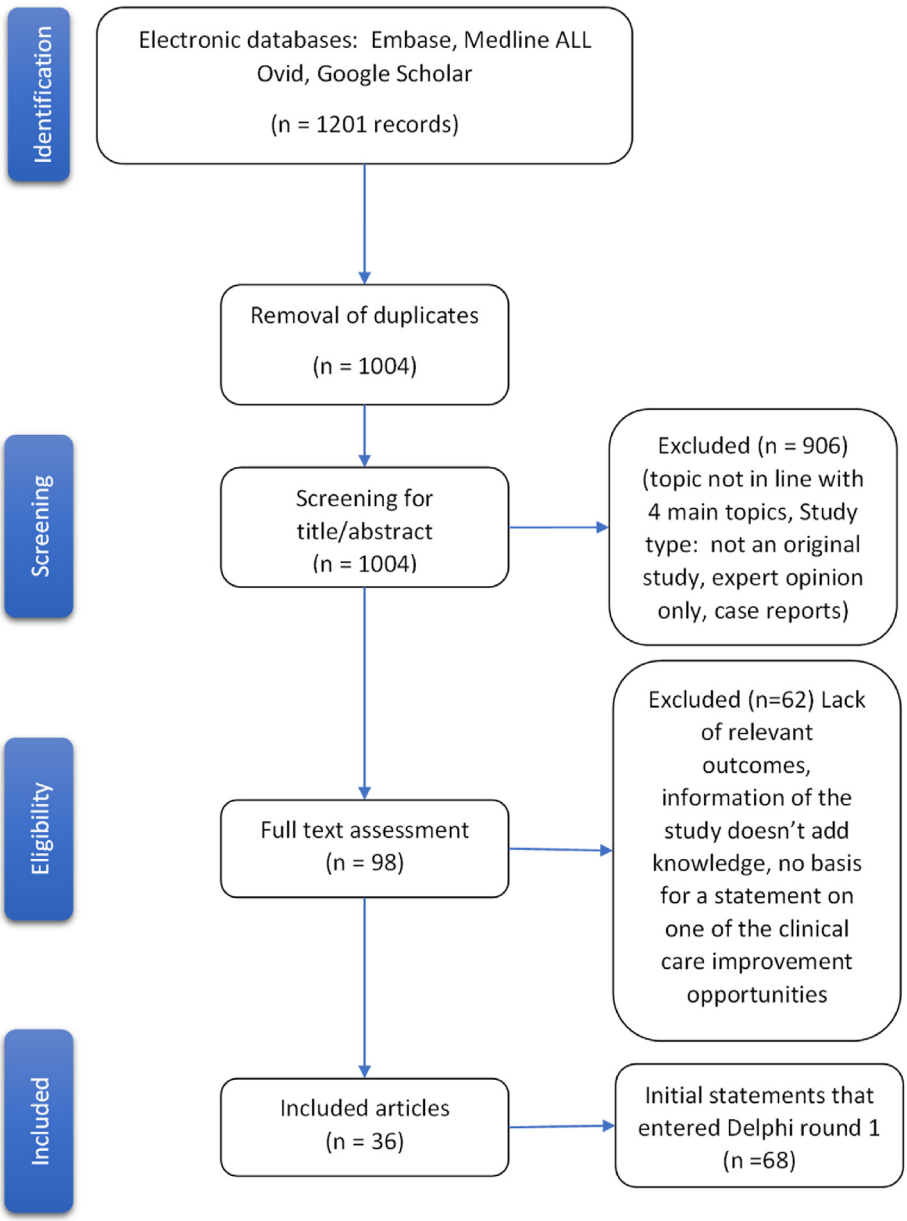


**Fig. 1.** Prisma chart of the literature search.

### 2.4. Delphi method

For this clinical consensus statement, a modified Delphi method was used. The Delphi method is a systematic approach to identify consensus among a group of experts and is recommended by the European Reference Network methodology handbooks as a method for formal consensus in case of large (>12 experts) panels that are geographically dispersed [10]. The panel composed an initial list of statements formulated as statements of fact, rather than statements of action. The initial list consisted of statements derived from the included literature, supplemented with statements based on expert opinion. Panel members were asked to complete 3 surveys each using a 9-point Likert scale to measure agreement, where 1 corresponds to 'completely disagree' and 9 to 'completely agree' [11]. For every statement there was the possibility to select 'not voting' if a panel member felt that the topic was outside their field of expertise. Consensus criteria as displayed in Table 2 were agreed upon before voting.

After each round a group discussion was organized where statements with a near or no consensus were discussed to determine whether they should be refined and revoted or omitted completely. These discussions provided panel members with the opportunity to explain their vote to the rest of the panel and listen to the motivation of others. If a statement was refined and entered a new survey, the initial statement as well as the score from the previous round was added to the survey information. Each of the surveys contained comment boxes to allow panel members to provide an immediate rationale that enhanced the discussions. An overview of the process to create this clinical consensus statement is displayed in Fig. 2.

