

ERNICA Consensus Conference on the Management of Patients with Esophageal Atresia and Tracheoesophageal Fistula: Follow-up and Framework

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Abstract

Keywords

- ▶ esophageal atresia with tracheoesophageal fistula
- ▶ pediatric surgery
- ▶ follow-up
- ▶ management
- ▶ consensus conference

Introduction Improvements in care of patients with esophageal atresia (EA) and tracheoesophageal fistula (TEF) have shifted the focus from mortality to morbidity and quality-of-life. Long-term follow-up is essential, but evidence is limited and standardized protocols are scarce. Nineteen representatives of the European Reference Network for Rare Inherited Congenital Anomalies (ERNICA) from nine European countries conducted a consensus conference on the surgical management of EA/TEF.

Materials and Methods The conference was prepared by item generation (including items of surgical relevance from the European Society for Pediatric Gastroenterology Hepatology and Nutrition (ESPGHAN)-The North American Society for Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN) guidelines on follow-up after EA repair), item prioritization, formulation of a final list containing the domains Follow-up and Framework, and literature review. Anonymous voting was conducted via an internet-based system. Consensus was defined as $\geq 75\%$ of those voting with scores of 6 to 9.

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Results Twenty-five items were generated in the domain Follow-up of which 17 (68%) matched with corresponding ESPGHAN-NASPGHAN statements. Complete consensus (100%) was achieved on seven items (28%), such as the necessity of an interdisciplinary follow-up program. Consensus $\geq 75\%$ was achieved on 18 items (72%), such as potential indications for fundoplication. There was an 82% concordance with the ESPGHAN-NASPGHAN recommendations. Four items were generated in the domain Framework, and complete consensus was achieved on all these items.

Conclusion Participants of the first ERNICA conference reached significant consensus on the follow-up of patients with EA/TEF who undergo primary anastomosis. Fundamental statements regarding centralization, multidisciplinary approach, and involvement of patient organizations were formulated. These consensus statements will provide the cornerstone for uniform treatment protocols and resultant optimized patient care.

Introduction

Since the first successful primary repair of esophageal atresia (EA) in 1941, improvements in operative and perioperative care have led to better outcomes and have shifted the focus from mortality to morbidity and quality-of-life-issues.^{1–9} Esophageal atresia is no more just a neonatal surgical challenge, but rather a lifelong issue for the patient.^{1,6,7,10} It appears that respiratory, nutritional, and gastroenterological issues are the most prevalent sequelae—not only in the first years of life, but also in adolescence and adulthood^{6,7} requiring constant long-term follow-up following standardized protocols in specialized centers including interdisciplinary transition programs.

However, precisely formulated guidelines on the follow-up of patients with EA are scarce.^{10,11}

In 2016, the gastrointestinal working group of the *International Network on Esophageal Atresia* (INoEA) comprising members from *The European Society for Pediatric Gastroenterology Hepatology and Nutrition* (ESPGHAN) and *The North American Society for Pediatric Gastroenterology, Hepatology and Nutrition* (NASPGHAN) published guidelines for the management of gastrointestinal and nutritional complications in children with EA with (TEF) tracheoesophageal fistula.¹

In 2017, the European Reference Network on Rare Inherited and Congenital Anomalies (ERNICA) has been established in response to the European Commission's call for the setup of European Reference Networks for rare diseases.¹² The mission of ERNICA is to promote optimal patient care for rare inherited and congenital digestive track-related disorders from pediatric age to adulthood providing high quality and accessible education, supporting research, improving clinical standards and services and reducing health inequalities in Europe.^{13–17}

During recent ERNICA meetings, participants agreed to establish consensus on all relevant aspects of the surgical management of patients with EA including *Follow-up* as an urgent objective of ERNICA.

In this first ERNICA consensus conference focusing on the management of patients with EA and TEF, two priorities were addressed: The recently published results of the first part of

the ERNICA consensus conference focused on *Diagnostics, Preoperative, Operative and Postoperative Management*.¹⁸ The second part of the conference mainly dealt with *Follow-up and Framework* from a surgical perspective which will be presented in the following.

