UPDATE ON OESOPHAGEAL ATRESIA-TRACHEOESOPHAGEAL FISTULA

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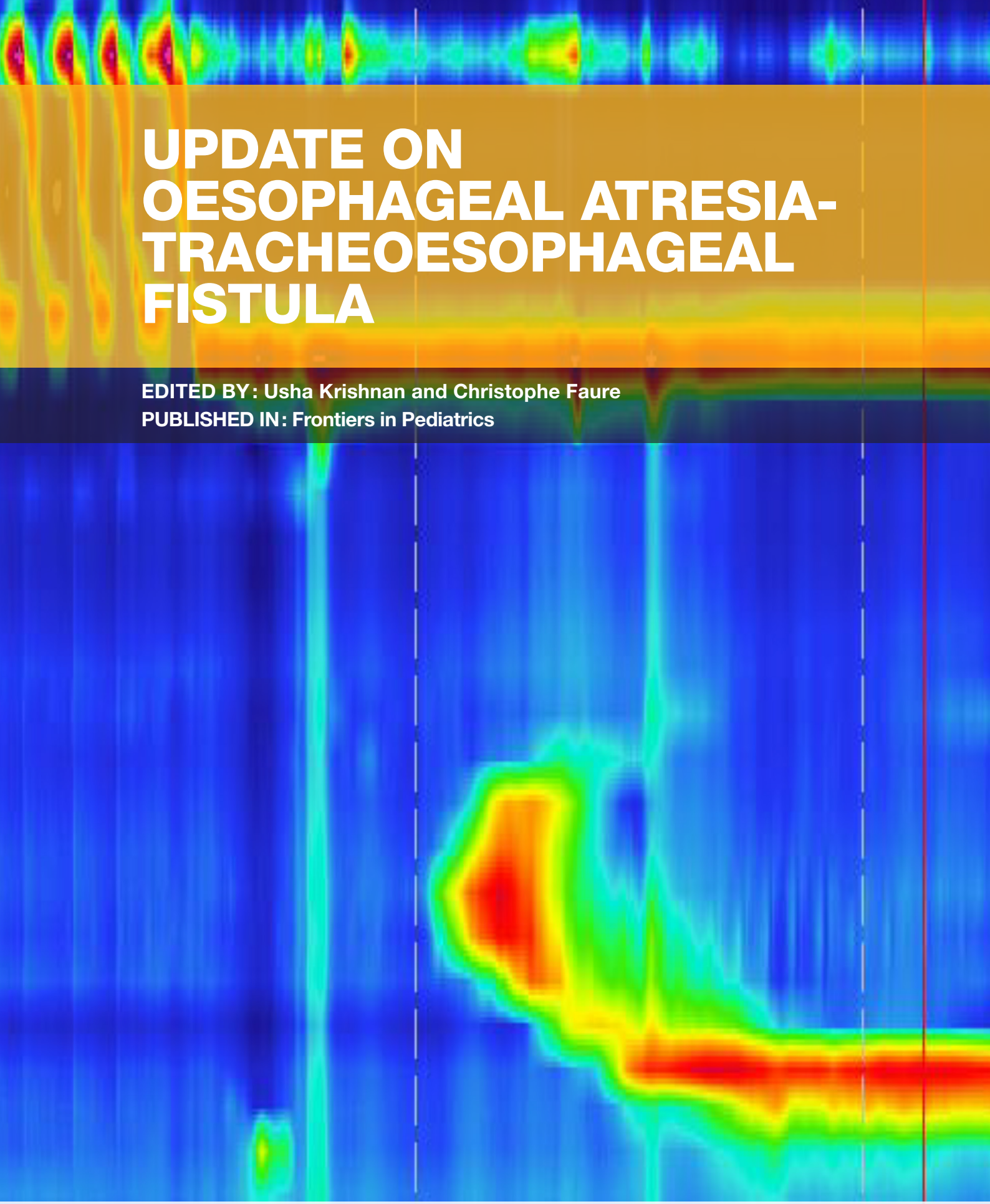

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UPDATE ON OESOPHAGEAL ATRESIA-TRACHEOESOPHAGEAL FISTULA

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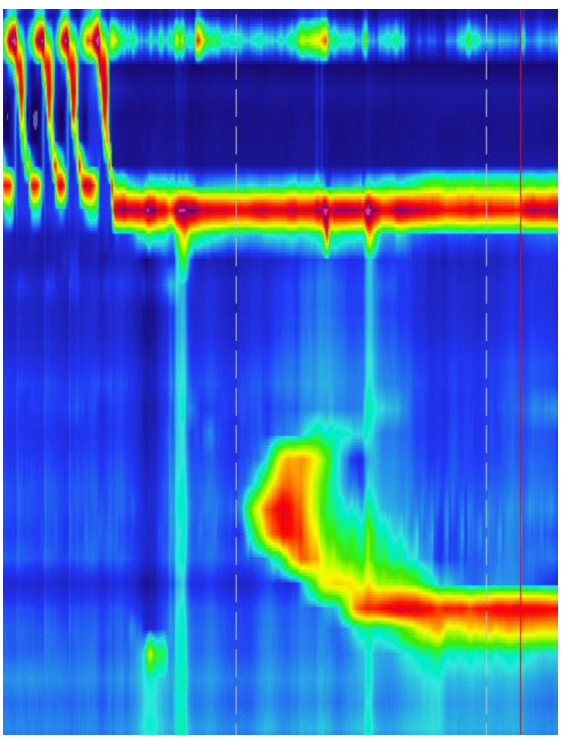

High resolution oesophageal manometry pattern in Oesophageal Atresia-Tracheoesophageal Fistula. Image: Christophe Faure.

Oesophageal atresia-tracheoesophageal fistula (OA-TOF) is a congenital digestive malformation. With improvements in surgical techniques and perioperative care, survival rates now exceed 90% and OA-TOF is no more just a neonatal surgical problem, and the focus has now shifted from mortality to morbidity with focus on long-term survival and quality of life issues. The primary complications experienced by these patients include gastroesophageal reflux, peptic and eosinophilic esophagitis, anastomotic stricture, esophageal dysmotility, abnormal gastric function, feeding difficulties and respiratory disorders including tracheomalacia and "cyanotic spells". Concerns in adults include oesophageal adenocarcinoma and epidermoid carcinoma which have been recently reported. This highlights the need for careful multidisciplinary follow up not only in childhood but also after transition to adulthood. Data regarding long-term outcomes and follow-ups are limited for patients following OA-TOF repair. The determination of the risk factors for the complicated evolution following OA-TOF repair may positively impact long-term prognoses. This e-book contains review articles and position paper on all aspects of management of this condition. The material

presented in the following articles is primarily based on the presentations by world experts during the recent Fourth International Conference on Oesophageal Atresia held in Sydney in 2016.

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EDITORIAL
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Editorial: Oesophageal Atresia-Tracheoesophageal Fistula

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Editorial on the Research Topic

Oesophageal Atresia-Tracheoesophageal Fistula

Esophageal atresia is among the most common congenital digestive malformations, affecting 1 in 3,000 newborn babies at birth. Since the first successful primary repair of esophageal atresia (EA) in 1941, improvements in operative and perioperative care have led to better outcomes, and thus we have seen an evolvement from mortality to morbidity and quality-of-life issues. In fact, EA is no longer a mere neonatal surgical problem but rather a lifelong problem for the patient. 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. Hence a multidisciplinary approach has been advocated by many centers in order to coordinate and optimize the management of these patients at all stages of life. In 2010, the First International Workshop on Esophageal Atresia was held in Lille, France. The success of that event established a new model of conference based not on medical subspecialty but specifically on disease, bringing together diverse disciplines all linked together by their common interest and expertise in treating EA. The International Network of Esophageal Atresia (INoEA) was founded in 2013. *On September 15–16, 2016, the fourth International Conference on Esophageal Atresia "Coming Together" took place in* Sydney, NSW, Australia. More than 200 participants from all over the world attended the conference. There were over 80 scientific abstracts submitted. All the categories of people involved in the care of EA patients were represented; not only neonatologists, pediatricians, surgeons, gastroenterologists, otolaryngologists, pulmonologists, radiologists, anesthesiologists, intensivists, but also, nurses, dieticians, speech pathologists, psychologists, occupational therapists, social workers, parents of patients, and children and adults with EA. The scientific program was both comprehensive and innovative, covering the entire spectrum of disease from genetic predisposition and pathophysiology, aspiration risk and chronic respiratory morbidity (CRM), investigation and management of gastroesophageal reflux disease including risk of Barrett's and esophageal cancer, tracheomalacia, and its management including novel techniques like posterior aortopexy, newer techniques of reflux and motility testing, techniques of surgical repair and role of fundoplication, stricture management, feeding difficulties and their practical management, quality of life of these patients, the need for ongoing care with transition to adulthood, and the need for an international registry. For the first time, the ESPGHAN–NASPGHAN consensus guidelines on the management of gastrointestinal complication in children with EA were presented and very well received not only by the clinicians involved in the care of these patients but also the parent support groups. Innovative topics, which were presented for the first time and which stimulated interesting discussions included: deliberations from the InoEA working group on Long Gap Esophageal Atresia, Preliminary deliberations from the respiratory working group, Prevalence of abnormal Gastric Function and Dumping syndrome in this cohort, the role of pH-impedance

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testing for GERD and high-resolution impedance manometry for pharyngoesophageal function testing, a validated quality of life score and academic performance in EA patients, molecular profiling of EA patients with eosinophilic esophagitis (EoE), the Sydney experience with the Foker technique, risks associated with general anesthetic and radiation exposure and role of stem cell therapy and neo esophagus in the future. Experts from India, China, and Japan spoke for the first time about management of EA in their countries. The talks from a teenager and adult EA survivors were especially inspiring for the audience. The success of the event confirmed the importance of adopting a multidisciplinary approach and creating links between not only pediatric and adult medicine but also with parent support groups.

This special edition of "Frontiers in Pediatrics" contains summaries and review articles of selected presentations delivered by the distinguished guest speakers during the conference.

The comprehensive review by Kovesi on "*Aspiration risk and respiratory complications in patients with esophageal atresia*" summarizes current knowledge on the degree to which aspiration is responsible for CRM in this cohort. While the etiology of aspiration is multifactorial, diagnosing aspiration remains medically challenging.

The paper by Bergeron et al. looks at the "*Management of cyanotic spells in children with oesophageal atresia*." In concordance with the recently published ESPGHAN–NASPGHAN Guidelines on the management of gastrointestinal complications in children with EA/tracheoesophageal fistula (TEF), this article highlights the importance of a multidisciplinary diagnostic evaluation of cyanotic spells prior to surgical intervention with aortopexy and or fundoplication (1).

The paper by Faure and Grunder looks at "*Dysmotility in esophageal atresia: pathophysiology, characterisation and treatment*."

Anastomotic stricture (AS) is the most common complication following operative repair of EA, and this is looked at in the comprehensive review article "*Anastomotic Strictures after esophageal Atresia Repair: incidence, investigations, and Management, including Treatment of Refractory and Recurrent Strictures*" by Tambucci et al. Since AS formation is likely influenced by GER, and the ESPGHAN–NASPGHAN Guidelines suggest a systematic routine treatment with PPI for 1 year after surgical correction, including in asymptomatic patients (1); it will be interesting to investigate whether this routine practice will decrease the stricture formation in the future. The Guidelines also state that "Eosinophilic esophagitis (EoE) needs to be excluded in EA patients of all ages with dysphagia, reflux symptoms, coughing, choking, or recurrent strictures that are refractory to PPI" (1), and prospective studies will help delineate the true incidence of EoE in EA patients with recurrent strictures.

Feeding difficulties are common in patients with repaired EA, and this review by Mahoney and Rosen on "*Feeding problems and their underlying mechanisms in esophageal atresia-tracheoesophageal fistula patient*" highlights multifactorial etiology for abnormal feeding in this cohort.

The article by Rintala looks at "*Fundoplication in patients with esophageal atresia: patient selection, indications, and outcomes*." Fundoplication is frequently required in EA patients; however, the indications for fundoplication are often not scientifically delineated. The recent ESPGHAN–NASPGHAN guidelines list refractory anastomotic stenosis, long-gap EA, poorly controlled GERD despite maximal medical therapy, long-term dependency on transpyloric feeding, and cyanotic spells as indications to consider anti-reflux surgery in children with EA (1). The guidelines also state that EoE needs to be excluded in EA patients of all ages with dysphagia, reflux symptoms, coughing, choking, or recurrent strictures that are refractory to PPI; and other abnormalities like laryngeal cleft, vocal cord paralysis, missed or recurrent fistula, AS, congenital stenosis, and vascular ring should be ruled out in EA patients with respiratory symptoms before proceeding to anti-reflux surgery (1).

In the EA spectrum, long-gap esophageal atresia (LGEA) is only a small portion (10%), but the inability to perform a primary esophageal anastomosis poses additional challenges. The position paper by Van Der Zee et al. on "*Position paper of INoEA Working Group on Long Gap Esophageal Atresia (LGEA)*," after review of the literature and expert discussion concluded that LGEA should be defined as any EA that has no intra-abdominal air, realizing that this defines EA with no distal tracheoesophageal fistula (TEF). In light of the infrequent occurrence of LGEA and the technically demanding techniques involved to achieve esophageal continuity, the working group strongly advised to develop centers of expertise for the management and follow-up of these very complex patients.

Esophageal atresia patients are predisposed to gastroesophageal reflux as a result of the altered esophageal anatomy and motility. The article *on* "*Impedance testing in esophageal atresia patients*" by Hassan and Mousa looks at the role of multichannel intraluminal impedance testing in the investigation and treatment of GERD in this population.

The article on "*Recent advances in motility testing in patients with esophageal atresia*" by Rommel et al. looks at the recent developments in this field. The authors elegantly describe how high-resolution manometry combined with impedance measurements characterizes the interplay between esophageal motor function and bolus clearance. The authors use a novel pressure flow analysis method as an integrated analysis method of manometric and impedance measurements, to differentiate patients with impaired esophagogastric junction (relaxation) from patients with bolus outflow disorders.

While much is known about the abnormal esophageal function and poor motility in EA–TEF patients, little is known about gastric function in this cohort. The review by Duvoisin and Krishnan on "*Gastric function in children with esophageal atresia-tracheosophageal fistula*" gives us a comprehensive understanding of gastric function and potential treatment modalities in EA–TEF patients with abnormal gastric function.

The management of EA remains challenging. This article by Perin et al. on "*An update on foregut molecular embryology and the role of regenerative medicine therapies*" outlines the most current understanding of the molecular embryology underlying foregut development and EA, and also explores the promise of regenerative medicine.