## 3. Results

### 3.1. Delphi process

After screening the 1004 publications for the title and abstract, 98 publications were included for full text evaluation. Based on the literature and a group discussion during the ERNICA meeting in Helsinki, 68 statements were created to enter the Delphi process. After the first round, consensus was reached for 34 statements. A total of 21 statements with no or near consensus were reworded or clarified, the remaining 13 were omitted. One statement was split into 3 more specific statements and statements 12 and 52 were added. 26 statements entered the second Delphi round, resulting in an additional 11 statements for which consensus could be reached. Four statements with a near-consensus score (11, 14, 37 and 48) were re-worded and entered a final third round. This resulted in consensus for only one of these statements. After 3 rounds the panel reached consensus on 45 statements, and the key information for these consensus statements is summarized below. An overview of the Delphi process is displayed in Fig. 3.

### 3.2. Key statements

In total 45 statements reached consensus after the Delphi surveys (Table 3). They were subcategorized into the four major topics: Surgical treatment of TCA, surgical treatment of (near) TIA, poor bowel function and long-term follow up, including organization of care.

**Table 2**
Consensus criteria of statements voted on during the Delphi process.

| Category | Mean Score | | Outliers[a] |
|---|---|---|---|
| Consensus | ≥7.00 | and | ≤1 |
| Near consensus | ≥6.50 | and | ≤2 |
| No consensus | <6.50 | or | ≥3 |

[a] >2 from the mean in each direction.

#### 3.2.1. Surgical management of TCA and (near) TIA

Since TCA is a rare disease, an expert center should be involved in the evaluation and management of a patient with TCA (Statement 12). Due to differences between health care systems in European countries, the exact definition of an expert center is problematic, but the panel agreed that an expert center should offer multidisciplinary care by a complete team including pediatric surgeon, pediatric gastroenterologist or specialized pediatrician, nurses, dietician, pathologist and psychologist, as previously described by Kyrklund et al. [8]. For patients with suspected or verified (near) TIA, the panel agreed that early referral to an expert intestinal rehabilitation center may prevent complications related to long-term parenteral nutrition dependence (Statement 16) [2,5,12–22], and promote timely listing for small bowel transplantation if needed [23].

At initial surgery, intraoperative representative mapping biopsies are needed to determine the level of aganglionosis and appropriate level to form a stoma. This may optimize positioning of a stoma and prevent stoma revisions (Statement 5 and 13) [14,15,24–28]. Representative histological intestinal mapping includes multi-level biopsies starting from the rectum and continuing orally beyond the level where the pathologist reports ganglion cells. A 360-degree biopsy is recommended at the most distal part of the ganglionic bowel, usually at the level of the stoma. The mapping biopsies should be performed prior to pull-through surgery to confirm the diagnosis and allow for an adequately performed pull-through of normally gangliated bowel.

Due to a lack of evidence no unambiguous expert opinion was reached regarding whether one specific pull-through procedure is preferable over others. The panel therefore concurred that the pull-through technique should be chosen based on the experience of the operating surgeon (Statement 3) [29,30]. It may be considered to leave a covering stoma after the reconstruction in selected patients (Statement 4), particularly patients undergoing ileo-anal J-pouch anastomosis, neonates, syndromic patients, or patients in suboptimal general condition [29]. The panel failed to reach consensus on timing for surgical reconstruction but agreed that the optimal timing of definitive pull-through depends on the length of the aganglionic segment, stoma output, the patients' age, and the caregivers' preferences (Statement 11). Remaining diverted bowel may increase the risk of enterocolitis and therefore timely removal can be beneficial (Statement 17) [14].

#### 3.2.2. Poor bowel function after pull-through surgery

To accurately treat patients with poor bowel function, the panel agreed that diagnosing the underlying cause of fecal incontinence and, or obstructive symptoms provides important information to guide the treatment strategy (Statement 24). In addition to clinical examination of a patient with fecal incontinence and, or, obstructive symptoms, investigations should include imaging, examination under general anesthesia, re-biopsies as well as endoscopic examination to exclude surgical complications (twisted pull-through, transition zone or stenosis) as appropriate. It may also be helpful to include a pediatric gastroenterologist or specialized pediatrician to rule out other gastro-intestinal causes. Patients with a damaged anal canal are at higher risk of fecal incontinence (Statement 23) [8,31]. The panel agreed that plain abdominal radiographs and contrast enema are appropriate to diagnose bowel dilation or twisted pull-through (Statement 19) but MRI could also be indicated in selected cases. In patients with dysmotility, full thickness small bowel biopsies may be indicated to exclude remaining