Materials and Methods

The general methodological approach has been recently published when presenting the first part of the ERNICA consensus conference on *Diagnostics, Preoperative, Operative and Postoperative Management*.¹⁸ The second part which is reported in this manuscript differed from the first part in details. Therefore, the two parts are presented separately.

The conference, which dealt exclusively with the management of patients with EA with TEF who undergo primary anastomosis, took place in Berlin on the October 25th and 26th, 2018. In total, 14 pediatric surgeons, one pediatric gastroenterologist, three representatives of patient support groups acting under the umbrella of the Federation of Esophageal Atresia and Tracheo-Esophageal Fistula Support Groups (EAT),¹⁹ and one non-surgeon pediatric surgery academic took part in all steps of the preparation and the conference itself. All participants were members of the ERNICA Workstream *Congenital Malformations and Diseases of the Esophagus*.

The preparation and implementation of the conference included the following steps:¹⁸ (1) generation of a list of items; (2) prioritization of the items using the online REDCap electronic data capture tools;²⁰ (3) discussion of all items during the conference, formulation of statements; (4) anonymous voting via the internet-based system VoxVote.²¹

The items of this second part of the conference focused on the domains *Follow-up* and *Framework*. For the domain *Follow-up*, the ESPGHAN-NASPGHAN guidelines¹ were reviewed to identify matches or similarities in both lists as both focused on patients with EA with TEF—from a pediatric gastrointestinal and from a pediatric surgical perspective. It has been consciously decided not to adopt the entire list of

ESPGHAN-NASPGHAN guidelines including 36 statements. Only items of surgical relevance were finally included.

With regard to literature search, publications with the highest grade of evidence according to the CEBM (center for evidence-based medicine) classification were suggested to be preferred²² as previously reported.¹⁸ Literature was distributed and made available to all participants via a DropBox (Dropbox Inc., San Francisco, California, United States, 2007) link prior to the conference.

In case of available ESPGHAN-NASPGHAN statements, the previously presented literature was applied and supplemented with recent literature where appropriate. All participants were aware of the ESPGHAN-NASPGHAN statements. The wordings of the statements on items were updated during the discussion by the participants of the conference and prepared for voting by the non-surgical academic (S.E.) who did not vote himself. In the majority of items, the final wording of the statements somehow differed from the wording of the ESPGHAN-NASPGHAN guidelines although both dealt with the same topic (see Supplementary Material, available in the online version).

Consensus was defined as $\geq 75\%$ of those voting scored 6, 7, 8, or 9, excluding those who declared no relevant expertise on that statement.¹⁸

Results and Consensus Statements

Item Generation and Prioritization

The systematic literature search and the discussion of the members of the ERNICA Workstream *Congenital Malformations and Diseases of the Esophagus* during the ERNICA conference in Stockholm on the 18th to 20th April 2018 resulted in a total of 16 items.

After the online prioritization phase, two items were excluded. Following the participants' suggestions, 12 items were added as new items. Consequently, the list included 26 items prior to the conference, for which literature was obtained and circulated.

As a result of the presentations by the domain leaders and discussion during the conference, six items were excluded, and nine items were added as new items as some items were split into several separate questions. Finally, 29 items were confirmed for voting and included 25 items in the domain *Follow-up* (→ **Table 1**), and four items in the domain *Framework* (→ **Table 2**).

ESPGHAN-NASPGHAN Guidelines

In the domain *Follow-up*, corresponding ESPGHAN-NASPGHAN statements were available for 17 items (68%). Mapping of the ERNICA consensus conference items to the ESPGHAN-NASPGHAN statements is shown in the Supplementary Material (available in the online version). The participants of this conference divided two of the ESPGHAN-NASPGHAN statements into several items and voted separately: three items (item N° 11, 12, 13) referred to a single ESPGHAN-NASPGHAN statement (statement N° 28); and two items (item N° 18, 19) also referred to a single ESPGHAN-NASPGHAN statement (statement N° 7); (→ **Supplementary Material**, available in the online version).

Consensus

In the domain *Follow-up*, complete agreement, defined as 100% consensus amongst voters, was achieved on seven items (28%) and general consensus ($\geq 75\%$ of those voting having scored 6–9) on 18 items (72%). Eight items (32%) were particularly controversial in that the votes ranged from 1 to 9; in four (50%) of these consensus was not reached. Detailed results are summarized in → **Tables 1** and **3**.