Data on EA prevalence, management, and long-term outcome are lacking because the available data come from small

retrospective series from tertiary referral centers. The article on "*The importance of an international registry for and collaborative research on esophageal atresia*" by Gottrand et al. describes how an international multicenter registry would provide strong epidemiological data from large population-based cohorts on EA prevalence, incidence, treatment, long-term morbidity, and prognosis and thereby provide accurate data for evaluation of the current guidelines for EA management.

We look forward to the next fifth international conference on EA in Rome in 2019 where we are sure that many new advancements and innovations in the field will be presented.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

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PERSPECTIVE
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Importance of an International Registry for and Collaborative Research on Esophageal Atresia

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Esophageal atresia (EA) is a rare congenital defect. Data on EA prevalence, management, and long-term outcome are lacking because the available data come from small retrospective series from tertiary referral centers. An international multicenter registry would provide strong epidemiological data from large population-based cohorts on EA prevalence and incidence, treatment, long-term morbidity, and prognosis and would thus provide accurate data for evaluation of the current guidelines for EA management. The future challenge of the new international network on EA, which was created in 2013, is to promote the creation of a collaborative database and further studies.

Keywords: esophageal atresia, congenital defect, international registry, population-based cohort, collaborative research

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CURRENT LEVEL OF EVIDENCE ABOUT ESOPHAGEAL ATRESIA (EA)

Esophageal atresia is a rare congenital anomaly whose origin remains unknown. Most available studies on EA are small retrospective series from tertiary centers, and the quality of the data remains limited because of the low statistical power and selected population. Moreover, the results cannot be extrapolated to the general population of EA patients. At the recent international conference on EA organized by the International Network on Esophageal Atresia (INoEA) in Sydney, Australia,[1] only 14 of 76 selected abstracts were multicenter studies. However, the number of patients included in these 14 collaborative studies ($n = 2{,}238$) exceeded the total number of patients included in the other 62 single-center studies ($n = 1{,}901$).

When preparing a consensus statement on the available evidence about EA, a systematic literature search was performed using the classification system of the Oxford Centre for Evidence-Based Medicine and Grade evidence profile. Although the importance was classified as "critical" for most of the 167 references selected for this consensus, only 29 were classified as providing high-quality evidence, 18 were classified as providing moderate evidence, and 130 were qualified as providing a low or very low quality of evidence (1). As a consequence, all statements and recommendations on EA available today are opinion based (i.e., all of the 40 statements in the consensus mentioned above) (1). Even now, collaborative studies on EA remain rare. At the end of January 2017, only 10 studies on EA were registered in the Clinical Trials registry.

[1] http://www.oa2016.com.au.

CURRENT REGISTRIES AND DATABASES FOR EA

The prevalence of EA has been established from global birth surveillance programs (network of malformation registers) throughout the world (2). Data from these programs (EUROCAT in Europe and the National Birth Defects Prevention Network in the USA) suggest that the prevalence of EA is similar between countries and stable over time (3). However, because these registers focus on prenatal and neonatal diagnosis of several malformations, they include limited details about neonatal treatment and no information about the early or late outcome of EA patients (4, 5). There are recent initiatives to set up specific population-based EA registers at a country level (e.g., Australian and French registers) (6, 7). The advantages of these registers are that they are population based and can provide precise and detailed information about EA and early outcomes (8). As for other rare diseases, one of the main gaps in understanding and treating EA is the lack of in-depth knowledge about the natural history of the malformation, which is one prerequisite for undertaking clinical trials.

INTERNATIONAL COLLABORATIVE REGISTRIES

There are arguments for and against multicenter studies (**Table 1**). One argument is that there is a need to set up multicenter studies to include a large number of EA patients to answer the many questions about the impact of prenatal diagnosis on the outcome and live birth prevalence, optimal surgical treatment for long-gap EA, treatment of gastroesophageal reflux disease, and risk for cancer over the long term. The positive aspects of collaborative efforts at the international level include providing strong epidemiologic data, monitoring the birth prevalence of EA, detecting new or continuing trends, identifying new potentially teratogenic exposures, and evaluating the effects of different prenatal policies. Such registers also provide a unique opportunity to set up prospective population-based cohort studies, nested case–control studies, and case–cohort design studies. Furthermore, multicenter studies may provide unique information for health authorities about the prevalence, long-term morbidity, and disabilities of EA, which will help in determining health policy priorities. These rare disease registries are also an opportunity to pool data from many centers to achieve a sufficient sample size for epidemiological and clinical research. They will also be useful for assessing the feasibility of clinical trials, planning appropriate clinical trials, and supporting patient enrollment.

TABLE 1 | Arguments for and against multicenter studies of esophageal atresia (EA).

Opportunities	Limitations
• High power of studies (stratification/ subgroup analysis) • Population-based studies vs. highly selected population • No other option for some rare forms of EA (i.e., long gap) • Sharing knowledge, harmonization of care • Collaborations between centers/countries • Evaluation of the recommendations • Better acknowledgment (health authorities, scientific societies, journals) • Special funding for rare diseases	• Long process • Differences in ethical/regulatory rules between countries • Need to harmonize care • Need to harmonize data to be collected (questionnaire) • Difficulty in achieving and maintaining quality control of data • Need for support (research personnel, database manager) • Authorship • Higher cost/lack of funding

One example of such a network is the recently reported successful establishment of a multicenter network for hepatoblastoma. The development of biological markers for this very rare tumor and identification of reliable prognostic risk factors for tailoring treatment remain challenging. The consortium comprises the four multicenter trial groups that have performed prospective controlled studies on hepatoblastoma over the past two decades. A centralized online platform has been created in which data from eight completed hepatoblastoma trials have been merged to identify prognostic factors and to confirm existing established factors (9). There is also a successful initiative for multicenter studies of some forms of neuronal ceroid lipofuscinoses (10). These examples show the value of compiling, in a single database, the natural history data available in different countries, clinics, research institutions, and families.

The PedNet registry is a multicenter observational research database for hemophilia. All patients with hemophilia born after January 1, 2000, and treated in 1 of the 29 participating hemophilia treatment centers are included (11). All centers prospectively collect data, including treatments and outcomes, for all included patients. By using the data from this database, two major studies compared the effects of the type of factor concentrate and prophylaxis treatment vs. on-demand treatment on inhibitor development in severe hemophilia (11). The observational cohort design does not interfere with the day-to-day clinical management of patients and improves the clinical management over time. The monitoring of centers in this cohort by experienced study coordinators has been shown to be critically important for improving the quality of the data. It is important to note that all patients from the participating centers must be included to prevent selection bias (11).

There is a recent initiative of the European Union to set up a European platform for rare disease registries. The main objectives of this platform are to provide a central access point for information on registries of patients with rare diseases for all stakeholders and to support existing registries in view of their interoperability. However, international registries and databases have constraints and disadvantages when compared with national registries or databases, such as interoperability problems, cost, and regulations. Another possible disadvantage of collaborative registries is the lack of exhaustiveness. The Children's Cancer Research Network was created to explore the epidemiological landscape of rare childhood cancers in the USA and Canada. In addition to poor registration rates, tissue samples of these cancers were scarce, and tissues for banking were submitted for only 11% of all cases of rare tumors in this registry (12).

The necessary studies would be easier to conduct within the context of a unique homogeneous database or interoperable national databases. Building this kind of structure would encourage every participating state to encourage local and

national authorities to create a national rare disease database or specific EA atresia register. For all such databases or registries, it is essential that the data should be sharable. A future international database setting would have many advantages (**Table 1**), the most important being the homogeneity of data. Having these data in a centralized register could provide greater visibility for future research projects, even for the smallest group of patients (stratification), which would allow comparisons of results and techniques within and between homogenous groups of patients (e.g., type A EA, esophageal replacement techniques) and the wide distribution of findings.

NECESSARY FACTORS FOR CREATING A SUCCESSFUL INTERNATIONAL COLLABORATIVE REGISTRY FOR EA

There is a movement toward increasing research collaboration, greater data sharing, and increasing engagement and active involvement by patients, advocates, and foundations for rare diseases (13). The growth in networks and social networking tools presents opportunities to help reach other patients, to find researchers, and to build collaborations. Engagement of patients' and parents' associations with other stakeholders in clinical research may help to ensure that research efforts related to rare diseases address the relevant clinical questions and provide patient-centered health outcomes. Rare disease organizations may provide an effective means of facilitating patient engagement in research (14). The success of such approaches and common challenges inherent in directly engaging patients, patient advocacy groups, and investigators in the creation, growth, and productivity of multicenter research groups involved in clinical research on rare diseases has been reported (15). From this perspective, the INoEA collaboration with the international federation of patient support groups (EAT)[2] provides opportunities for collaborative studies on EA through joint lobbying, communication, and fundraising. The recent appointment by the European Commission of a European reference network for rare digestive diseases and malformation[3] may also provide an opportunity to structure international collaborations for research on EA.

Another example is Castleman's disease, a very rare disease whose cause and pathogenesis of the idiopathic form are unknown. Researchers studying the idiopathic form have never received National Institutes of Health funding, and a single disease research organization has been the only source of research funding. The small sample sizes at individual institutions have prevented research from being adequately powered to test for significance. In 2012, the Castleman's Disease Collaborative Network (CDCN) was created by assembling a group of physicians, researchers, and patients to create and accelerate research through a targeted, collaborative, and patient-centric approach. Their aims are first to build a global community, to leverage the community to prioritize studies and share research samples, and to fund community-prioritized research by seeking proposals and funding strategically directed research grants to experts (16). In the past year, the CDCN has supported more than 6,000 patients and support groups through an online patient forum, patient summit, and website. Engagement of patients in the research process has aligned stakeholders' incentives to conduct research that will have the greatest impact on patients' lives (16).

The Consortium for Clinical Investigations of Neurological Channelopathies and the Clinical Research Consortium for Spinocerebellar Ataxias engage patients with rare neurological channelopathies with investigators and with advocacy groups in multicenter networks (17). These two networks have created patient registries, stratified on the basis of genetic characteristics, and included longitudinal clinical data. By using these patient registries, disease-relevant outcome measures have been identified. Moreover, phase I and II trials have been conducted by the networks. Patient advocacy groups provide essential support for networks by providing financial and logistical support for research activities, such as organizing patient registries and investigator meetings (17).

The informed consent process is a challenge to sharing data among research consortia and adds a layer of complexity that requires coordination between research centers worldwide. Rare disease consortia face specific challenges because the available data and samples may be very limited. Therefore, it is especially relevant to ensure the best use of available resources but at the same time to protect patients' right to integrity. Achieving this aim requires the ethical duty to plan in advance the best possible consent procedure to address the potential ethical and legal hurdles that could hamper research in the future. It is especially important to identify the key core elements to be addressed in informed consent documents for international collaborative research in two different situations: (i) new research collections (biobanks and registries) for which information documents can be created according to current guidelines and (ii) established collections obtained without informed consent or with previous consent that does not cover all key core elements (18).

Another challenge is the standardization of definitions and data collection (19). Uniform approaches are necessary for robust collaborative research, particularly involving rare diseases. Collaborative research involving multiple centers and groups requires critical procedures to be coordinated to facilitate accurate comparisons of data. The use of standard operating procedures for the collection and handling of samples and data is a critical first step in ensuring high-quality translational research (19). Disseminating such information among researchers requires a flexible and secure data-sharing infrastructure (19).

The specific goals of an international registry of EA should include epidemiological surveillance of the malformation, first-year outcome, prospective population-based cohort studies, and nested case–cohort studies. The resources needed would include coordinators to define the minimal data set and interoperability, to standardize and monitor the quality of the data, and to develop a centralized database platform. Recent international or government initiatives on rare diseases (e.g., the recently launched

[2] www.we-are-eat.org/.

[3] http://ec.europa.eu/health/rare_diseases/european_reference_networks/erf_en.

European networks of reference for rare diseases) may represent a unique opportunity to achieve these goals within a realistic time frame.

CONCLUSION

To face these challenges, the international network on EA, INoEA, was created in 2013. The INoEA is an informal multidisciplinary group of clinicians, researchers, allied health professionals, and family support group representatives who have joined efforts to improve research and care for EA patients. The goals of INoEA are to favor collaboration and to share information between centers throughout the world. Initiating a collaborative database and further studies are challenges for the future.

AUTHOR CONTRIBUTIONS

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Position Paper of INoEA Working Group on Long-Gap Esophageal Atresia: For Better Care

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INoEA is the International Network of Esophageal Atresia and consists of a broad spectrum of pediatric specialties and patient societies. The working group on long-gap esophageal atresia (LGEA) set out to develop guidelines regarding the definition of LGEA, the best diagnostic and treatment strategies, and highlight the necessity of experience and communication in the management of these challenging patients. Review of the literature and expert discussion concluded that LGEA should be defined as any esophageal atresia (EA) that has no intra-abdominal air, realizing that this defines EA with no distal tracheoesophageal fistula (TEF). LGEA is considerably more complex than EA with distal TEFs and should be referred to a center of expertise. The first choice is to preserve the native esophagus and pursue primary repair, delayed primary anastomosis, or traction/growth techniques to achieve anastomosis. A cervical esophagostomy should be avoided if possible. Only if primary anastomosis is not possible, replacement techniques should be used. Jejunal interposition is proposed as the best option among the major EA centers. In light of the infrequent occurrence of LGEA and the technically demanding techniques involved to achieve esophageal continuity, it is strongly advised to develop regional or national centers of expertise for the management and follow-up of these very complex patients.

Keywords: long-gap esophageal atresia, definition, diagnosis, management, centers of expertise

INoEA is the International Network of Esophageal Atresia and consists of a broad spectrum of pediatric specialties and patient societies. Esophageal atresia (EA) is not only a congenital malformation that warrants surgical correction, but the malformation is complex, frequently associated with other concomitant anomalies, and requires life-long multidisciplinary follow-up and support.

In the EA spectrum, long-gap esophageal atresia (LGEA) is only a small portion (10%), but the inability to perform a primary esophageal anastomosis poses additional challenges to bring the two esophageal ends together and restore continuity (1, 2).

There are several techniques available, reflecting that no one technique is ideal, and the patients are left with many challenges to overcome (2–5). Also, the infrequent occurrence of LGEA means that few surgeons will develop adequate experience, which will preclude the development of improved techniques. Most surgeons will see less than 1 LGEA every 10 years, so even the most senior surgeons may be very inexperienced with their treatment challenges (6).

A literature search leaves only small retrospective series or case histories with little incentive for technical advances (2–5). What has become clear is that it is best to try to preserve the native esophagus (3). Where the distance between the two ends appears to preclude approximation directly after birth (immediate primary repair), this may become possible after waiting for several weeks (delayed primary repair).