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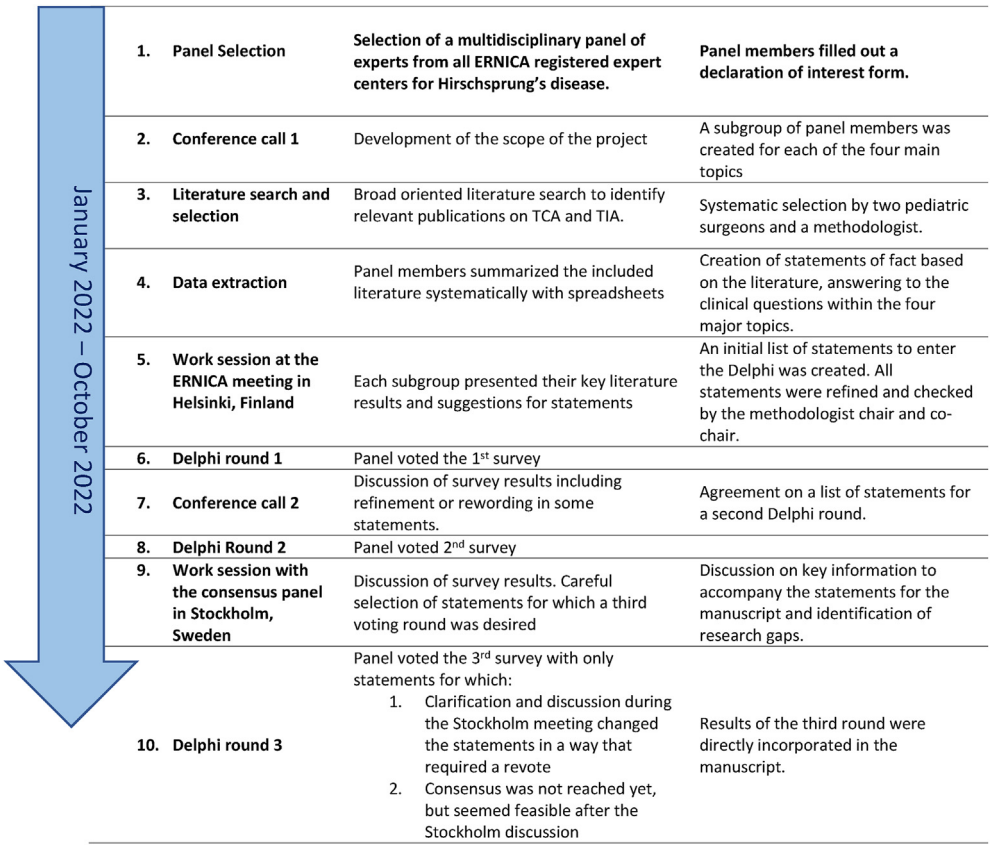


**Fig. 2.** Workflow for the development of this consensus statement.

aganglionosis or other causes of dysmotility (Statement 22). Obtaining a second opinion by another experienced pathologist may be helpful.

For patients with diarrhea, loperamide (Statement 28) and cholestyramine can be used (Statement 31) although there is little evidence for their efficacy, especially for patients without a colon. Treatment with loperamide should be evaluated every two weeks to weigh beneficial effect against side effects [8,32]. In patients with diarrhea, sodium chloride supplementation may be needed to prevent hyponatremia, based on the dosage of sodium/potassium ratio on a single micturition (which must be > 1) (Statement 33). If a patient does not pass stools for 24 h or has signs of HAEC, treatment with loperamide is no longer indicated and should be stopped (Statement 29). As per loperamide, the use of Cholestyramine should be evaluated every two weeks and may continue long-term if monitoring for any deficiencies of fat-soluble vitamins is ensured. By binding bile acids and reducing their osmotic effect, cholestyramine may also have a beneficial effect on perineal rash.

For suspected small bowel bacterial overgrowth, single courses or cyclic use of broad-spectrum antibiotics may be considered ensuring that HAEC has been excluded (Statement 38). This treatment is indicated in exceptional circumstances and after carefully considering other medical and surgical causes and treatment options [33]. Patients with outlet obstruction and HAEC may benefit from decompression with a transanal tube (Statement 43) [34]. Based on current evidence, the role of probiotics to prevent HAEC is unclear (Statement 39) [35,36].

For patients with poor bowel function and intractable fecal incontinence or diarrhea, an ileostomy can be considered (Statement 35). The panel agreed that it is necessary to involve patients and parents in discussions regarding this decision. In cases with persistent obstructive symptoms and recurrent HAEC, redo pull-through may be considered (Statement 46) [29]. Before proceeding with a redo procedure, a thorough investigation including a pathology review is needed, to rule out residual aganglionsis and other options (Statement 7).

### 3.2.3. *Long-term follow up and organization of care*

The long-term management of TCA can be challenging. Therefore, the panel agreed that patients benefit from long-term management and follow-up by a multidisciplinary team (Statement 52). Like other ERNs, ERNICA also offers consultation of expert panels for such ultra-rare cases. Regular follow-up is an effective approach that may improve long-term outcomes (Statement 47) [3,34], as it can help to improve residual symptoms and identify complications early. Close monitoring with personalized management of growth- and bowel function is required (Statement 49) [37]. Treatment and follow-up in an expert center may reduce mortality and morbidity (Statement 51) [3,8]. The regular follow-up in an expert center is important for these patients, but the frequency needs to be personalized for each patient depending on the length and function of the remaining bowel, nutritional status, and comorbidities. To avoid delayed discovery of clinical issues that could have been addressed at an early stage, regular check-ups remain of great importance even if patients are doing well.