In the domain *Framework*, complete consensus was achieved on all items with no controversial items ($n = 4$; 100%). Detailed results are summarized in → **Tables 2** and **3**.

Abstention

In the domain *Follow-up*, one or more participants declared “no relevant expertise on this statement” for seven (28%) items; for one (4%) item, one participant abstained; for two (8%) items, two participants abstained; in two items (8%) three participants abstained; in one (4%) item, four participants abstained from voting. There was no abstention from voting in the domain *Framework*.

Controversial Discussion

Several items were discussed controversially as indicated by a wide range from 1 to 9 (→ **Tables 1** and **3**). The controversial discussion included eight items (32%) in the domain *Follow-up*, of which four items (50%) did not reach consensus. There was no controversial discussion in the domain *Framework*.

Concordance with ESPGHAN-NASPGHAN Guidelines

The majority ($n = 14$; 82%) of items that mapped directly to ESPGHAN-NASPGHAN guidelines¹ were voted in consensus, so were in concordance with the ESPGHAN-NASPGHAN recommendations. Concerning the other three items (18%), consensus was not reached, meaning the votes of the participants of the conference were not in line with the ESPGHAN-NASPGHAN recommendations,¹ (→ **Table 1**):

- Duration of antacid medication.
- Topical application of mitomycin C as a therapeutic option for recurrent strictures.
- Administration of intralesional/systemic steroids as a therapeutic option for recurrent strictures.

Discussion

The ESPGHAN-NASPGHAN guidelines for the evaluation and treatment of gastrointestinal and nutritional complications in children with EA and TEF¹ provide a major contribution to the development of generally accepted guidelines for patient care. These guidelines were set up during two consensus meetings using the nominal voting technique. Expert opinion was used where no randomized controlled trials were available to support the recommendations.¹ However, the ESPGHAN-NASPGHAN guidelines approach the field of *Follow-up* from a rather gastroenterological/non-surgical perspective. The medical and surgical follow-ups of this particular group of patients are undoubtedly similar in many respects. Nonetheless, the already existing guidelines needed to be evaluated also by pediatric surgeons as being

Table 1 Consensus statements on the follow-up of patients with esophageal atresia and tracheoesophageal fistula

N°	Statement	ESPGHAN-NASPGHAN Statement available ⁸	Consensus	%	Votes	Median (range)
1	There should be a structured schedule for life-long follow-up.	-	+	100	18/18	9 (8-9)
2	There should be an interdisciplinary follow-up program including surgery, gastroenterology, pulmonary, nutrition counselling, otolaryngology, and others, with one specialist leading.	+	+	100	18/18	9 (8-9)
3	Antacid medication should be routinely administered to all patients after correction of EA.	+	+	88.9	16/18	9 (2-9)
4	Proton pump inhibitors should be used for antacid prophylaxis in EA patients.	+	+	100	16/16	8 (6-9)
5	Antacid medication should be routinely administered for 12 mo after correction of EA, although it is noted that the evidence base is limited.	+	-	66.7	12/18	7 (1-9)
6	Antacid therapy should be tapered at the end of prophylaxis.	-	+	94.4	17/18	9 (4-9)
7	Anastomotic stricture should be diagnosed by either contrast study and/or endoscopy	+	+	94.4	17/18	8.5 (3-9)
8	Anastomotic stricture should be managed by balloon or semirigid dilatation.	+	+	100	15/15	9 (6-9)
9	The definition of recurrent anastomotic stricture is three anastomotic stricture relapses requiring dilatation.	+	+	94.4	17/18	9 (4-9)
10	The maximum number of esophageal dilatations for recurrent anastomotic strictures until a fundoplication should be considered is five.	-	+	83.3	15/18	8 (1-9)
11	Topical application of mitomycin C should be recommended as an option in patients with recurrent strictures.	+	-	26.7	4/15	3 (1-9)
12	Intralesional/systemic steroids should be recommended as an option in patients with recurrent strictures.	+	-	46.2	6/13	5 (3-9)
13	Customized stents /indwelling balloons should be recommended as an option in patients with recurrent strictures.	+	+	100	14/14	8 (6-9)
14	24-h-pH- or pH-impedance monitoring should be routinely used for monitoring children and adolescents with EA according a specific schedule.	+	+	93.8	15/16	9 (5-9)
15	24-h-pH- or pH-impedance monitoring should be routinely performed at time of discontinuation of antacid therapy.	+	+	83.3	15/18	8.5 (2-9)
16	At least two additional pH studies should be routinely performed until transition.	-	-	55.6	10/18	6 (1-9)
17	Endoscopies of the upper gastrointestinal tract should be routinely used for monitoring children and adolescents with EA according to a specific schedule.	+	+	94.4	17/18	9 (2-9)
18	Endoscopies of the upper gastrointestinal tract should be routinely performed at 1 y.	+	+	83.3	15/18	9 (2-9)
19	At least two additional endoscopies of the upper gastrointestinal tract should be routinely performed until transition.	+	+	100	18/18	9 (6-9)