In the literature, it is unclear what exactly defines LGEA. Quite often, a difficult to approximate esophageal atresia (EA) with the distal esophagus ending in the trachea (type C) is determined as a LGEA. Probably, in experienced hands, most of these types of EA could have been brought together with a primary anastomosis (7, 8).

It is, therefore, important to come to a clear and unambiguous definition of LGEA:

Definition

Any esophageal atresia (EA) that has no intra-abdominal air should be considered a long gap and is advised to be referred to a center of expertise (CoE)

and

All other types that technically prove to be difficult to repair are not necessarily long gap, but should be referred to CoEs in any case, after the first failed attempt

A CoE can be defined as:

A CoE is a pediatric surgical center that is equipped and experienced in the treatment of patients with long-gap esophageal atresia (LGEA)

What are the criteria for a CoE?
A CoE:

- Has a protocol describing the management of all types of EA, including LGEA
- Has a highly specialized department of neonatology and anesthesiology available for pre-, peri-, and postoperative care
- Preferably has prenatal diagnosis and counseling facilities
- Routinely performs a preoperative rigid trachea-bronchoscopy
- Has extensive experience in repair of all types of LGEA
- Can manage all kinds of concomitant anomalies associated with LGEA (VACTERL association, laryngeal anomalies)
- Can manage all sequelae, like anastomotic stricture, gastroesophageal reflux disease, tracheomalacia, tracheoesophageal fistula (TEF), and recurrent TEF.
- Has a structured follow-up program including pediatric surgery, neonatology, pediatric pulmonology, pediatric gastroenterology, pediatric radiology, pediatric cardiology, pediatric urology, ENT, orthopedics, genetics, pediatric neurology, psychology, social work, occupational therapy, dietician, speech therapy, and physiotherapy. Provides basic life support
- Organizes transition to adult care
- Develops collaboration with family and patients support groups
- Has/collaborates with a dedicated database
- Has a research program dedicated to EA

After having defined the correct diagnosis, the next issue is how to determine the gap between the ends of the esophagus and the existence of concomitant anomalies.

There was general consensus that a preoperative rigid tracheobronchoscopy (9, 10) is mandatory to exclude the presence of a proximal fistula that has been described to be found in more than half of the cases (11) and to determine if tracheomalacia is present.

In order to be able to perform a contrast study of the distal esophagus a (laparoscopic) gastrostomy may be constructed. Some centers use bougies to determine the distance between the proximal and distal pouch. The preference depends on the center and the experience with their chosen technique.

There was general consensus that a cervical esophagostomy should be avoided, because this may increase the difficulty of a delayed primary anastomosis, or the use of jejunal interposition as such a graft may not be able to reach up to the neck without microvascular supercharging. Good nursing care with the use of a Replogle® sump drain will adequately prevent aspiration from saliva in the proximal pouch (12).

In recent years, the esophageal traction technique has become more popular, and this can even be performed thoracoscopically directly after birth without the need for a gastrostomy (5).

Only if primary esophageal anastomosis is not possible in the judgment of the CoE, esophageal replacement techniques should be used. In major centers for EA, the jejunal interposition is preferred, because the graft grows at a similar rate as the child and maintains intrinsic motility (13). In addition, the risk of gastroesophageal reflux, leading to pulmonary complications in the long term is less than in gastric pull-up and colonic interposition.

The advantage of a gastric pull-up is that blood supply is very good, only one anastomosis is necessary. However, reflux is a dominant issue (14). When only 1–3 cm of defect remains, some formation of a gastric tube can avoid the usage of replacement technique, although this is also not without complications of gastroesophageal reflux (15).

Colon interposition is mainly reserved as a last option, when all other techniques have failed or are considered unfeasible. Sequela include kinking due to inappropriate growth, bulging of the graft in the neck, persistent stasis of food residue in the graft with reflux, and aspiration and gastroesophageal reflux (2, 16).

Centers of expertise should master the whole armamentarium to be able to deal with restoration of the esophagus.

If not possible to preserve the native esophagus, the following options are available

a. Jejunal interposition

- In the neonate with vascularized stalk
- In the older child with micro anastomosis

b. Gastric pull-up

- In some cases where only 1–3 cm defect remain, it may be possible to perform an alternative technique of tube elongation.

c. Colon interposition

Because there are so many sequelae like kinking etc., this is often a last resort.

This brings us back to what a CoE should be. Is every pediatric surgical center automatically a CoE for LGEA? There are countries where designated centers of expertise have been appointed by the government, like in France or the Netherlands (17). Some countries have major esophageal airway centers, like in the USA (18, 19). Distance should not really be an issue, because the reconstruction usually takes place at a later time and traveling is not exceptional for patients nowadays. Many patients travel all over Europe or even to the USA for restoration of the esophagus in LGEA. It is probably more a matter of acceptance or acknowledgment that patients can travel more freely to centers of expertise.

Regional or national discussions should be started about referral centers for specific conditions.

For anomalies, such as congenital diaphragmatic hernia, there are ECMO centers available, biliary atresia is being concentrated into a limited number of centers in the UK as in many other countries (20). Similar centers could be determined for bladder extrophy, Hirschsprung disease, tracheomalacia, and EA.

Pediatric surgeons are dedicated to give their patients the best care for some specific congenital malformations that requires centers of expertise.

AUTHOR CONTRIBUTIONS

This is a position paper by the working group on long-gap esophageal atresia. All authors have equally contributed to this paper.

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Impedance Testing in Esophageal Atresia Patients

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Esophageal atresia patients are predisposed to gastroesophageal reflux as a result of the altered esophageal anatomy and motility. These patients experience significant morbidity from gastroesophageal reflux. As a result, an effective way to diagnose and monitor for reflux is crucial. pH-metry is able to quantify acid burden, ensure that acid suppression is adequate during long-term follow-up, and correlate acid reflux to symptoms. pH with impedance is additionally able to detect non-acid reflux as well as volume clearance, both of which also correlate with patient symptoms. It is also able to correlate extra-gastrointestinal symptoms to reflux, which may help guide treatment. If complications associated with uncontrolled reflux are identified, aggressive reflux management is necessary, oftentimes requiring surgical intervention.

Keywords: esophageal atresia, gastroesophageal reflux, esophageal pH, impedance, tracheoesophageal fistula, multichannel intraluminal impedance, pH impedance

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Gastroesophageal reflux disease (GERD) is the most common long-term complication of esophageal atresia (EA)–tracheoesophageal fistula (TEF), affecting between 22 and 75% of pediatric patients (1–3). The increased risk of GERD in this group is due to both intrinsic dysmotility and structural factors. Primary dysmotility is a result of abnormal development of esophageal smooth muscle, with histopathologic features including distortion of smooth muscle, fibrous tissue in between smooth muscle layers (4), and tracheobronchial remnants present in the esophagus (5). In addition, there is abnormal congenital neural innervation of the esophagus, with a hypoplastic Auerbach plexus (6) and decreased interstitial cells of Cajal (7). Structurally, after surgical repair, most EA patients lose some function of the anti-reflux barrier. While anatomic changes vary from patient to patient, those most affected are patients with long gap EA. With gastric pull-up surgery, the lower esophageal sphincter (LES) is displaced proximal to the hiatus formed by the crural diaphragm, and without the overlap between the two, the anti-reflux barrier becomes incompetent (8). Gastric content can get trapped in the sac created between the LES proximally and the crural diaphragm distally, and can reflux up during swallow-induced LES relaxation. Surgical mobilization of the lower esophagus also weakens the phrenoesophageal ligament, and decreases the angle of His, further affecting the anti-reflux barrier (9).

COMPLICATION RISKS SECONDARY TO GASTROESOPHAGEAL REFLUX

Given how common reflux is in EA patients and the high-risk of complications associated with GERD, it is imperative to diagnose and manage GERD appropriately in this population. Complications include dysphagia, esophagitis, Barrett's esophagus, stricture formation, silent aspiration, and failure to thrive (**Table 1**). GERD is a frequently reported symptom in children and adolescence, with symptoms of GERD being reported in 22–58% of these patients (2, 3, 10, 11). As the majority of reflux experienced in these patients is acidic in nature, chronic acid exposure leads to esophagitis,

TABLE 1 | Complications of gastroesophageal reflux experienced by esophageal atresia patients (10, 11, 16–18).

	Percentage
Esophageal	
Dysphagia	40–72
Esophagitis	25–53
Barrett's esophagus	1–11
Esophageal stricture	18–50
Feeding difficulty	6–52
Extraesophageal	
Cough	39–80
Chronic lung disease	11
Worsening airway reactivity	13–35
Recurrent lower respiratory tract infection	13–60
Brief responsive unexplained events	Up to 53

increased risk of Barrett's esophagus, and increased risk of recurrent anastomotic strictures (12–15).

While strictures can contribute to symptoms of dysphagia and feeding difficulties, they can also atypically present with pulmonary symptoms such as cough, chest pain, and hoarseness (16). Brief resolved unexplained events (BRUE), formerly known as apparent life-threatening events, are thought to result from either aspiration, with reflux contents from the proximal esophagus entering the larynx, or from GER in the lower esophagus stimulating respiratory symptoms (17). Further aerodigestive complications resulting from GER include chronic aspiration pneumonia, chronic lung disease with bronchiectasis and increased oxygen requirement, worsening of tracheomalacia and airway reactivity, and persistent atelectasis (13). Supporting the association between GERD and pulmonary complications is a study that demonstrated increased risk of chest infections in EA patients with early strictures compared to those without (19). Aspiration and respiratory problems can contribute to feeding difficulties in EA.

DIAGNOSTIC METHODS

Diagnosing Gastroesophageal Reflux by Quantifying Acid Exposure

The utility of diagnosing GERD accurately and tailoring treatment accordingly is necessary to prevent the complications mentioned above. These patients are in a high-risk category given they have increased GER and almost universally have esophageal dysmotility (20, 21), which can impair reflux clearance. pH probe testing, pH-impedance testing, and wireless pH testing are currently the best objective measures for quantifying esophageal reflux (12), with each modality having its own benefits and limitations (**Table 2**). Twenty-four hours esophageal pH monitoring measures the frequency and duration of esophageal acid reflux, thereby quantifying esophageal acid burden. A drop in intraesophageal pH <4 for more than 5 s is considered acidic exposure (22). The reflux index (RI) is the percentage of time during the entire recording time with pH <4, with RI >7% considered abnormal, an RI <3% considered normal, and an RI between 3 and 7% indeterminate (22). While the sensitivity of abnormal esophageal pH in predicting erosive esophagitis in adults and children is high, ranging from 83 to 100% (23, 24), there are limitations to standard pH monitoring. It is a poor detector of weakly acidic (pH 4–7) reflux (25) and can also overestimate acid exposure by picking up "pH-only" episodes, in which there is no detected retrograde liquid refluxate (26). In infants and children, weakly acidic GER is more prevalent than in adults (26, 27), which can explain why symptoms are not always detected by esophageal pH monitoring (23). This elucidates the limitation in depending on only pH monitoring to diagnose reflux.

TABLE 2 | Benefits and limitations of pH-only versus pH-impedance testing (23, 25, 28, 29).

	Benefits	Limitations
pH-only	• Quantifies frequency and duration of acid exposure • Measures chemical clearance • Able to correlate acid reflux to symptoms • Readily available • Easier to interpret than pH-impedance	• Unable to detect non-acid and weakly acid reflux • Can overestimate acid exposure by picking up "pH-only" episodes • Limited utility in patients on acid suppression, continuous feeds, or frequent feeding schedule
pH-impedance	• Quantifies acid and non-acid reflux • Detects liquid, gas and mixed refluxate • Measures volume and chemical clearance • Quantifies the height of refluxate	• Analysis is time consuming • Low baseline impedance in esophageal atresia patients makes it difficult for automated analysis to detect reflux events, and must be manually reviewed • Limited availability in certain medical centers and practices

Utilizing Multichannel Intraluminal Impedance (MII) in the Diagnosis of Gastroesophageal Reflux

Multichannel Intraluminal Impedance is an alternative diagnostic tool that utilizes change in impedance to measure the anterograde and retrograde movement of fluid, solids, and air in the esophagus. Dual pH-multichannel intraluminal impedance (pH-MII) is able to detect both acid and non-acid GER, detect anterograde versus retrograde flow thereby distinguishing between swallows and GER, determine the height of refluxate, and differentiate between liquid, gas, or mixed refluxate (28, 30). MII also provides information about bolus transit, duration of bolus presence, time of bolus clearance, and time of acid clearance.

Though initially used as a research tool, pH-MII has been shown to be very useful in assessing reflux and clearance. The definitions listed below have been established based on several studies (26, 31):

- Liquid reflux: drop in impedance to ≤50% of the baseline value, with subsequent recovery, in two or more of the distal-most channels.
- Acid reflux: liquid reflux (using the aforementioned definition) in which the pH decreases and remains <4 for ≥5 s.
- Non-acid reflux: liquid reflux (using the aforementioned definition) in which the pH increases, is unchanged, or decreases by at least 1 pH unit while maintaining pH ≥4.

- Gas reflux: simultaneous and rapid increases in impedance (>3,000 Ω) in two or more of the distal-most channels.
- Proximal reflux/"high reflux": the refluxate reaches either/or both of the most proximal channels.
- Distal reflux: the refluxate is confined to the two most distal impedance channels.
- Bolus clearance time (BCT): time for bolus clearance from the esophagus.
- Acid clearance time (ACT): time for acid clearance from the esophagus.

Reference values for reflux parameters in infants and children on pH-MII over a 24 h period were previously published by a multicenter study (**Table 3**) (32). Patients were selected based on having no evidence of acid reflux or symptoms associated with regurgitation, off anti-reflux medications at the time of the procedure, and no fundoplication. Based on the study findings, the following would be considered abnormal over a 24 h period, as it is above the 95th percentile in this selected group of infants and children: >48 acid reflux episodes or more than 67 non-acid reflux episodes in an infant; >55 acid reflux episodes or >34 non-acid reflux episode in a child; >93 total GER events in an infant and >71 total GER events in a child. A limitation in this study, as well as all studies done in children, is in the ethics of performing pH-MII in asymptomatic children. As all patients were symptomatic, true normal values cannot be established. However, by setting strict selection criteria, it is likely that the patients selected have physiologic GER and can be used as a reference. Reflux parameters have also been described by a prior large-scale study of 700 children (33). Patients with normal RI had a mean of 39 ± 31 reflux episodes, compared to patients with pathological RI that had a mean of 58 ± 43 reflux episodes. The children selected were all symptomatic, with 21% having documented acid reflux. In this study, reflux was not differentiated into non-acid and acid reflux. A study to establish normal reflux parameters was additionally done in preterm infants, who were otherwise healthy (34). This study was limited due to all patients being on tube feedings, which can affect the number of reflux episodes, as the tube stents open the LES.

pH-MII in Determining Esophageal Clearance

pH-multichannel intraluminal impedance is useful in calculating esophageal clearance. Volume clearance involves primary and secondary peristalsis, and is followed by chemical clearance that neutralizes acid. The efficiency of volume clearance of a reflux episode is generally assessed using the most distal impedance channel. The presence of reflux is identified by the impedance waveform dropping to 50% of the baseline. The bolus is cleared from the distal esophagus when the impedance waveform again reaches 50% of impedance baseline (35). Reference values have been published, with the upper 95th percentile of bolus clearance being 20 s in infants and 32 s in children (**Table 3**).