More specifically, monitoring of growth (Statement 53) as well as fluid and electrolytes in blood and urine provides important information regarding the intestinal nutrient uptake (Statement 54) [38]. Growth should be monitored with standardized growth charts (Statement 61). The monitoring of sodium in urine is especially important in patients with TCA (Statement 55). Optimal sodium balance is defined as U−Na >30 mmol/l and, or U−Na/U−K≥1

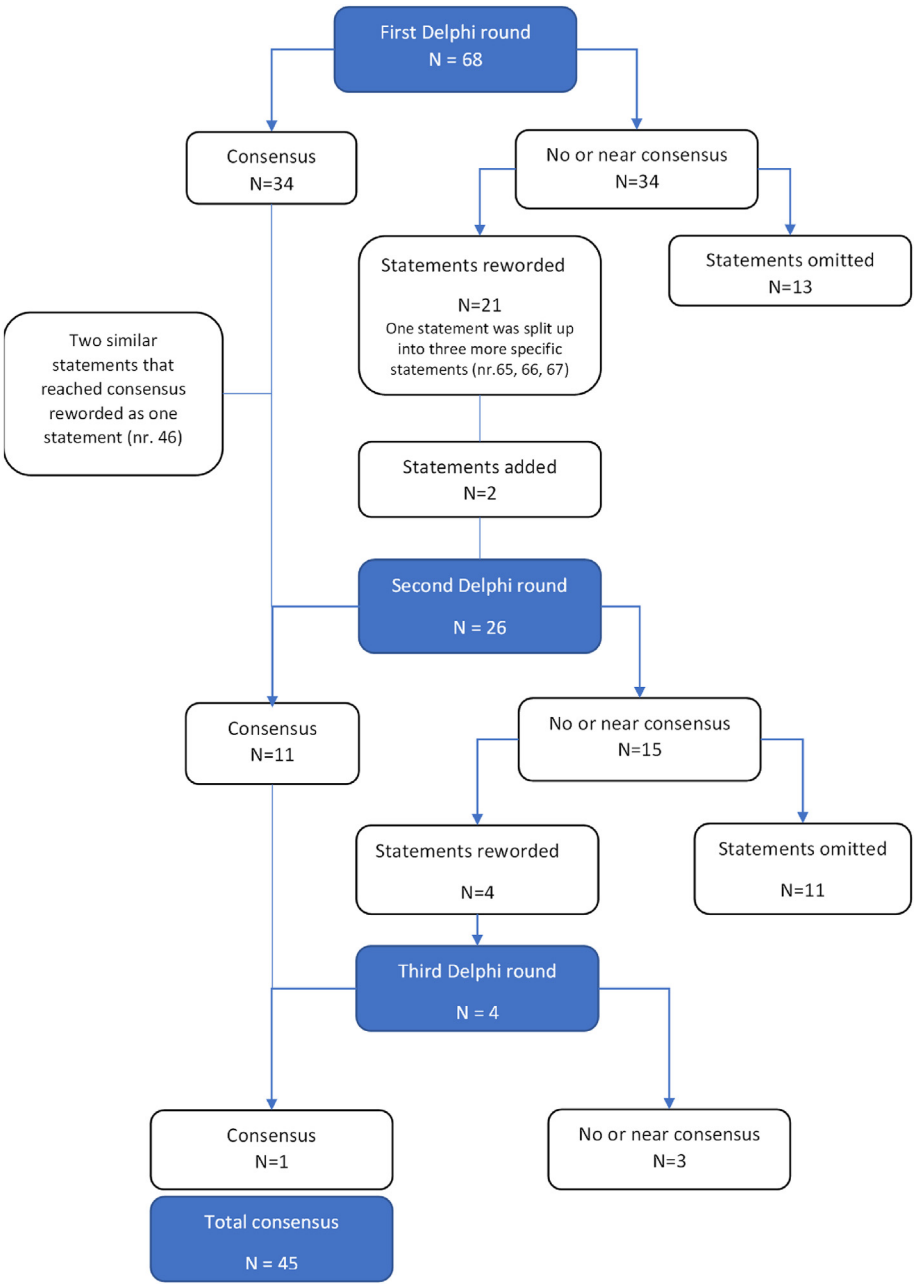


**Fig. 3.** Delphi process.

(Statement 56) [39]. The monitoring of vitamins also provides important information in the follow-up of patients as well (Statement 57) and the panel agreed that patients benefit from being regularly reviewed by a dietitian (Statement 60). Regular monitoring was difficult for the panel to define, but they agreed that closer monitoring, is always indicated when a patient has signs or symptoms of fluid imbalance (Statement 59).

Children with less than 80 cm of remaining small bowel may have a poorer chance to wean off parenteral nutrition (Statement 62). It is important to keep the balance between benefits and harms of parenteral nutrition and avoid excessive enteral feeding [14]. For patients with home parenteral nutrition, the panel agreed to recommend the ESPGHAN guidelines for monitoring (Statement 63) and that referral to a center with home parenteral nutrition team is warranted if patients still depend on parenteral nutrition by the age of transition of care (Statement 64) [23].

Panel members agreed that patients and parents should be offered referral for genetic consultation (Statement 66). *RET* gene mutation analysis is beneficial for the exclusion of the rare possibility of MEN 2A associated mutations (Statement 65). Patients with associated syndromes may be referred for more specific genetic screening (Statement 67). Since genetic testing is evolving rapidly, genetic counseling is essential but only if approved by the family.