Table 1 (Continued)

N°	Statement	ESPGHAN-NASPGHAN Statement available ⁸	Consensus	%	Votes	Median (range)
20	Lung function tests should be routinely used for monitoring children and adolescents with EA according to a specific schedule.	–	+	77.8	14/18	8 (1–9)
21	Contrast study of the upper gastrointestinal tract should be routinely used for monitoring children and adolescents with EA according to a specific schedule.	–	–	27.8	5/18	3.5 (1–9)
22	Bronchoscopy should be routinely used for monitoring children and adolescents with EA according to a specific schedule.	–	–	11.8	2/17	2 (1–7)
23	The following are potential indications for fundoplication: (1) recurrent anastomotic strictures, (2) poorly controlled GERD despite maximal PPI therapy, (3) long-term dependency on transpyloric feeding, (4) cyanotic spells.	+	+	94.4	17/18	8.5 (1–9)
24	Adult EA patients need surveillance as per ESPGHAN guidelines: (1) routine endoscopy (with biopsies in four quadrants at gastroesophageal junction and anastomotic site) at time of transition into adulthood and every 5–10 y, (2) additional endoscopy if new or worsening symptoms develop, (3) in presence of Barrett as per consensus recommendations.	+	+	100	18/18	9 (6–9)
25	Quality of life assessment using a validated instrument should be offered during follow-up in children.	–	+	94.4	17/18	9 (1–9)

Abbreviations: EA, esophageal atresia; ESPGHAN, European Society for Pediatric Gastroenterology Hepatology and Nutrition; GERD, gastroesophageal reflux disease; NASPGHAN, The North American Society for Pediatric Gastroenterology, Hepatology and Nutrition; PPI, proton pump inhibitors.

Table 2 Consensus statements on framework conditions in the management of patients with esophageal atresia with tracheoesophageal fistula

N°	Statement	Consensus	%	Votes	Median (range)
1	When EA is suspected, referral to antenatal multidisciplinary counselling in a specialized center should be made.	+	100	18/18	9 (8–9)
2	There should be a minimum average caseload of five new EA per year to meet the requirement of a specialized center.	+	100	18/18	9 (6–9)
3	EA patients should be operated on and treated in specialized centers with a multidisciplinary team with follow-up including transition.	+	100	18/18	9 (6–9)
4	Parents of EA patients should be recommended to be involved in parent and patient support groups as early as possible.	+	100	18/18	9 (6–9)

Abbreviation: EA, esophageal atresia.

not only responsible for a crucial intervention—the esophageal anastomosis²³—but also taking part in subsequent follow-up. Besides the overlap of certain aspects, additional items from a surgical angle needed to be addressed supplementary to the already existing ESPGHAN-NASPGHAN guidelines.

We hereby present for the first time the results of a consensus conference focused on *surgical* aspects of the management of patients with EA with TEF. In line with the ESPGHAN-NASPGHAN guidelines, this conference was based on two keystones: (1) on evidence from literature, and (2) on expert opinion.