While volume clearance is known to be accomplished by esophageal peristalsis, chemical clearance is known to be accomplished primarily by bicarbonate-rich saliva that neutralizes acid and washes the esophageal walls of gastric and duodenal debris (36). Chemical clearance is defined as the duration of esophageal acidification immediately followed the end of volume clearance (37). It begins the moment the impedance waveform in the distal-most channel returns to 50% of baseline and ends when the pH waveform reaches pH 4. Physiologic norms were determined for infants up to 1 year of age, and children between ages 1 and 18 years (38): the upper 95th percentile of physiologic chemical clearance duration was 148.5 s for infants and 114.4 s for children. These children had no fundoplication, no positive reflux-symptom associations, were not taking anti-reflux medications at the time of the study, and had acid gastroesophageal reflux indices ≤3% for the children and ≤6% for the infants.

Clearance, particularly of non-acid reflux, cannot be picked up by pH testing alone. Comparing infants with EA and controls with GER, the mean ACT and mean BCT are significantly longer in the EA group (39). Correlation between symptoms and clearance time in the EA group showed that the median ACT and BCT were significantly shorter in patients without symptoms than in those with symptoms. This suggests that it is not the acidity of the reflux is that influences symptoms, but the clearance. Findings of prolonged bolus and ACT were similarly found in older children (40). Studies have shown that esophageal clearance can indicate the severity of esophageal dysmotility. In one study, while 79% of swallows were accompanied by abnormal motility patterns, approximately 60% of swallows showed abnormal bolus transit, and 66% of all GER episodes initiated no clearing mechanism (41). Furthermore, EA patients have a significantly lower percentage of complete bolus transit for liquid and viscous swallows,

TABLE 3 | Normal values for reflux on pH-multichannel intraluminal impedance per 24 h in infants and children.

	Infants		Children	
	Median (IQR)	**95th %**	**Median (IQR)**	**95th %**
Index of acid regurgitation (%)	0.6 (0.3–0.9)	1.4	0.4 (0.2–0.8)	1.3
Number of acid regurgitation episodes in 24 h	20 (11–26)	48	14 (11–15)	55
Index of non-acid regurgitation (%)	0.7 (0.5–1.2)	2.5	0.1 (0–0.3)	1
Number of non-acid regurgitation episodes in 24 h	32 (16–45)	67	6 (3–11)	34
Index of GER episodes (%)	1.4 (0.9–1.2)	2.9	0.6 (0.3–1.2)	2.4
Number of GER episodes in 24 h	54 (33–69)	93	21 (11–41)	71
Mean GER bolus clearance time (s)	13 (11–16)	20	15 (12–19)	32

Adapted from Mousa et al. (32).

and their higher bolus index and reflux indices are significantly related to increased symptom scores (29).

Correlating Symptoms with Reflux

Three indices are used to quantify the temporal relationship between GER and symptoms. Though they have been validated in adults, currently there are few studies validating the use in children (33, 42, 43).

- Symptom index (SI): the number of symptoms associated with reflux divided by the total number of symptoms in 24 h. SI >50% is considered abnormal.
- Symptom sensitivity index (SII): the number of symptoms associated with reflux divided by the total number of reflux events in 24 h. SII >10% is considered abnormal.
- Symptom associated probability (SAP): calculation of statistical relation between reflux and symptoms using Fisher's exact test. SAP >95% is interpreted as good temporal association between GER and the recorded symptom.

The SI and SSI are simple to calculate, with the former being used to determine the percentage of symptoms that are associated with reflux events and the latter used to determine the percent of reflux events associated with symptoms (30). The SI does not take into account all reflux episodes and can provide false-positive results when the number of reflux episodes is large or the number of symptoms is small. The SSI does not take into account the total number of symptoms and can result in false positives when the number of reflux episodes is small or the number of symptoms is small. The SAP takes all parameters into account and is the strongest statistical parameter for symptom association analysis. The minimal number of symptoms to obtain an accurate and reliable SAP is uncertain (27, 44). Positive symptom association, which suggests causality between reflux and symptoms, is defined when both SI and SSI are positive or when SAP is positive. Further limitations to these symptom indices include (44): (1) registration of symptoms in a timely fashion is dependent on the child and/or parent. (2) The time interval of 2 min between a reflux event and symptom is the accepted interval, based on consensus, to demonstrate a time association. However, this time interval is not evidence based and may differ based on symptoms. For some symptoms that have a chronic GER relation such as wheezing, laryngitis, or bronchial hyperreactivity, temporal symptoms association may not be achieved. Symptoms such as cough, apnea, and chest pain likely have a shorter time frame.

pH-multichannel intraluminal impedance monitoring is useful in evaluating and correlating non-acid reflux with symptoms in the following patient groups: symptomatic patients on proton pump inhibitor (PPI), patients on continuous feeds, patients with extraintestinal symptoms, patients with BRUE, and GER symptoms with normal pH probe and endoscopy results (22). Since many EA patients are already on anti-reflux therapy, may have a frequent feeding schedule, or may be on tube feeds, the majority of their refluxate is non-acidic and would otherwise be missed by conventional pH testing (28). In a study comparing infants with EA and controls with GER, reflux events in both groups were mainly non-acid (39). Weakly acid reflux has also been shown to be responsible for a significant percentage of symptoms in EA patients (29). In a separate study comparing EA patients and controls with GER, there was no difference in the total retrograde bolus movements between the two groups, though the EA group had significantly higher non-acid RI (21, 29). In the EA patients, 28–42% of symptom occurrences were associated with retrograde bolus movements. The utility of pH-impedance compared to pH-metry alone is further elucidated when comparing the SI between the two modes. Significantly more EA patients had a positive SI when using pH-MII than pH probe alone (42).

pH-impedance is useful in quantifying the proportion of reflux reaching up to the proximal esophagus, referred to as "high reflux." EA patients frequently experience extraesophageal symptoms, and pH-MII has the unique ability to determine if these symptoms correlate with reflux episodes, whether they are acid or non-acid. In one study, 39% of the coughs recorded were associated with reflux (29). In that study, of the four patients who showed more than 50% high-reflux episodes, three had chronic pulmonary problems with frequent postprandial coughing. Of these high refluxes, 47% were weakly acidic and 53% were acidic. In another study, 62% of coughs were associated with reflux in children ≤1 year old, and 58% of coughs were associated with reflux in children >1 year old (39). Cough episodes were more commonly seen with acid reflux, though compared to children >1 year old, younger children had more frequent cough episodes related to non-acid reflux. In a study correlating symptoms in EA to the presence of GERD, the most frequent symptoms in children with GERD included cough, recurrent bronchitis, and heartburn, though this did not reach clinical significance (45).

When patients with EA have non-acid reflux associated with complications, particularly pulmonary or stricture related, medical management with prokinetics is recommended. If this fails, fundoplication or transpyloric feeds should be considered. While fundoplication can have higher complications in EA patients, it is indicated in the following cases: patients with significant extraesophageal symptoms related to GERD including cyanotic spells, patients with recurrent anastomotic strictures, and esophagitis despite maximal PPI therapy (12).

BENEFITS OF pH-MII

As discussed above, pH-MII provides multiple benefits over pH probe alone, and should be considered, when available, for diagnosing and monitoring for GER in EA. It not only quantifies acid and non-acid exposure, but also is more effective in correlating symptoms to reflux, and can measure both volume and chemical clearance. In a pH-MII study of 700 children with GERD symptoms, 45% of the patients with abnormal GER would not have been recognized by 24-h pH measurement alone (33). In addition, extraintestinal symptoms of GER, which were more common in younger children, were more often correlated with pH-MII as compared to pH alone.

It should be noted that GERD is often more severe than predicted based on the clinically reported symptoms (21, 29). Reliance on symptoms is insufficient in determining whether acid suppression is needed. Given the high-risk of complications from GERD, particularly the high-risk of anastomotic stricture in the first year of life, it is recommended that patients stay on

empiric therapy with acid suppression for the first year of life. They should also undergo monitoring of GER with impedance/pH and/or endoscopy at the time of antacid discontinuation and during long-term follow-up (12).

LIMITATIONS OF pH-MII

One of the limitations of pH-MII in patients with EA is that the baseline impedances are 75% lower than control patients (29). Because of this, software analysis often does not detect reflux events. As a result, manual analysis must be done in addition to automated, to prevent underreporting of reflux (12). While there is a single large study that has reported age-related normal data for reflux indices (32), symptom association statistics are largely based on adult data. The time interval between symptoms and reflux events is based on consensus, with little evidence on the ideal time frame between different types of symptoms. As there are no large outcomes, studies on treating weakly acid and non-acid reflux with anti-reflux surgery, medications that decrease transient LES relaxation, or promotility agents, the clinical relevance of measuring this type of reflux remains debatable. In addition, the analysis of pH-MII requires special training and it is time consuming. These tests are also not available to every medical practice. pH probe testing is easier to interpret and more accessible to providers.

CONCLUSION

Because of the increased prevalence and significant morbidity associated with GER in EA/TEF patients, diagnosing and monitoring for GER is essential. The recommendations are to treat all EA patients in the first year of life with PPIs, and to monitor for GER thereafter. pH monitoring is recommended to evaluate the severity of acid reflux and the symptoms associated with it. pH-impedance monitoring provides additional benefits of correlating non-acid reflux and esophageal clearance with symptoms. These tools help guide the duration of antacid therapy and the need for surgical intervention.

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MH is the primary author, and she drafted the paper. HM is the supervisor and corresponding author, and she reviewed and edited the paper.

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REVIEW
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Fundoplication in Patients with Esophageal Atresia: Patient Selection, Indications, and Outcomes

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Patients with esophageal atresia (EA) suffer from abnormal and permanent esophageal intrinsic and extrinsic innervation that affects severely esophageal motility. The repair of EA also results in esophageal shortening that affects distal esophageal sphincter mechanism. Consequently, gastroesophageal reflux (GER) is common in these patients, overall approximately half of them suffer from symptomatic reflux. GER in EA patients often resists medical therapy and anti-reflux surgery in the form of fundoplication is required. In patients with pure and long gap EA, the barrier mechanisms against reflux are even more damaged, therefore, most of these patients undergo fundoplication during first year of life. Other indications for anti-reflux surgery include recalcitrant anastomotic stenoses and apparent life-threatening episodes. In short term, fundoplication alleviates symptoms in most patients but recurrences are common occurring in at least one third of the patients. Patients with fundoplication wrap failure often require redo surgery, which may be complicated and associated with significant morbidity. A safe option in a subset of patients with failed anti-reflux surgery appears to be long-term medical treatment with proton pump inhibitors.

Keywords: esophageal atresia, fundoplication, anti-reflux surgery, gastroesophageal reflux, anastomotic stricture, acute life-threatening events, long-gap atresia

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INTRODUCTION

The esophagus is not normal following repair of an esophageal atresia (EA). The motility of the esophagus is permanently altered, and the esophagus is usually shorter than normal (1–3). The tension and abnormal perfusion at the anastomotic site commonly cause stricture formation that requires anastomotic dilatations. Pathological gastroesophageal reflux (GER) that is caused by shortening of the esophagus and abnormal clearance of esophageal contents due to abnormal motility affects up to two thirds of patients with EA (1, 4). Some EA patients experience acute life-threatening events (ALTE) that may be associated with proximal extension of GER and also with tracheomalacia that commonly accompanies EA. Recurrent respiratory disease has been attributed to GER but evidence supporting this is not convincing. Medical therapy, today mainly by proton pump inhibitors (PPI), is always the first-line approach for these patients but a significant percentage ultimately undergoes surgery in the form of fundoplication. Most pediatric surgeons agree that patients with pure or long-gap EA very often require fundoplication to overcome severe GER and anastomotic strictures associated with the significant shortening of the esophagus. In the literature, the overall rate of fundoplication in patients with EA ranges between 10 and 45% (1, 4, 5).

INDICATIONS FOR FUNDOPLICATION IN EA

Gastroesophageal Reflux Disease (GERD)

The abnormal esophageal anatomy after repair of EA plays a significant role in the etiology of GERD. The esophageal repair often causes esophageal shortening that may displace the gastroesophageal junction upward causing an obtuse angle of His. This is especially true in patients with long-gap atresia and significant anastomotic tension (6).

The esophageal peristalsis that is responsible for esophageal clearance is damaged in patients with EA (2, 3). The abnormal and ineffective peristalsis does not improve by age as most adult patients with repaired EA still show highly abnormal and decreased motility in manometric studies (5). The cause of poor motility is probably multifactorial. The arrangement of muscular layers may be abnormal in EA (1). Both extrinsic and intrinsic innervation of the esophageal wall is congenitally deficient (7, 8), and there is additional damage that is caused by the extensive dissection required for the making of esophago-esophageal anastomosis (9).

Symptomatic GER is very common in infants with EA, the incidence ranges between 25 and 70% (1). Moreover, unlike GER that is not associated with anatomical defects, the proportion of significant EA-associated GER tends to increase over time (10). GER in infants with EA does not respond well to standard methods of management such as thickening of milk and postural treatment. Medical treatment may also be unsuccessful although most pediatric surgeons routinely treat their EA patients with long-term anti-acid medication, today usually with PPI.

Of patients who suffer from significant GERD 30–64% undergo fundoplication. Most patients require fundoplication before the age of 1 year. There are no generally accepted indications for fundoplication in EA patients who suffer from significant GER. The usual causes leading to operation are failure of medical treatment to control symptoms, failure to thrive, and GER-related refractory anastomotic stenosis.