The panel uniformly agreed that patients benefit from a standardized transition program from pediatric to adult care (Statement 50). The positive impact of a structured transition to adult care has previously been shown for patients with HSCR and especially for patients with TCA at risk of nutritional deficiencies. The transition of care is important for future monitoring and treatment [3,8,40]. Overall, the assessment of the literature indicates that TCA is a drastically more severe condition with respect to short segment

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**Table 3**
Consented statements for TCA.

| Consensus statements on Surgical management of TCA | | | | | |
|---|---|---|---|---|---|
| Number | Statement | Mean | Outliers | Quality improvement opportunity[a] | Evidence/Expert opinion |
| 3 | Choosing a pull-through technique, based on experience of the operating surgeon, may lead to better outcomes | 7.73 | 1 | Educating and empowering clinicians and patients | Evidence 2b |
| 4 | A covering stoma may be considered in selected patients | 7.75 | 0 | Promoting appropriate care | Evidence 4 |
| 5 | Intraoperative frozen section biopsy may optimize the ostomy position and prevent stoma revisions | 8.36 | 1 | Educating and empowering clinicians and patients | Evidence 4 |
| 9 | Redo surgery may be beneficial for patients with residual agangliosis AND long term functional problems resistant to conservative treatment or botox | 7.85 | 1 | Promoting appropriate care | Expert |
| 11 | The timing of pull-through depends on length of aganglionosis, stoma output, the patients'age, and the caregivers' preferences | 7.83 | 1 | Promoting appropriate care | Expert |
| 12 | An expert center should be involved in the evaluation and management of a patient with TCA | 8.43 | 0 | Improving access to care | Expert |
| 13 | Representative multi-level mapping biopsies are appropriate to determine the level of aganglionosis and stoma | 8.59 | 0 | Reducing inappropriate or harmful care | Evidence 4 |
| Consensus statements on Surgical management of (near) total intestinal aganglionosis | | | | | |
| Number | Statement | Mean | Outliers | Quality improvement opportunity[a] | *Evidence/Expert opinion* |
| 16 | Early referral to expert intestinal rehabilitation group may prevent complications related to long-term parenteral nutrition dependence | 8.36 | 1 | Promoting appropriate care | Evidence 2a |
| 17 | Remaining diverted bowel may increase the risk of enterocolitis, therefore timely removal can be beneficial | 7.10 | 1 | Promoting appropriate care | Evidence 2a |
| Consensus statements on poor bowel function investigation | | | | | |
| Number | Statement | Mean | Outliers | Quality improvement opportunity[a] | *Evidence/Expert opinion* |
| 7 | A pathology review provides important information to guide the indication for a redo pull-though | 8.40 | 0 | Educating and empowering clinicians and patients | Expert |
| 19 | Plain abdominal radiographs and contrast enema are appropriate to diagnose bowel dilatation or twisted pull through in patients with poor bowel function. | 7.50 | 1 | Promoting appropriate care | Expert |
| 22 | In case of dysmotility in patients, full thickness small bowel biopsies may be a part of the investigation | 7.85 | 0 | Promoting appropriate care | Expert |
| 23 | Patients with a damaged anal canal are at higher risk of fecal incontinence | 8.41 | 0 | Educating and empowering clinicians and patients | Evidence 2a |
| 24 | Diagnosing the cause of fecal incontinence and/or obstructive symptoms provides important information to guide the treatment strategy | 8.55 | 0 | Promoting appropriate care | Expert |
| Consensus statements poor bowel function management | | | | | |
| Number | Statement | Mean | Outliers | Quality improvement opportunity[a] | *Evidence/Expert opinion* |
| 28 | Loperamide can be used for the treatment of diarrhea if no clinical signs or symptoms of suffering from a gastrointestinal infection or small bowel bacterial overgrowth | 7.70 | 1 | Promoting appropriate care | Expert |
| 29 | If patients pass no stool for 24 h or have signs of Hirshprung's associated entereocolitis, treatment with loperamide is no longer indicated | 7.95 | 0 | Reducing inappropriate or harmful care | Expert |
| 31 | Cholestyramine can be helpful in the treatment of diarrhea and perineal rash | 7.00 | 1 | Promoting appropriate care | Expert |
| 33 | Treatment with sodium chloride supplementation can be used in case of diarrhea or failure to thrive with a low sodium excretion in urine (Na <30 mmol/L and Na/K < 1) | 8.63 | 0 | Promoting appropriate care | Expert |
| 35 | Ileostomy can be considered for patients with intractable fecal incontinence or intractable diarrhea | 8.09 | 1 | Educating and empowering clinicians and patients | Expert |
| 38 | One single treatment period or cyclical use (1 week per month) of broad-spectrum antibiotics (e.g., metronidazole or ciprofloxacin) may be considered in children with TCA and suspected small bowel bacterial overgrowth in exceptional circumstances and after re-considering other medical or surgical management options | 7.40 | 1 | Promoting appropriate care | Evidence 4 |
| 39 | Based on the current evidence, it is unclear what the role of probiotics is to prevent Hirschsprung-associated enteritis | 7.80 | 0 | Educating and empowering clinicians and patients | Evidence 1b |
| 43 | Patients with obstructive symptoms and Hirschsprung-associated enteritis may benefit from decompression with a transanal tube | 7.60 | 1 | Promoting appropriate care | Evidence 4 |