Participants of this conference achieved general consensus (defined by $\geq 75\%$ of votes scoring higher 6–9) in 72% of the items in the domain *Follow-up* and even 100% in the domain *Framework* suggesting predominantly homogeneous approaches in ERNICA institutions. When comparing the results in terms of general consensus in the individual domains including the previously reported domains *Diagnostics* (50%), *Preoperative* (50%), *Operative* (82%), and *Postoperative Management* (70%),¹⁸ it appears that consistency of expert opinion reaches the highest level in the domains *Operative Management*, *Follow-up*, and *Framework*.

Table 3 Summary of the voting results of the first ERNICA consensus conference on the management of patients with esophageal atresia and tracheoesophageal fistula; Part I was published elsewhere¹⁸

Part of the consensus conference	Domain	Complete consensus, 100% consensus	General consensus, ≥75% consensus ^a	No consensus, <75% consensus	Controversial discussion, (range 1–9)	Total number of items per domain	Total number of items per part
I	Diagnostics	3 (50%)	3 (50%)	3 (50%)	3 (50%)	6	52
	Preoperative management	3 (38%)	4 (50%)	4 (50%)	1 (13%)	8	
	Operative management	9 (32%)	23 (82%)	5 (18%)	7 (25%)	28	
	Postoperative management	5 (50%)	7 (70%)	3 (30%)	2 (20%)	10	
II	Follow-up	7 (28%)	19 (76%)	6 (24%)	8 (32%)	25	29
	Framework	4 (100%)	4 (100%)	0 (0%)	0 (0%)	4	
							81

^aIncluding items with complete consensus.

One-third of the items in the domain *Follow-up* were discussed controversially, out of which half did not reach consensus:

According to the ESPGHAN-NASPGHAN guidelines, it is recommended that gastroesophageal reflux should be systematically treated for prevention of peptic complications and anastomotic stricture up to the first year of life or longer, depending on the persistence of gastroesophageal reflux disease¹; (Supplementary Material, available in the online version). Stenström et al investigated the incidence of stricture formation, comparing outcomes of 3- and 12-month antacid prophylactic regimens.²⁴ They demonstrated in their study including 63 patients with EA that the development of anastomotic stricture in the first year after esophageal reconstruction was not reduced by prolonged antacid prophylaxis (12 vs. 3 months), but initial balloon dilation procedures were performed later in infants who were treated longer.²⁴ In contrast, another study by Donoso and Lilja aimed to assess the efficacy of postoperative antacid prophylaxis in reducing the incidence of anastomotic strictures in 128 patients with EA.²⁵ They concluded that prophylactic antacid treatment does not appear to reduce the rate of anastomotic strictures at all.²⁵

Participants of the conference discussed these details intensively and did not reach consensus on the item “duration of administration of antacid medication” as they felt a lack of evidence from the current literature.¹

There was also controversial discussion on the item “topical application of mitomycin C as an option in patients with recurrent strictures.” Mitomycin C is an antineoplastic and antifibroblastic agent which has been described to exert inconsistent results at different drug concentrations, when used as a topical agent applied to the anastomotic stricture after dilatation.²⁶ According to the ESPGHAN-NASPGHAN guidelines, mitomycin C has been recommended as potential adjuvant treatment for the management of recurrent strictures in EA patients among other options¹ (Supplementary Material, available in the online version). Recently, treatment

with mitomycin C has been reported to significantly reduce stricture recurrence after endoscopic dilatation.^{27,28} In contrast, Chapuy et al postulated that there is no benefit in the resolution of the stricture when adding mitomycin C treatment compared with repeated esophageal dilations alone.²⁹ Madadi-Sanjani et al also failed to demonstrate a beneficial effect of mitomycin C.³⁰ Given the fact that there is limited data to prove the beneficial effect of mitomycin C treatment, it should be carefully considered whether the advantages of this therapy outweigh the necessity of life-long endoscopic follow-ups. Therefore, participants of the conference agreed that further randomized controlled studies are mandatory and did not reach consensus on this item.

During the conference, participants agreed on the routine use of pH-studies for monitoring patients with EA according to a specific schedule and at time of discontinuation of antacid therapy. However, due to a lack of evidence in the current literature and controversial opinions among the participants, no consensus could be achieved on the frequency of pH studies until transition.