Anastomotic Stricture

Anastomotic strictures requiring dilatation occur in 30–60% of EA patients (4, 5, 11). Most strictures respond well to anastomotic dilatations but the choice of the timing of dilatations and the number of dilatations remain arbitrary. Most pediatric surgeons dilate only symptomatic patients. A small proportion of patients who suffer from recalcitrant strictures are commonly considered to have significant GER that contributes to refractory stenosis formation. Anti-reflux surgery has been suggested to be curative in most of these patients (12, 13). However, there are no scientifically based definitions for recalcitrant strictures or for the timing of surgery. The surgeon's judgment based on personal or institutional experience dictates the timing of surgery. Moreover, the efficacy of fundoplication in the management of anastomotic strictures remains scientifically unproven. This is especially true today in the era of PPI's that are more or less routinely used in patients with EA (14).

Pure/Long-Gap EA

There is a lack of generally accepted definition for long-gap EA. Some surgeons consider only pure (type A) or type B atresia with proximal fistula as long-gap atresia, some include also "long-gap" type C (with distal fistula) atresia. There are also no uniformly accepted methods to measure the gap between the esophageal ends. It has been clearly shown that long-gap predisposes to symptomatic GERD and anastomotic strictures (4, 6, 15), mainly because of considerable tension in the anastomosis. The recent esophageal lengthening techniques are associated with GERD, and fundoplication is required in most patients (16). Anti-reflux surgery is considered as a routine and predictable step in the management of long-gap EA patients by some surgeons (6, 16, 17), others perform fundoplication only in patients with severe symptoms and abnormal GERD tests (15).

Acute Life-Threatening Events

Acute life-threatening events in the form of cyanotic or dying spells occur in some patients with EA. The actual incidence is not very well documented but operative treatment is required in 5–12% of patients (15, 18). The pathophysiology of ALTE in patients with EA is not fully understood. Many of these patients have significant tracheomalacia, which is commonly associated with GERD. In the literature, ALTE is considered as an absolute indication for surgical treatment (19, 20). There is no consensus concerning the optimal management of ALTE. In the presence of tracheomalacia, some surgeons perform primary aortopexy that may be followed by fundoplication (19, 20), some favor simultaneous aortopexy and fundoplication (18). Some patients may be treated by fundoplication alone if the etiology of ALTE is considered to be mainly GERD (21).

Severe Respiratory Disease

Up to 74% of patients with repaired EA suffer from chronic or recurrent respiratory symptoms (22). Pulmonary lung function test has revealed that 70–90% of EA patients have detectable ventilatory impairment. The defect may be restrictive or obstructive or both (22). Moreover, a significant proportion of patients have abnormal airway reactivity suggesting susceptibility to asthma. It appears, however, that these symptoms are not related to GER (23). In addition, fundoplication has not been shown to protect from respiratory symptoms or ventilator defects (24). Anti-reflux surgery probably has no role in the management of respiratory disease in EA patients.

PREOPERATIVE WORK-UP

In most cases, the decision to perform fundoplication in patients with EA is based on clinical symptoms and findings. Diagnostic tests are not always helpful but may support decision-making in selected cases. Esophagogastroduodenoscopy is helpful in detecting inflammatory changes in the esophagus of patients with symptomatic GER. Detection of chronic inflammation in symptomatic EA patients is considered to support surgical therapy. Endoscopy is also useful to assess the severity of anastomotic stricture and its response to dilatations. Esophageal pH-metry and impedance

pH-metry may be useful adjuncts in surgical decision-making; high reflux indices support surgical therapy in a symptomatic patient. Esophageal manometry is usually not applicable and is anyway almost always pathological in EA patients (22). Gastric emptying studies are often abnormal in EA patients and not very useful in clinical practice.

WHAT TYPE OF ANTI-REFLUX SURGERY FOR EA PATIENTS?

The selection of the type of anti-reflux surgery in patients with EA has been a matter of debate between pediatric surgeons. Partial wraps such as Thal (anterior wrap) or Toupet (posterior wrap) operation may be associated with less adverse effect, but a higher failure rate (25, 26). On the other hand, complete fundoplication such as Nissen operation may result in more dysphagia, retching, and gas–bloat (27). This is, however, not supported by solid scientific evidence, and some studies have not found any differences between complete and partial wraps (28). There is absolutely no consensus as to whether partial or complete fundoplication should be used in patients with EA. There is even less valid scientific evidence to support superiority of either approach in this patient population. Anti-reflux surgery may be performed laparoscopically with similar success rate than in open surgery, whether with partial or complete hiatal wrap (29).

Practically, all patients with EA have abnormal esophageal motility (2) that makes them a special group compared to otherwise healthy patients requiring fundoplication. They have more often esophagitis and higher rate of strictures, and they have commonly delayed gastric emptying. The motility problems predispose EA patients to postoperative dysphagia and ultimately to wrap failure. Some patients may not be able to generate enough propulsion to overcome the increased resistance at the esophagogastric junction created by the fundoplication and may develop respiratory tract problems caused by regurgitation of esophageal contents (30). Postoperative dysphagia is typical for laparoscopic anti-reflux surgery occurring in one third of the patients (29), but it usually disappears within a couple of months.

Some surgeons prefer to use esophageal lengthening procedures in association with anti-reflux surgery (31). The most popular approach is the Collis–Nissen procedure where the esophagus is lengthened by stapling the esophagogastric junction longitudinally. This operation is mainly used in redo surgery. The main problem with this procedure is that it leaves acid secreting mucosa in the chest that may result in the development of chronic esophagitis and Barrett's esophagus.

OUTCOMES OF FUNDOPLICATION IN EA

Typically, in most EA patients who have undergone anti-reflux surgery the symptoms are initially alleviated (17, 32, 33). Unfortunately, the positive effect of fundoplication is transient in a significant proportion of patients. Partial wrap may be associated with fewer symptoms at least after short-term follow-up (25), but the scientific basis remains vague.

The wrap failure rates range between 20 and 45% (17, 32–35). This is significantly higher rate than in those who undergo fundoplication without any underlying anatomic defect (33). The wrap failure is usually detected 1.5–2.5 years following the primary fundoplication (17). The failure rate appears to be similar for both complete and partial wraps or open and laparoscopic approaches. The main problem in the literature is that the wrap failure is poorly defined. Most studies define failure as a need for reoperation but the actual reasons for reoperation are not fully described. The length of follow-up, symptoms, investigations, and findings leading to a decision to redo the fundoplication are inconsistently characterized in the literature. The main reason for these problems is that all studies on the fate of fundoplication in EA patients are retrospective. As wrap failure is usually defined as need to redo the fundoplication, it is likely that the actual failure rate is much higher as patients with milder symptoms are most likely managed conservatively. Moreover, if all patients would undergo regular and long-term endoscopic follow-up, the anatomical failure rate (wrap failure and thoracic dislocation of the wrap) would be significantly higher than reported.

The causes of wrap failure are likely to be the same anatomical and physiological abnormalities that have caused GERD in these patients. The short length and poor propulsive activity of the repaired esophagus interfere very likely with the persistence of the fundoplication (34). The stomach may also be smaller than normally, especially in patients who originally have had a pure type A EA, which may influence performing of a reliable fundoplication. Delayed gastric emptying is a common and persisting finding in EA patients and may contribute to high incidence of wrap failures (36).

WHAT ARE THE OPTIONS WHEN FUNDOPLICATION HAS FAILED?

The high incidence of wrap failure following primary fundoplication in patients with EA raises the question: what to do next? For pediatric surgeons, the natural response is to do a redo operation to correct the failed wrap (17, 34, 37). Diagnostic work-up is required in patients with symptoms of wrap failure. The typical tests are contrast X-ray studies, upper gastrointestinal endoscopy, and pH-metry. The typical findings at imaging and endoscopy are partial or complete unwrapping of the fundoplication or dislocation of the wrap partially or completely into the chest. pH-metry usually shows a high reflux index compared with previous postoperative measurements.

Reoperation following failed wrap is significantly more demanding than the primary fundoplication. There is always major scarring and adherence of the stomach and wrap area to the spleen, liver, and diaphragm. The operative times are longer, and blood loss and postoperative complication rates are increased (35, 38).

The literature offers very little data on the outcomes of re do fundoplication. Redo fundoplication has been reported to be successful in 70–80% of cases overall (35, 38); however, the failure rate may be higher than following the primary operation, especially in patients with EA (34). This is not unexpected because the factors

that have caused the failure of the primary wrap are still present. It appears to be imperative to put effort in patient selection for redo fundoplication.

An alternative to repeat fundoplication may be maintenance therapy with PPI's. Although prophylactic PPI therapy does not reduce the incidence of anastomotic stenosis in infants who have undergone repair of EA (39, 40), PPI's can induce long-term remission of erosive esophagitis (41). Marked improvement has been noted in symptoms of GERD and severity of esophagitis in patients who have received PPI maintenance therapy after failed fundoplication (42). Long-term maintenance therapy has also been shown to be safe with few adverse effects (43).

Severely symptomatic patients who have undergone one or several redo fundoplications and who often do not tolerate oral feeding or feedings through gastrostomy are a problematic group in EA patients. These patients often suffer from associated malformations or syndromes and have often undergone multiple revisional operations (44). Feeding jejunostomy may decrease GER-related symptoms and provides a route for enteral feeding at least temporarily for this unfortunate group. Another option is esophagogastric disconnection that has been used as rescue therapy following failed fundoplications (45). Esophagogastric disconnection provides a reliable route for gastrostomy feedings and may eliminate GER and its consequences completely.

CONCLUSION

Fundoplication is frequently required in EA patients, however, the indications for fundoplication are not scientifically delineated. Partial wraps may be associated with better functional outcome but, again, the scientific basis for the statement is vague. This clinical equipoise calls for multicenter randomized controlled studies to evaluate partial and complete wraps in EA patient population. After fundoplication most patients have excellent relief of their symptoms. However, wrap failure is much more common than in patients without EA and is not related to the type of fundoplication. Many patients with wrap failure require redo surgery but long-term PPI therapy deserves to be considered before subsequent surgical intervention.

AUTHOR CONTRIBUTIONS

RR reviewed the literature and wrote the manuscript.

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REVIEW
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Dysmotility in Esophageal Atresia: Pathophysiology, Characterization, and Treatment

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Esophageal dysmotility is almost universal after esophageal atresia (EA) repair and is mainly related to the developmental anomaly of the esophagus. Esophageal dysmotility is involved in the pathophysiology of numerous symptoms and comorbidities associated with EA such as gastroesophageal reflux disease, aspiration and respiratory complications, and symptoms of dysphagia and feeding disorders. High-resolution esophageal manometry (HREM) has facilitated the characterization of the dysmotility, but there is an incomplete correlation between symptoms and manometrical patterns. Impedance coupled to HREM should help to predict the clinical outcome and therefore personalize patient management. Nowadays, the management of esophageal dysmotility in patients with EA is essentially based on treatment of associated inflammation related to peptic or eosinophilic esophagitis.

Keywords: esophageal motility disorders, gastroesophageal reflux, aspiration, dysphagia, feeding disorders, high-resolution esophageal manometry, impedancemetry

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Following esophageal atresia (EA) repair, motility disorders of the esophagus are almost universal and may lead to gastroesophageal reflux (GER), aspiration, feeding disorders, and dysphagia in the first few months and years of life. Later on, chronic acid exposure of the esophageal mucosa due to abnormal esophageal motility can lead to Barrett's esophagus and esophageal carcinoma, which are a major concern (1). In this review, we will focus on the definition, pathophysiology, and treatment of esophageal dysmotility in patients operated for EA.

THE BURDEN OF ESOPHAGEAL DYSMOTILITY AFTER EA REPAIR

In patients operated for EA, abnormal motility of the esophagus remains the key pathophysiological catalyst leading to digestive and respiratory morbidity throughout life. Indeed, esophageal motility is involved not only in the process of transporting food from the mouth to the stomach but also plays a central role in the defense of the esophagus against gastric reflux. Furthermore, a well-organized swallowing process, from the mouth to the esophagus guarantees an adequate protection of the respiratory tract against aspiration. The following section highlights the consequences of the impaired esophageal motility in patients with EA.

Esophageal Dysmotility and GER

After EA repair, GER is highly prevalent from birth to adulthood. A recent review reports that 22–63% of patients are affected by GER (1). Complications such as peptic esophagitis, peptic strictures, worsening of anastomotic strictures, gastric and intestinal metaplasia of the esophageal mucosa, and even esophageal adenocarcinoma have been described in EA patients, thereby highlighting the severity of the GER in this population (1). EA patients likely develop a severe GER for various reasons including anatomical anomalies (hiatal hernia, abnormal position of the intrathoracic part of esophagus),

vagal nerve surgical injury with abnormal gastric emptying and esophageal dysmotility. The latter leads to abnormal esophageal clearance, which increases the duration of mucosal exposure to gastric juice and acid. Several authors have shown in children and in adults that the greater the degree of esophageal dysmotility, the more the GER is complicated by epithelial metaplasia suggesting a correlation between motor disturbances and severity of reflux (2–4).

Esophageal Dysmotility and Dysphagia

Dysphagia as a symptom is reported in a majority of patients with EA even though most patients learn to adapt to their unique anatomical and physiological state and do not report any complaints. Studies have reported that dysphagia occurs in 21–84% of patients with EA at all ages after surgical repair (2, 4–7). A recent review reports a prevalence of more than 50% in patients older than 10 years (8). Symptoms of dysphagia are not specific and vary according to the age of the patient and whether or not solid food has been introduced. Dysphagia should be evoked in patients with EA who present with food aversion, food impaction, difficulty in swallowing, odynophagia, choking, cough, pneumonia, alteration in eating habits, vomiting, and malnutrition (1). Children may have occasional difficulties with swallowing, are reported as sloweaters or excessive drinkers during meals. Up to three of four of patients with dysphagia report significant changes in their eating habits (need to drink, change in diet, last to finish meal) (2). The etiology of the dysphagia may include inflammatory (peptic or eosinophilic esophagitis) and anatomic causes (anastomotic stricture, congenital stenosis, peptic stricture, post-fundoplication obstruction, vascular compression, anastomotic diverticulum, or mucosal bridge), and abnormal esophageal motility (1). Dysphagia therefore warrants a systematic workup to rule out all of the abovementioned etiologies. In the absence of one of the previously outlined causes, esophageal dysmotility, which impairs a normal bolus transit, remains the most likely explanation (1).

Esophageal Dysmotility As a Risk Factor for Aspiration and Feeding Disorders

Abnormal esophageal motility, thereby hampering an adequate coordination between aerial and digestive tracts, may also foster feeding disorders and aspiration during swallowing, with extraesophageal complications such as recurrent pneumonia, bronchitis, or chronic cough. Once again many hypotheses such as anastomotic stricture, congenital esophageal stenosis, recurrent or missed fistulae, laryngeal cleft, or developmental issues must be carefully ruled out. If the workup is negative, the motor disturbance of the esophagus remains the explanation. The esophageal dysmotility may involve upper esophageal sphincter (UES) dynamics (9, 10) and/or abnormal bolus clearance leading to secretions or food retention in the proximal pouch or distal esophagus or an esophageal pooling over a fundoplication.