(*continued on next page*)

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**Table 3** (*continued*)

| Consensus statements poor bowel function management | | | | | |
|---|---|---|---|---|---|
| Number | Statement | Mean | Outliers | Quality improvement opportunity[a] | *Evidence/Expert opinion* |
| 46 | Redo surgery may be considered in patients with persistent obstructive symptoms and recurrent Hirschsprung-associated enteritis | 7,78 | 1 | Promoting appropriate care | Evidence 4 |
| **Consensus statements on organization of care** | | | | | |
| Number | Statement | Mean | Outliers | Quality improvement opportunity[a] | *Evidence/Expert opinion* |
| 47 | Regular follow-up is an effective approach that may improve long-term outcomes in patients | 8.24 | 1 | Promoting appropriate care | Evidence 4 |
| 49 | Close monitoring with personalized management of growth and bowel function is required in the follow-up | 8.55 | 1 | Promoting appropriate care | Evidence 4 |
| 50 | Patients benefit from a transitional program from pediatric to adult care | 8.64 | 0 | Promoting appropriate care | Evidence 4 |
| 51 | Treatment and follow-up in an expert center reduces mortality and morbidity | 8.55 | 1 | Educating and empowering clinicians and patients<br>Reducing inappropriate or harmful care | Expert |
| 52 | Treatment and follow-up should be carried out in a multidisciplinary team | 8.71 | 0 | Promoting appropriate care | Expert |
| **Consensus statements on Long-term management** | | | | | |
| Number | Statement | Mean | Outliers | Quality improvement opportunity[a] | *Evidence/Expert opinion* |
| 53 | Routinely monitoring growth during follow-up provides important information of the intestinal nutrient uptake | 8.63 | 0 | Promoting appropriate care | Expert |
| 54 | Regular monitoring of fluid and electrolytes in blood and urine may provide important information on growth and nutrient uptake or loss | 8.41 | 1 | Promoting appropriate care | Evidence 4 |
| 55 | Monitoring of sodium in urine provides important information in the follow up of patients | 8.30 | 1 | Promoting appropriate care | Evidence 4 |
| 56 | A healthy fluid balance for patients is defined as Na >30 mmol/l in urine and Na/K $\geq$ 1. | 7.94 | 1 | Reducing regional variations in delivery of care | Evidence 4 |
| 57 | Monitoring of vitamins, including at least B12 and iron, provides important information in the follow-up of patients | 7.95 | 1 | Promoting appropriate care | Expert |
| 59 | Closer monitoring is indicated when a patient has signs or symptoms of fluid imbalance | 7.90 | 1 | Promoting appropriate care | Expert |
| 60 | Patients should be regularly reviewed by a dietitian, especially during childhood and growth | 7.90 | 1 | Promoting appropriate care | Expert |
| 61 | Growth monitoring with standardized growth charts provides important information in the follow up of patients | 8.41 | 0 | Promoting appropriate care | Expert |
| 62 | Children with less than 80 cm of remaining small bowel may have poorer chance to wean off parenteral nutrition | 7.39 | 1 | Educating and empowering clinicians and patients | Expert |
| 63 | Recommendations in the ESPGHAN guideline for home parenteral nutrition are appropriate for the monitoring of TCA patients dependent on home parenteral nutrition | 8.45 | 0 | Educating and empowering clinicians and patients | Expert |
| 64 | Referral to a center with a home parenteral nutrition team is warranted if patients still depend on parenteral nutrition by the age of transition of care | 8.41 | 0 | Facilitating coordination and continuity of care | Expert |
| 65 | Genetic testing of RET is beneficial as it allows a more accurate estimation of the risk of recurrence, and exclusion of the rare possibility of a MEN 2A-associated RET mutation | 7.78 | 1 | Promoting appropriate care | Expert |
| 66 | Offering referral for genetic consultation is appropriate | 8.36 | 1 | Educating and empowering clinicians and patients | Expert |
| 67 | Referral for genetic screening of the specific gene associated with the syndromic phenotype is appropriate for patients with an associated syndrome | 8.17 | 1 | Promoting appropriate care | Expert |
| 68 | Routinely offering patients and their families psychological support is part of appropriate care | 8.41 | 1 | Promoting appropriate care | Expert |
| 69 | Referral to a psychologist is appropriate if patients experience psychological problems | 8.50 | 0 | Promoting appropriate care | Expert |
| 70 | Referral to an endocrinologist is appropriate for patients with pubertal delay | 8.59 | 0 | Promoting appropriate care | Expert |

[a] Chosen between the following options.
1. Promoting appropriate care.
2. Reducing inappropriate or harmful care.
3. Reducing regional variations in delivery of care.
4. Improving access to care.
5. Educating and empowering clinicians and patients.
6. Facilitating coordination and continuity of care.
7. Facilitating ethical care.