For the same reasons, no consensus could be reached on the routine use of contrast study of the upper gastrointestinal tract for monitoring patients with EA according to a specific schedule. As in the previous presented item, participants of the conference hold very divergent opinions and approaches on these aspects indicating certain heterogeneity of applied protocols in ERNICA centers.

In the vast majority of votes (82%), results from this ERNICA consensus conference were consistent with the ESPGHAN-NASPGHAN guidelines¹ except in three (18%) votes: The items “administration of antacid medication for 12 months” and “topical application of mitomycin C” have already been discussed above.

The third item with divergent results is on the “administration of intralesional/systemic steroids as a therapeutic option in patients with recurrent strictures.” The use of intralesional steroids has been reported with inconsistent improvement of anastomotic strictures.^{28,31,32} Potential

complications such as perforation, infection, pleural effusion, or adrenal suppression are well known.¹ Side effects have been reported neither for local nor for systemic short-term steroid treatment.¹ Based on a recently published case series by Ten Kate et al,³³ a multicenter, single-blind randomized controlled trial (*STEPS-EA trial*; approval number MEC-2018-1586/NL65364.078.18) involving ERNICA centers is currently being conducted on the use of intralesional steroid injections to prevent refractory strictures in patients with EA. After extensive discussion, participants of the conference did not reach consensus on this item.

The domain *Framework* focuses on centralization, multidisciplinary treatment, and participation of patient organizations in the management of patients with EA. Particular attention should be paid to the fact that complete consensus (defined as 100% consensus) was achieved on all items in this domain. The uniformity of opinions regarding these aspects is also reflected by the lack of abstention from voting on these items.

Over the last two decades, important contributions were made at national, European, and international levels to foster collaboration in rare diseases research.¹³ The European legislation calls for multidisciplinary centers treating children with rare diseases and proposes clear and demanding quality criteria.³⁴ Centralization in surgical patient care is a topic that is increasingly becoming important due to the growing number of reports that the level of care has improved and the number of complications, including mortality, have decreased with an elevation in the number of treated patients per surgeon and center.^{14,34-36} Pediatric surgery is a specialty of rare cases and low numbers.³⁵ It is therefore all the more important to pool expertise and corresponding infrastructure in a specialized center. Thus, participants of this conference strongly believe that the implementation of a minimum average caseload of new patients with EA per year per center is mandatory to define the requirements of a “specialized” center.

Until today, the optimal way to concentrate on pediatric surgical experience in each European country remains undefined and most likely depends on multiple national features, such as size and distribution of the population, geographical distances, local surgical expertise, organization of the health care system, and political agendas.^{15,34,37,38} The archetype for centralization in the United Kingdom, for example, is the management of biliary atresia being exclusively managed in three centers.³⁹ All the Nordic countries (Finland, Norway, Sweden, and Denmark) have a relatively small population making it necessary to concentrate advanced pediatric surgical care to a few specialized centers to ensure adequate caseload and high-quality care.^{15,36} In France, the available data strongly suggest that centralization, specialization, and connections between specialized and routine pediatric surgical departments can greatly improve management of and outcomes in children.³⁴

In this study, it was demonstrated that efforts toward further centralization of pediatric surgery have already resulted in reduced morbidity and mortality.^{34,38,39} These endeavors should be urgently pursued implementing the mission of ERNICA.

As defined in the European Commission Delegated Decision,⁴⁰ European Reference Networks have to demonstrate that they are patient-centered and empower patients.¹³ Patients and patient organizations play a critical role in rare disease European Reference Networks due to their expertise.^{13,41-43} Patients and/or their representatives become increasingly involved in addressing ethical issues, transparency in quality of care, safety standards, and contributing to research.^{13,44,45} The involvement of representatives of patient support groups in this consensus conference allowed a unique perspective to all discussed aspects of patient care and management and emphasizes the benefits of collaboration as already proved in the past.^{44,46}

Conclusion

Participants of this ERNICA conference reached significant consensus on the follow-up of patients with EA and TEF who undergo primary anastomosis. Fundamental statements regarding centralization, multidisciplinary approach, and involvement of patient organizations were formulated. These consensus statements will provide the cornerstone for uniform treatment protocols and resultant optimized patient care.

Conflict of Interest

None declared.

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