CHARACTERIZATION OF ESOPHAGEAL DYSMOTILITY

Esophageal motility has been assessed in children and adults with EA by esophageal manometry [water perfused (4, 11–16) or high resolution (2, 3, 7, 17–19)], impedancemetry (19, 20), or videofluoroscopy (21, 22). Studies have reported anomalies at each level of the esophagus including larynx and vocal cords (23–25) and gastric motor function (15, 26).

Upper Esophageal Sphincter

The UES function has been reported to be normal by most authors (2, 7), but incomplete relaxation has been described in newborns (27). When evaluated by videomanometry, an inadequate coordination between pharyngeal contraction and UES relaxation was found in adults (21). Aspiration during swallowing assessed by videofluoroscopy has been reported in 20–47% of children with EA (9, 10).

Esophageal Peristalsis

Abnormal esophageal peristalsis has been reported in almost all patients with EA. It is found in children (2, 3, 7, 14, 15, 17, 27–30) and persist throughout life as demonstrated by adult studies (4, 11–13, 15, 16). Esophageal dysmotility in EA was recently described using high-resolution manometry (HREM) with three types of abnormalities observed: aperistalsis (**Figure 1**), isolated distal contractions (**Figure 2**), and pressurization (2, 3, 19). GER-related symptoms are prominent in patients with aperistaltic esophagus (2, 3). Type A and long gap defect seem to have a more severe esophageal motor function than type C (2). Manometrical abnormalities are significantly worse in those with epithelial metaplasia (4). Interestingly, correlation between symptoms of dysphagia, motility abnormalities, and bolus transit is imperfect. Impedance associated with high-resolution manometry permits to correlate the degree of motility abnormalities with bolus transit (31).

Lower Esophageal Sphincter (LES)

In almost all studies including those using HREM, LES pressure, and function are similar to controls (2, 7, 12, 27, 28, 32, 33). A study conducted in children with non-complicated type C EA shows that transient LES relaxation is the pathophysiological mechanism in two of three of the reflux episodes (15). However, no data on transient LES relaxation are available in long gap EA, and the latter results may not be applied to patients with high-tension anastomosis leading to abnormal anatomic location of the LES as well as highly impaired esophageal body motility.

ETIOLOGY OF THE ESOPHAGEAL DYSMOTILITY

The etiology of the esophageal dysmotility remains controversial. It may be related to (1) factors due to abnormal development of the esophageal smooth muscle and intrinsic innervation and of the vagus nerve or (2) to factors associated with surgical techniques, fibrotic scars, and postoperative complications. Data indicating that the congenital malformative process plays a major role are prominent in the literature, although surgical repair may exacerbate the esophageal dysmotility.

Primary Motility Disorder

Pathological data are supportive of the role of abnormal intrinsic and vagal innervation of the esophagus. Analysis of

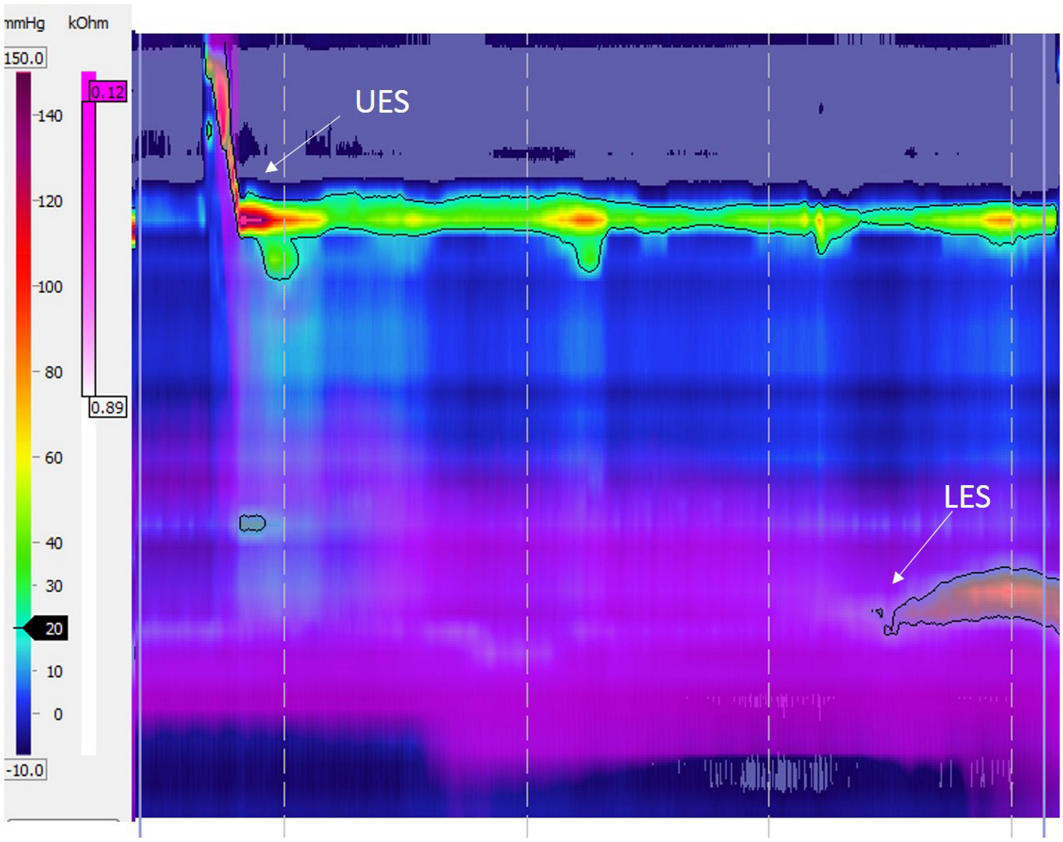

FIGURE 1 | High-resolution esophageal manometry tracing recorded in a patient with type C esophageal atresia: normal upper esophageal sphincter (UES), pattern of aperistalsis, and normal lower esophageal sphincter (LES) pressure and relaxation. The purple color displays intraesophageal impedance variations after a liquid swallow. Note that the bolus clearance is not complete with residual liquid in the distal esophagus.

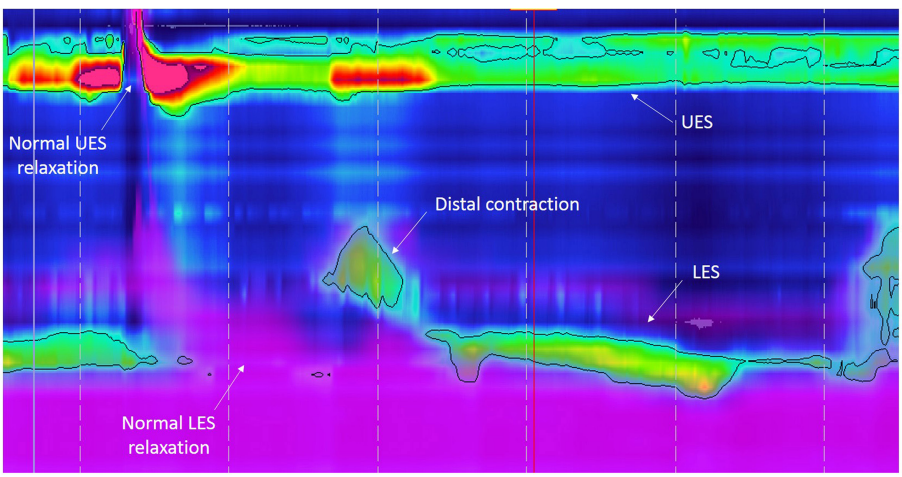

FIGURE 2 | High-resolution esophageal manometry tracing recorded in a patient with type C esophageal atresia: normal upper esophageal sphincter (UES), pattern of distal contraction, and normal lower esophageal sphincter (LES) pressure and relaxation. The purple color displays intraesophageal impedance variations after a liquid swallow. Note that the bolus clearance is almost complete with very few residual liquid in the esophageal body.

esophageal innervation in dead EA newborn has reported abnormalities in the Auerbach plexus (plexus hypoplasia and abnormal interganglionic network) (34). Other studies have also reported hypoplasia of esophageal innervation or smooth muscle (35, 36) or interstitial cells of Cajal (37) in the proximal pouch (36, 38, 39), distal esophagus (36, 37, 39, 40), or in the fistula (35, 41). Animal

studies in a rat adriamycin model of EA have similarly shown abnormal vagal and intrinsic innervation of the esophagus (36, 42). Esophageal manometry performed prior to surgery in 20 newborns with EA demonstrated motor abnormalities in the proximal (pouch) and distal esophagus (27). Likewise, abnormal esophageal motility patterns have been reported in children and adults with isolated TEF without atresia before surgical repair (43, 44) suggesting that abnormal development of the esophagus has consequences on the esophageal motility function.

Secondary Motility Disorder

The dysmotility may also be secondary to the dissection during surgery, which can damage the vagal nerve and its esophageal branches as shown by Davies in autopsied newborns with EA (40). Therefore, the operative dissection may also likely worsen the dysmotility.

TREATMENT

There is no controlled study on prokinetic drugs for treatment of esophageal dysmotility associated with EA. Since esophageal muscle and innervation are deficient and since the anastomotic zone is fibrotic, the efficacy of such drugs is unlikely to be significant especially in those patients with aperistalsis. However, in patients with remnants of distal peristalsis, one could expect some benefit with prokinetic medications, but objective data are lacking. Cisapride, a 5HT4 agonist, and bethanechol, a cholinergic agonist, are supposed to enhance esophageal motility. Cisapride has been reported to increase amplitude of esophageal peristalsis (45), but its availability is restricted due to risk of prolonged QT interval and severe cardiac arrhythmia. Bethanechol acts on muscarinic receptors of the smooth muscle and thereby increases esophageal contractions and clearance (46). However, cholinergic side effects (bronchial constriction) limit its use in asthmatics. Baclofen inhibits the transient LES relaxations (47) and can be used for treatment of GER. Its use may be limited due to side effects (dizziness). Metoclopramide, domperidone, and erythromycin act on gastric emptying (48).

Treatment of acidic GER by PPIs or H2-receptor antagonists is mandatory as well as careful screening and treatment of eosinophilic esophagitis (topical corticosteroids and allergen withdrawal), which are aggravating factors for the esophageal mucosa with significant impact on esophageal motility (49–51) and esophageal wall compliance.

UNANSWERED QUESTIONS

Even though esophageal dysmotility has been reported in infants, toddlers, children, adolescents, and adults, the natural history of esophageal dysmotility in patient with EA is unknown since no prospective longitudinal study has been conducted thus far. The implementation of such a study would be extremely difficult for ethical reasons given the invasiveness of the techniques used for assessing esophageal motility.

The introduction of high-resolution manometry coupled with esophageal impedance should lead to a better understanding of the relationship between esophageal dysmotility, bolus clearance, and symptoms as well as clinical outcome and especially long-term complications such as esophageal metaplasia, Barrett esophagus, and cancer. A new method, the pressure-flow analysis (PFA), to analyze and measure esophageal motility and its effects on bolus clearance has been recently made available (52). PFA, by quantifying the interactions between bolus transport and pressure generation, may help in further investigating these patients. Validation and application of this method in EA patients are warranted and ongoing.

Anomalies of sensory function have not been studied even though sensory innervation is as affected as the motor nerves in EA. One study using the acid perfusion test conducted in adult EA patients with erosive esophagitis reports an absence of sensation in 11 of 14 patients suggesting an impairment of the visceral esophageal sensitivity (11). Pharyngeal sensitivity and esophageal sensitivity play an important role in swallowing and feeding processes, as well as in the perception of symptoms.

Tissue engineering of injured or fibrotic esophagus could ultimately lead to recovery of normal esophageal motility. On the other hand, the attempts to generate engineered tissues must carefully take into account the importance of all components of the esophageal wall involved to generate a neo-esophagus with normal peristalsis and sphincter function.

SUMMARY

Esophageal dysmotility is almost universal after EA repair and is mainly related to the developmental anomaly of the esophagus. Esophageal dysmotility is involved in the pathophysiology of numerous symptoms and comorbidities associated with EA such as GER disease, aspiration and respiratory complications, and symptoms of dysphagia and feeding disorders. High-resolution esophageal manometry (HREM) has facilitated the characterization of the dysmotility, but there is an incomplete correlation between symptoms and manometrical patterns. Impedance coupled to HREM should help to predict the clinical outcome and therefore personalize patient management. Nowadays, the management of esophageal dysmotility in patients with EA is essentially based on treatment of associated inflammation related to peptic or eosinophilic esophagitis.

AUTHOR CONTRIBUTIONS

CF and FG wrote the draft. CF finalized the manuscript.

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REVIEW
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The Potential Benefits of Applying Recent Advances in Esophageal Motility Testing in Patients with Esophageal Atresia

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Infants and children with esophageal atresia commonly present with swallowing dysfunction or dysphagia. Dysphagia can lead to a range of significant consequences such as aspiration pneumonia, malnutrition, dehydration, and food impaction. To improve oral intake, the clinical diagnosis of dysphagia in patients with esophageal atresia should focus on both the pharynx and the esophagus. To characterize the complex interactions of bolus flow and motor function between mouth, pharynx, and esophagus, a detailed understanding of normal and abnormal deglutition is required through the use of adequate and objective assessment techniques. As clinical symptoms do not correlate well with conventional assessment methods of motor function such as radiology or manometry but do correlate with bolus flow, the current state-of-the-art diagnosis involves high-resolution manometry combined with impedance measurements to characterize the interplay between esophageal motor function and bolus clearance. Using a novel pressure flow analysis (PFA) method as an integrated analysis method of manometric and impedance measurements, differentiation of patients with impaired esophagogastric junction relaxation from patients with bolus outflow disorders is clinically relevant. In this, pressure flow matrix categorizing the quantitative PFA measures may be used to make rational therapeutic decisions in patients with esophageal atresia. Through more advanced diagnostics, improved understanding of pathophysiology may improve our patient care by directly targeting the failed biomechanics of both the pharynx and the esophagus.