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HSCR, and that TCA patients and TCA families do require higher standards of care also during the transition to adulthood and potentially for the entire lifespan.

In some patients with TCA, additional disciplines of care can be of great value. A chronic and complex disease such as TCA can place stress on families, therefore the panel agreed that psychological support should, at least, be offered to patients and their families (Statement 70) and that such support should preferably be available within the regular multidisciplinary team. Referral to a psychologist is appropriate if the patients experience psychological problems (Statement 69). For patients with pubertal delay, a referral to an endocrinologist is appropriate (Statement 70).

## 4. Discussion

The purpose of this paper was to reflect opinions drafted by content experts for which consensus was sought using an explicit method. In doing so, areas of consensus were identified and areas of ambiguity that require further research were uncovered. The panel reviewed the current literature and could confirm that most studies were limited to retrospective reviews, small uncontrolled case series, and expert opinions with low levels of evidence. Therefore, some statements are based on expert opinion only. Important areas of disagreement or ambiguity and their research implications are discussed below. The accompanying statements are summarized in Appendix 1.

### 4.1. Surgical management of TCA and (near) TIA

The panel did not reach consensus on a preferable surgical method for patients with TCA. The statement "the current evidence indicates similar functional outcomes after different pull-through techniques" reached near consensus since a few panel members agree that J-pouch may result in better functional outcomes compared to other techniques [40]. There are several different techniques used for pull-through in TCA patients, with the largest series published on J-pouch and Duhamel, but the lack of comparative studies and ambiguous opinions in the panel left these statements without consensus (Appendix 1, Statement 1,2) [3].

The best timing of reconstructive surgery and stoma closure did not reach consensus (Appendix 1, Statement 10). In a small study from Reinshagen et al., including 12 TCA patients treated with J-pouch at 16 month of age and with stoma closure four months later, no postoperative complications were reported [39]. The panel was unable to reach consensus on a specific age that is optimal for pull-through, but could agree on the optimal patient clinical condition, which ended up in Statement 11.

The statement concerning TIA that Safest initial surgery involves formation of a jejunostomy at least 40 cm distal to the ligament of Treitz despite leaving a variable aganglionic segment of jejunum in continuity only reached near consensus given several panel members thought that a stoma should be created more distally (Appendix 1, Statement 14). One of the reviewed studies indicated that it would be preferable to create a gastrostomy at the time for jejunostomy formation. The panel did not reach consensus since some panel members thought that enteral feeding is, usually, not a problem, and that enteral feeding should be encouraged since it decreases the risk of intestinal failure-associated liver disease (Appendix 1, Statement 15) [24].

### 4.2. Poor bowel function

For the investigation of a patient with poor bowel function after reconstructive surgery, the panel could not reach consensus regarding the role of anorectal manometry (Appendix 1, Statement 20). Anorectal manometry is not available as a standard investigation at all expert centers and the panel concluded that further evaluation of anorectal manometry is needed before the method can be suggested as an appropriate investigation. For the same reason, statement for MRI as an appropriate investigation to exclude a twisted pull-through, also did not reach consensus with the panel suggesting that endoscopy should be the method of choice to exclude a twist until there is enough experience with MRI in these patients (Appendix 1, Statement 25). The statement "transanal neorectal biopsies are appropriate to provide insight into remaining aganglionosis and/or transition zone in patients with poor bowel function" reached near consensus (Appendix 1, Statement 21).

There is a lack of knowledge and experience regarding pharmacological management with proton pump inhibitors, histamine 2 receptor antagonists, diosmectide and glucagon-like peptides 2 (GLP-2) (Appendix 1, Statement 26,27,30,34). These medications may be used to decrease stoma output or diarrhea and there were positive clinical experiences among the panel members for the use of GLP-2 for patients with TIA, but none of these statements reached consensus. Normal daily intake of fiber is important for these patients, but the need for supplemental fibers was not universally agreed upon by the panel (Appendix 1, Statement 32), since it is unknown what effect, they have in individuals without a colon and given that a healthy daily fiber intake can also be reached through a patient's diet.

For patients with TCA and fecal incontinence, compared to rectosigmoid HSCR, the panel suggested that trans-anal decompression could be used instead of irrigations (Appendix 1, Statement 36).

For patients with HAEC, several statements did not reach consensus. The panel did not agree that the management of HAEC in TCA patients is similar to HAEC in rectosigmoid HSCR patients [8]. Since TCA patients lack a colon, handling fluid and electrolyte balance in cases with HAEC is challenging. Therefore, the panel suggested a low threshold for hospital admission for treatment of confirmed or suspected HAEC in TCA patients. Reaching consensus about HAEC and indications for the use of antibiotics was difficult since the panel had differing opinions on when and what type of antibiotic should be used, which was the reason this statement only reached near consensus (Appendix 1, Statement 37) [3,27]. Many panel members did agree that antibiotics should be reserved for confirmed HAEC with careful monitoring to avoid over prescription. The panel did not agree that patients with recurrent HAEC may benefit from a permanent ileostomy putting forward that the stoma does not necessarily need to be permanent (Appendix 1, Statement 40). The panel suggested that in difficult cases, where a stoma is discussed, the expert team should always consider the benefits and harms of life with and without a stoma. Intersphinteric botulinum toxin injections play a role in decreasing the risk for recurrent HAEC in patients with recto-sigmoid HSCR, however this statement reached only near consensus since obstructive symptoms were considered less common in patients with TCA (Appendix 1, Statement 41). [8]. For the same reasons the statement "intersphincteric botulinum toxin injections may be beneficial for patients with persistent obstructive symptoms" only reached near consensus. The quality of evidence for this intervention in TCA was very low and therefore this could not support the decision for many panel members. The larger part of the panel thought that botulinum toxin injection could be an option, but that transitional zone pull-through, anastomotic stricture, rolled cuff and twisted pull-through should be ruled out first (Appendix 1, Statement 48) [8].