Keywords: esophageal atresia, dysphagia, dysmotility, high-resolution manometry, pressure flow analysis

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INTRODUCTION

In EA, the resulting congenital malformation causes disruption to neural pathways and luminal continuity; further, the required esophageal repair via creation of surgical anastomosis may alter luminal compliance, and together, these factors lead to dysphagia and potentially life-threatening bolus hold up. Diagnostic investigations for esophageal dysphagia aim to describe esophageal anatomy and peristaltic function. Radiological upper gastrointestinal studies can visualize structural abnormalities in the esophagus, such as strictures; however, the motility of the esophagus that

arises through CNS and ENS mechanisms is best elucidated using high-resolution manometry (HRM), ideally combined with impedance topography.

CURRENT DIAGNOSTIC METHODS TO INVESTIGATE DYSPHAGIA IN EA

In EA patients, an esophageal anastomotic stricture index was proposed to diagnose esophageal strictures (1). Although esophageal function is often clinically assessed using radiological esophagram, manometry has been the diagnostic tool of choice to evaluate esophageal motor function. Through the innovation of HRM, the clinical applicability of esophageal manometry has been revolutionized by improved reliability of the equipment, increased resolution of sensors, the change from perfused to solid state measurements, and the decreased catheter diameter (2). For children with EA, the catheter technology has been suitably miniaturized improving procedural tolerance. HRM is worldwide accepted as a diagnostic tool that offers new perspectives to identify motility patterns through visualization of pressure patterns, as line tracings as well as pressure topography color plots (also known as "Clouse" plots) (**Figure 1**). Based on these plots, different patterns of motor function can be plotted, recognized, and categorized into a diagnostic algorithm called "the Chicago Classification" (CC), providing normative values and guidelines for evaluating esophageal motor function (3). The CC differentiates four categories of esophageal motor dysfunction: (1) disorders of esophago-gastric junction (EGJ) outflow obstruction (including achalasia); (2) major disorders of peristalsis (including distal esophageal spasm, jackhammer esophagus, and absent contractility); (3) minor disorders of peristalsis (including ineffective motility and fragmented peristalsis); and (4) normal motor function. When using the CC in pediatrics, adjustments for age and size cutoffs are needed as shorter esophageal length and smaller esophago-gastric function diameter influence the metrics (3). Therefore, the available diagnostic criteria need to be adjusted for age and size, specifically the integrated relaxation pressure (IRP4) reflecting deglutitive EGJ relaxation and distal latency (3). Although the CC appears to be applicable for use in the general pediatric population (4, 5), its use in EA as a specific patient subgroup requires further consideration. EA patients often show no motor patterns, and therefore bolus transport to, and through, the EGJ needs to be considered. The pattern of bolus transport and esophageal emptying into the stomach is important to elucidate.

In clinical practice, the interpretation of the HRM motor patterns alone does not easily elucidate aberrant bolus flow, which may lead to symptom generation. Therefore, the evaluation of pressure in relation to bolus flow as measured by manometry with impedance monitoring (a technique with a long-standing history of use in both adult and pediatric populations) has been suggested as a method to also assess esophageal function in children with EA. Combining these diagnostic tools allows assessment of the interplay between structural and functional capacity of the esophagus. Although manometry and impedance can be easily acquired simultaneously, the currently applied paradigm of independent analysis of both recordings has largely failed to bring the anticipated diagnostic gain and to determine a relation with clinical symptoms (6, 7). A lack of sensitivity of the used technologies

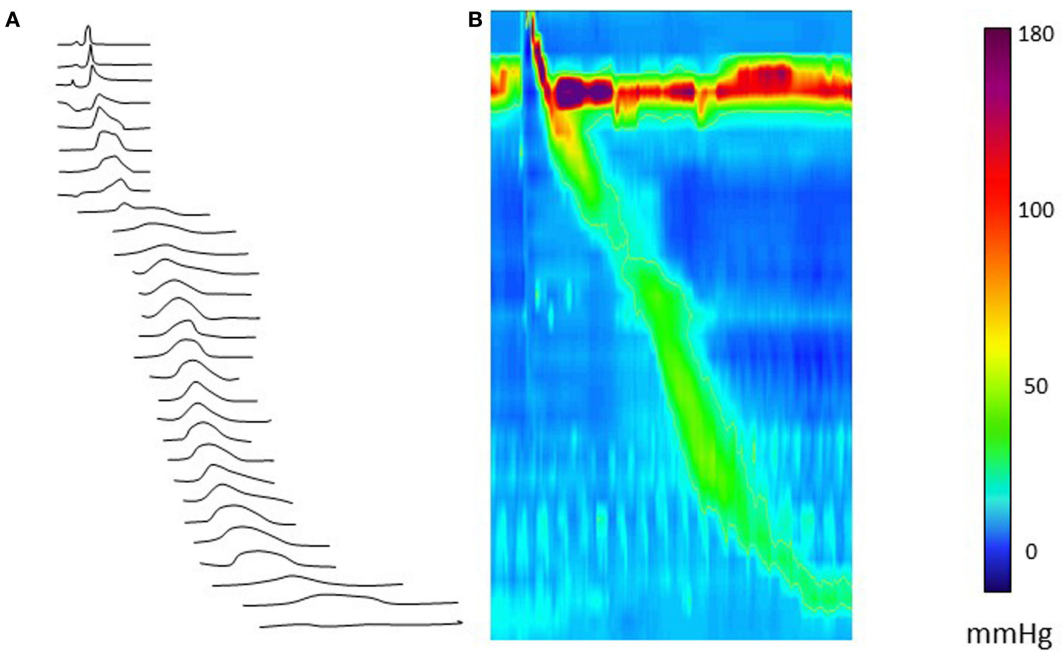

FIGURE 1 | Esophageal high-resolution manometry tracing of a normal liquid swallow, presented as a line plot **(A)** and as a color (Clouse) plot line plot **(B)**. The color panel shows the corresponding pressure values.

and/or the absence of an integrated analysis method of manometry and impedance recordings or the fact that normal clearance can also be achieved with abnormal motility patterns may be potential reasons (8). Given children with EA may undergo many radiological investigations over their lifetime, a non-radiological alternative for radiology requires investigation (9–11).

PRESSURE FLOW ANALYSIS (PFA) TO INVESTIGATE DYSPHAGIA

Over the last 5 years, the methodology for combined pressure-impedance analysis has developed to the point where it allows for objective, integrated analysis of simultaneously recorded esophageal motility (from pressure topography) and bolus flow (from impedance topography) (5, 12, 13). It is hoped that this method can provide additional physiological and pathophysiological insights because the impedance segments enhance the assessment of bolus flow and clearance/bolus residual. Further, when combined with pressure, impedance can be used to map the point of maximal luminal distension, pinpointing exactly where intrabolus distension pressure (IBP) should be optimally derived. Esophageal symptoms due to a motility disorder generally occur as a response to increased esophageal wall tension because of bolus retention and/or increased IBP, and our ability to directly measure these features therefore enhances the evaluation of esophageal symptoms. Hopefully, this can better guide the approach to diagnosis and management of esophageal disease through objective longitudinal measurements before and after medical/surgical intervention. These newer approaches of combining and analyzing pressure and impedance measurements are collectively called "pressure flow analysis." PFA was first validated for pharyngeal dysphagia in adults (14, 15) and subsequently has been applied for the evaluation of esophageal dysphagia (12).

A number of studies support the notion that the pressure flow approach can better detect flow resistance and esophageal stasis in patients with dysphagia (16, 17). More recently, new pressure flow measures have been found to reliably detect flow-permissive conditions that predict bolus emptying across the EGJ (18–20). Furthermore, while seemingly complex, derivation of pressure flow measures is relatively easy to apply using software that only requires

TABLE 1 | Pressure flow metrics.

Nadir impedance	NI	Ohms	Bolus presence
Peak pressure	PP	mmHg	Pressure recorded at maximum contractile tension
Impedance at peak pressure	IPP	Ohms	Bolus presence at time of maximum contractile tension
Impedance ratio: nadir impedance to impedance at peak pressure ratio	IR		Marker for incomplete bolus transit
Pressure at nadir impedance	PNI	mmHg	Intrabolus pressure (IBP) recorded when the esophageal lumen is maximally filled by the bolus
Intrabolus pressure	IBP	mmHg	IBP recorded during luminal emptying
Intrabolus pressure slope	IBP-slope	mmHg	Rate of change in IBP recorded during luminal emptying
Time from nadir impedance to peak pressure	TNIPP	s	Time interval from maximally full lumen to maximal contractile tension
Pressure flow index	PFI (IBP × distal IBP-slope)/(TNIPP) ratio		Relationship between peristaltic strength and flow resistance in the distal esophagus

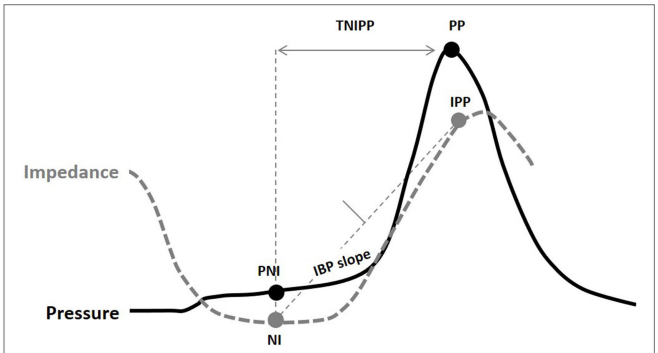

FIGURE 2 | Pressure flow analysis metrics indicated on a combined pressure (black) and impedance (gray) line plot [Omari et al. (24)]. Abbreviations stand for NI, nadir impedance; PP, peak pressure; IPP, impedance at peak pressure; PNI, pressure at nadir impedance; IBP-slope, intrabolus pressure slope; TNIPP, time from nadir impedance to peak pressure.

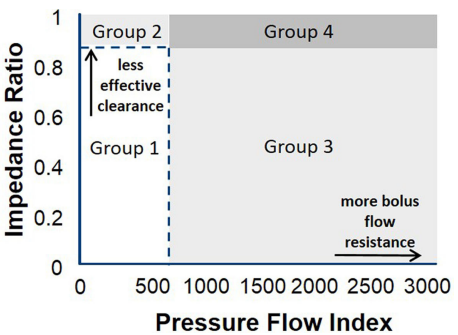

FIGURE 3 | Pressure flow matrix: this matrix visually presents the combination of pressure flow index (PFI) with the impedance ratio (IR), aiming to dichotomously separate outpatients with dysphagia who have predominantly abnormal bolus clearance and/or those with abnormal bolus resistance at the esophago-gastric junction (EGJ) (16). The pressure flow matrix shows on the vertical axis the bolus data of patients with normal and abnormal flow resistance and on the horizontal axis the bolus data of patients with normal and abnormal bolus clearance. Depending on the combined value of these two metrics, the predominant pressure flow pattern becomes clear. The matrix consists of four quadrants and indicate the following groups: Group 1: patients with normal effective transit and normal flow resistance across the EGJ; Group 2: ineffective transit and normal bolus flow resistance across the EGJ; Group 3: effective transit but increased bolus flow resistance across the EGJ; Group 4: ineffective transit and increased bolus flow resistance across the EGJ. It is expected that control subjects will have a low PFI and a low IR, and these are indicated by the dotted line. Patients with esophageal atresia are hypothesized to present in Groups 2 and 4, but further research is needed to consolidate this hypothesis (13).

the analyst to identify space-time landmarks on the pressure map of a swallow. Such software has been found to be reliable in the hands of analysts with differing levels of expertise (21).

Some of the key PFA metrics currently being evaluated are described in **Table 1** and illustrated in **Figure 2**. Some studies suggest utility for the evaluation of dysphagia (16, 17, 22).