The statement that rectal irrigations can be beneficial to prevent recurrent enteritits reached near consensus since there was a difference of opinion in the panel on the use of small bowel irrigations compared to transanal decompression (with a rectal tube) (Appendix 1, statement 45) [41,42].

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### 4.3. Long-term follow up

For long-term follow up, the panel tried to define an appropriate interval for follow up of patients with TCA, but this was difficult since the panel agreed that individualized care is warranted. Unnecessary testing should be avoided, hence why the intervals between testing of blood and urine may be prolonged if a patient is stable (Appendix 1, Statement 58).

### 4.4. Strengths and limitations

In rare diseases where large cohorts and randomized clinical trials are uncommon and almost impossible, clinical consensus statements are sufficient to reflect uncertainties and gaps in knowledge. Through a consensus development process, many of the uncertainties can be overcome, a consensual opinion reached, and statements formed. The strength of this study is the diverse and relevant panel of experts, representing several specialties with surgical and medical expertise in TCA care as well as patient representatives. In the process, we also chose an anonymized Delphi voting process, to decrease the risk of a single individual dominating the discussion and decisions. The whole process strictly followed the well-established, structured, systematic approaches recommended to the development of consensus [11,43].

There are several limitations that need to be recognized, including the limited published literature. This is due to disease characteristics of TCA and the clinical heterogeneity among TCA patients, which mean that either trials are difficult to interpret or that they may only be directly applicable to a subset of patients. This project was initiated before the Covid-19 pandemic and during the worst outbreak, there were no other possibilities than online meetings. For this kind of project, although many steps of the process of developing clinical consensus, can be done online, it has been obvious how important in person meetings are for dynamic and productive group discussions The project was fortunately able to restore such meetings for the finalization of this consensus. Also, to be able to progress with a project like this, strict definitions for TCA and near TIA were needed and decided on by the experts. Although, there are also other definitions used in the literature for both TCA and near TIA.

## 5. Future perspectives

This consensus statement has shown that there are knowledge or research gaps regarding several aspects of treatment and follow up of patients with TCA or TIA. The preferred surgical methods and timing of definitive surgery are two important aspects that will need further research. The role of using a J-pouch for the pull-through procedure needs to be defined. Furthermore, the role of diagnostic modalities such as anorectal manometry and MRI as tools to investigate for poor bowel function is still unclear. The efficacy or effectiveness of botulinum toxin injection treatment in patients with TCA or TIA has been insufficiently addressed both to treat outlet obstruction and prevent HAEC. The definitions, causes and predisposing factors for HAEC and bowel dysmotility in the remaining ganglionic bowel remain incompletely understood. Also, the composition of intestinal microbiota and the role of probiotics is a topic of current research interest in HAEC. The prevalence of small bowel inflammation and its impact on long term functional outcomes is unclear. Monitoring and medical treatment of TCA patients has barely been studied and more research should be focused also on this area. Most of these research questions need well designed, prospective, controlled, multicenter studies to answer. The research gaps that have been listed here are highly prioritized by the patient's representatives.

## 6. Conclusions

In this consensus statement, conducted by a multidisciplinary panel of 23 participants originating from 10 European countries, 45 statements reached consensus after 3 Delphi-rounds. Most statements were based on expert opinion. For treatment and follow-up of individuals with a rare disease as TCA, there is limited availability of high-quality clinical evidence. However, the expert panel agreed these patients require highly specialized, multidisciplinary, and personalized care, preferably in an expert center from infancy up to adulthood. Most statements were based on expert opinion. Further prospective and multicenter studies are needed for more clinical evidence.

Overall, the assessment of the literature indicates that TCA is a drastically more severe condition with respect to short segment HSCR, and that TCA patients and TCA families do require higher standards of care also during the transition to adulthood and potentially for the entire lifespan. Therefore, patients and parents should be informed about the availability of current guidelines and consensus statements and could benefit from information on the availability of patient and parent support groups as early as possible. These networks are active in many countries for information and peer support on lived experience of the disease.

## Ethics approval and consent to participate

Not applicable.

## Consent for publication

Not applicable.

## Availability of data and materials

Data sharing is not applicable to this article as no datasets were generated or analysed during the current study.

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Ernica.

## Declaration of competing interest

All contributing authors have submitted a declaration of interest form. No competing interests were noticed, all declarations are available on request.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jpedsurg.2024.04.019.

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