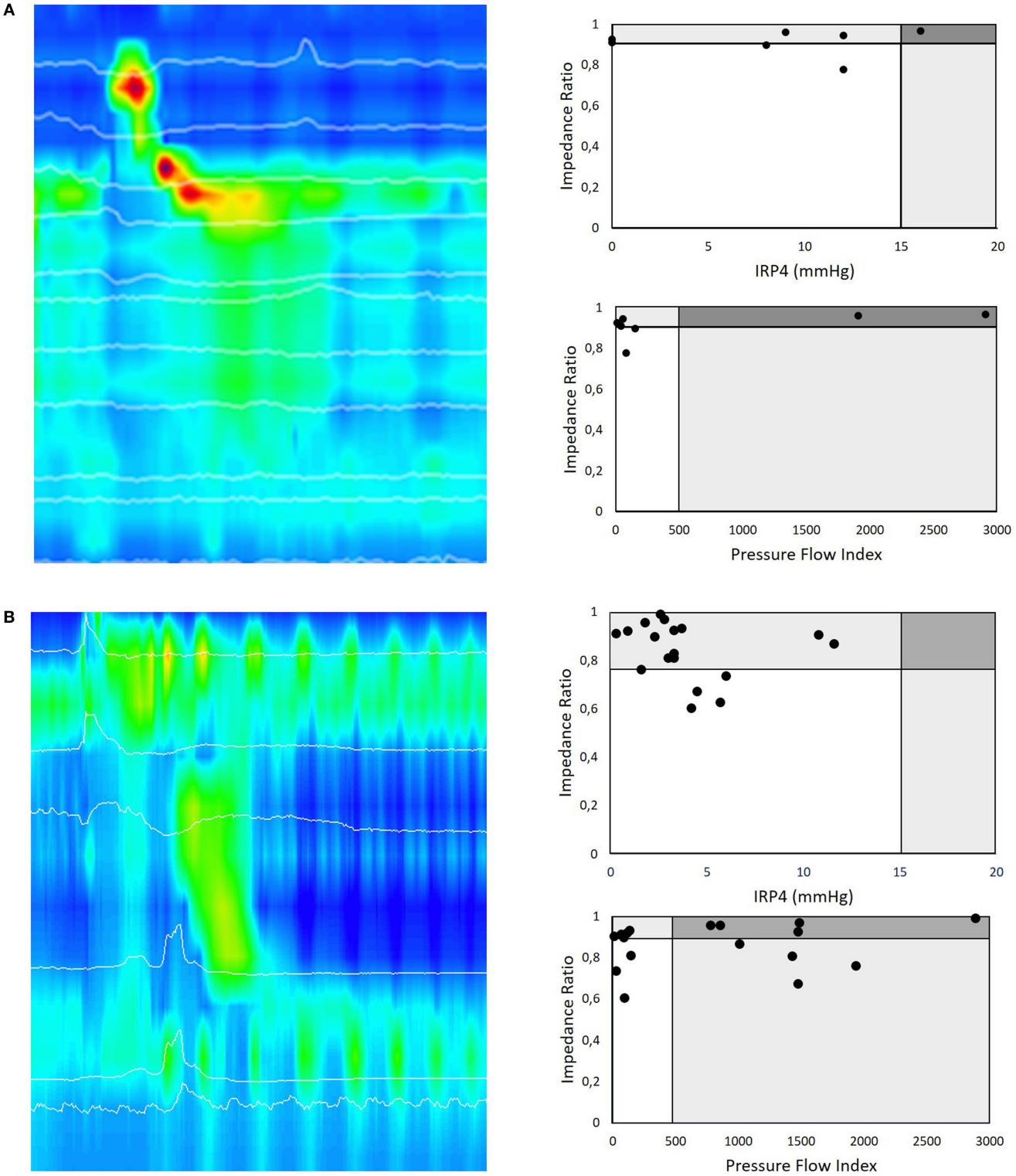

FIGURE 4 | Continued

FIGURE 4 | Continued
(A) HRMI color plot of a liquid swallow in a 16-month-old postoperative patient with Type C esophageal atresia. This girl underwent a primary anastomosis in the neonatal period and nine dilatations for esophageal strictures. Her main complaint was intermittent dysphagia on solids. All liquid swallows of this HRMI study of this patient are presented according to the pressure flow analysis (PFA) matrix paradigm. A first PFA matrix represents the impedance ratio (IR) versus the integrated relaxation pressure (IRP4), a manometric parameter to describe relaxation of the esophago-gastric junction (EGJ) during swallowing. This PFA matrix shows that many of the swallows look normal in terms of deglutitive relaxation as well as bolus clearance. The second PFA matrix of this patient shows the IR versus pressure flow index (PFI) for the same swallows. In this case, the PFA matrix confirms that the (for EA typical pattern) ineffective esophageal motility leads to ineffective esophageal bolus clearance. The EGJ deglutitive relaxation represented by the IRP4 is in most swallows normal and corresponds in this patient with low bolus flow resistance at EGJ as represented by the PFI. This HRMI study also revealed incomplete relaxation of the upper esophageal sphincter that corresponds with recurrent coughing episodes during the examination and her clinical symptoms of dysphagia. **(B)** Similar example of an HRMI color plot of a liquid swallow in a 2-month-old postoperative patient with Type A esophageal atresia. The first PFA matrix shows that many of the swallows have a normal deglutitive relaxation as well as bolus clearance. The second PFA matrix of this patient (IR versus PFI) shows that the PFI is increased in the majority of the swallows and thereby discloses that these swallows are abnormal in terms of bolus transit and clearance. This example illustrates that PFA allows a more differentiating diagnosis than high-resolution manometry assessment alone.

Further, a composite score based on three key variables, called the pressure flow index (PFI), has been derived. The PFI quantifies bolus pressurization relative to flow. A second global measure, called the impedance ratio (IR), quantifies bolus retention. A further extension of the PFA paradigm is to plot swallows on a "pressure flow matrix" (13, 16); this matrix visually depicts the PFI with the IR, allowing dichotomous separation of swallows associated with abnormal bolus clearance (vertical axis) and/or those associated with abnormal bolus flow resistance (horizontal axis) (16, 23).

An example of pressure flow matrix data is illustrated in **Figure 3**. Depending on the combined value of these two metrics across multiple repeat swallows, the predominant pressure flow pattern emerges. Typically healthy control subjects will have a low PFI and a low IR [i.e., will reside in the lower left-hand corner of the matrix (see **Figures 3** and **4**)]. The other three quadrants of the matrix indicate an abnormal pattern of (a) ineffective transit, (b) increased bolus flow resistance across the EGJ, or (c) ineffective transit and increased bolus flow resistance across the EGJ.

This matrix can be applied to patients with EA. In that case, it can be hypothesized that patients with EA will mainly be classified in Groups 2 and 4 due to the poor clearance capacity of the affected esophagus, but further research is ongoing to confirm this hypothesis and determine if information of this kind is relevant for management of, for example, esophageal anastomotic strictures or in relation to decisions to undertake anti-reflux surgery.

We illustrate this dichotomized PFA approach in clinical practice by presenting two cases (**Figure 4**). In the first case, we present a 16-month-old girl with Type C esophageal atresia with dysphagia for solids after multiple dilatation for strictures. EPT metrics indicate that the majority of the swallows showed abnormal esophageal peristalsis with complete EGJ function (IRP4 > 15 mmHg) (**Figure 4A**). In this case, PFA metrics confirm that in the majority of the swallows, the PFI was normal, suggesting no flow resistance during deglutition, as detected by HRM. The PFA matrix shows, however, a highly elevated IR and thereby confirms non-radiologically the inadequate bolus clearance secondary to abnormal contractility and which links in with the patient's clinical symptoms of dysphagia for solids.

The second example describes a 2-month-old postoperative boy with Type A esophageal atresia with dysphagia. Standard EPT metrics showed abnormal esophageal peristaltic integrity (ICD < 2 cm) and intermittent EGJ function (IRP4s = 3 mmHg) in the majority of the swallows (**Figure 4B**). However, PFA metrics demonstrated that in the majority of the swallows, the PFI was highly elevated, suggesting high flow resistance during deglutition, not detected by HRM as stand-alone technique. This highly elevated PFI may link to the abnormal bolus flow and thereby correspond with the patient's symptoms.

Relevance to the EA Population

In the first year of life, patients with esophageal atresia frequently present with respiratory problems (37%) and also with digestive problems (25). Many patients develop anastomotic stenosis (22–37%), recurrent fistula (4%), gastro-esophageal reflux requiring anti-reflux surgery (12%), or dysphagia (15–52%) (25–27). Throughout life, dysphagia is the most common symptom of patients with EA. Its incidence can vary depending on the definition (25, 26, 28, 29) but seems to be lower in young infants compared to that in children and adults (25–27). Dysphagia is defined as a swallowing disorder in the oral, pharyngeal, and/or esophageal phases of deglutition. Some patients display only mild symptoms and need to drink liquids to facilitate swallowing (30). Other children present with a wider spectrum of symptoms varying from hypersalivation, early satiety, gagging, vomiting, and food refusal (13).

Dysphagia can originate in the oral cavity, pharynx, and esophagus. Typically, patients with EA have normal oral motor function; however, it is important to recognize that oral aversion may be a sign of pharyngeal and/or esophageal dysphagia and is not necessarily directly (causally) linked to abnormal oral responsiveness or sensitivity. Pharyngeal dysphagia, in general, can relate to inadequate pharyngeal motor function and responsiveness, inadequate laryngeal closure, and/or inadequate relaxation and opening of the upper esophageal sphincter (UES). In children with EA, no systematic reports on pharyngeal or UES function are available.

A frequent cause of dysphagia in EA is inadequate motility of the esophagus. Severity is variable and is influenced by the presence of congenital esophageal stenosis and esophageal strictures. At the moment, the most commonly used clinical diagnostic tests to assess esophageal function are the radiological barium study and esophageal manometry. Both methods aim to evaluate the anatomy and motor function of the esophagus and EGJ

(6, 30). Dysphagia can be challenging as these traditional methods often fail to explain the clinical symptoms of dysphagia due to poor symptom correlation with the documented esophageal motor patterns. During the last 5 years, PFA became available, an automated analysis method that derives quantitative pressure flow metrics from simultaneously acquired impedance and manometry measurements (24). These pressure flow metrics elucidate the interplay between bolus flow, motor patterns, and symptomatology by combining data on bolus flow resistance and bolus transit. Symptoms of dysphagia and altered perception of bolus passage may indicate increased bolus flow resistance at the EGJ and ineffective esophageal propulsion.

CONCLUSION

The clinical diagnosis of dysphagia in patients with esophageal atresia should focus on both the pharynx and the esophagus. As clinical symptoms do not correlate well with conventional assessment methods of motor function such as radiology and manometry but do correlate with bolus flow, the current state-of-the-art diagnosis includes HRM combined with impedance measurements to characterize the interplay between bolus flow and esophageal motor function. Differentiation of patients with impaired EGJ relaxation from patients with bolus outflow disorders is clinically relevant and can be achieved using a novel PFAmethod, which is an integrated analysis method of manometric and impedance measurements; its pressure flow matrix is a useful tool for categorizing the quantitative PFA measures and may be used to make rational therapeutic decisions in patients with esophageal atresia. Through more advanced diagnostics, improved understanding of pathophysiology may improve our patient care by directly targeting the failed biomechanics.

AUTHOR CONTRIBUTIONS

Drafting of the manuscript: NR and TO. Critical revision of the manuscript for important intellectual content: NR, MR, CS, and TO. Administrative, technical, or material support: NR, MR, and CS.

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REVIEW
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Gastric Function in Children with Oesophageal Atresia and Tracheoesophageal Fistula

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Oesophageal atresia and tracheoesophageal fistula (OA–TOF) are a multifaceted condition which affects patients throughout their lives. Even though it is one of the most common gastrointestinal malformations, most of the current studies focus on gastro-oesophageal reflux disease, anastomotic strictures, and feeding difficulties. However, there is increasing evidence that a proportion of patients with OA–TOF also have abnormal gastric function. This review aims to provide a comprehensive understanding of studies of gastric function in patients with OA–TOF. The etiology of this abnormality has been hypothesized to be congenital and/or acquired. Several modalities are currently available for the investigation of gastric function, each of them trying to answer specific clinical questions. This review summarizes the studies that have looked at gastric function in the OA–TOF cohort with gastric emptying studies (gastric emptying scintigraphy and ^{13}C octanoic breath test), gastric manometry, electrogastrography, and oral glucose tolerance test. However, these modalities are limited due to poor age-specific normative values and heterogeneous methodologies used. The evaluation of symptoms in this cohort is crucial, modalities for abnormal gastric function are also described. With appropriate investigations and symptoms questionnaires, treatment strategies can be implemented to correct abnormal gastric function and thereby improve the outcomes and quality of life of patients with OA–TOF. This review highlights the need for large international multicentre collaborative studies and high-quality prospective randomized controlled trials to improve our understanding of gastric function in this cohort.

Keywords: oesophageal atresia/tracheo-oesophageal fistula, children and adolescents, gastric motility, gastric emptying, electrogastrography, octanoic breath test, dumping syndrome, prokinetic

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INTRODUCTION

Oesophageal atresia (OA) and tracheoesophageal fistula (TOF) are defined as an interruption of the continuity of the oesophageal lumen, which can be associated with or without the presence of a TOF. The abnormal communication can occur between the proximal and/or the distal oesophagus and the trachea. OA–TOF is known to be one of the most common malformations in the gastrointestinal tract. Regarding its incidence, OA–TOF has been reported in approximately 1 in 3,500 births (1).

Recently, there have been significant improvements in the care of patients with OA–TOF with the involvement of multidisciplinary teams including the surgeon, gastroenterologist, otorhinolaryngologist, pulmonologist, nutritionist, speech pathologist, and psychologist. This team approach to the care along with improvements in the initial neonatal management (intensive care, anesthesia, ventilatory, and nutritional support) in association with the primary surgical repair, has resulted in a significant reduction of the mortality with a current survival rate as high as 95% in centers with the best neonatal care (2). Most of the patients who do not survive the first months of life often have severe concomitant malformations. Despite this reduction in the mortality rate, children with OA–TOF can demonstrate a significant amount of long-term complications and suffer from lifelong morbidity due to complications, such as gastroesophageal reflux disease (GORD), oesophageal dysmotility, Barretts oesophagus, anastomotic strictures, and feeding difficulties.

The aim of the recent consensus guidelines on the management of gastrointestinal complications in these patients by NASPGHAN and ESPGHAN was to improve patient-related outcomes and the quality of life of patients by reducing the morbidity from gastrointestinal complications in this cohort (3).

While much is known about the abnormal oesophageal function and poor motility in OA–TOF patients (4, 5), little is known about gastric function in OA–TOF patients. It has been postulated that abnormalities in gastric function may contribute to high prevalence of gastrointestinal complications, such as GORD and feeding difficulties in this cohort. This review will discuss the etiology of abnormal gastric function, investigations of gastric function, symptoms that could be secondary to abnormal gastric functions, and finally potential treatment strategies for abnormal gastric function in this cohort.

PATHOPHYSIOLOGY

The normal gastric motor function is a complex sequence of events. All of them are controlled by an extrinsic nerve supply (brain and spinal cord), myenteric plexus within the wall of the stomach, and the result of local transmitters (amines and peptides), that modulate the excitability of the smooth muscle of the stomach.

Autonomic Nervous System

The parasympathetic pathway is transmitted to the stomach *via* the vagus nerves. Qi et al. (6) have described congenital abnormalities in the course and branching of the vagus nerves in a rat model with OA–TOF. The left vagus nerve consistently followed an abnormal path below the aortic arch, which could potentially increase the risk of damage to the vagus at time of initial repair of the OA–TOF. It has also been postulated that complications, such as postoperative infections, anastomotic strictures, leaks, and tension and ischemia at anastomotic site, could have a further adverse effect on the integrity of the vagi and thereby affect gastric function.

Enteric Nervous System

Focusing on the enteric nervous system, Nakazato et al. (7) documented an abnormal development of the myenteric plexus (Auerbach plexus) in the oesophagus as well as in the stomach in a small series of five patients. Most of the gastric biopsy specimens of patients showed significantly larger ganglia and thicker inter-ganglionic fibers than normal, and the network was also looser than normal. Interestingly, in an animal OA–TOF model, anomalies of the myenteric plexus of the oesophagus in OA–TOF rats were also reported by Qi et al. (8). They describe a reduction of the number of cell bodies within the ganglia and a decrease of the density of ganglia and nerve fibers. These abnormalities in the enteric nervous system could also have an adverse effect on gastric function.

Gastric Smooth Muscles

There are a paucity of studies investigating the role of the gastric smooth muscles contractility. Tugay et al. (9) reported physiologic changes of the smooth muscle of stomach in rat fetuses with OA–TOF in comparison with controls. This was investigated *via* both receptor-dependent (carbachol, serotonin, isoproterenol) and receptor-independent agonist (KCl, papaverine) mechanisms. The results showed an inadequate gastric muscular contraction in both mechanisms. However, this was an *in vitro* animal study which limits its extrapolation to *in vivo* gastric function.

In summary, there is limited evidence that congenital and acquired abnormalities of the autonomic nervous system (extrinsic), enteric nervous system (intrinsic), and potentially even the gastric smooth muscle could result in abnormal gastric function in OA–TOF patients. However, as a lot this evidence was either from animal studies or small case series, further corroboration needs to be done in larger cohorts' studies on patients with OA–TOF.

CLINICAL SYMPTOMS OF ABNORMAL GASTRIC FUNCTION

Most of the questionnaires currently available, such as the gastroparesis cardinal symptom index, which is itself a subset of the PAGI-SYM (patient assessment of upper gastrointestinal disorders-symptoms) are not validated in a pediatric population (10–12). No questionnaire exists for a proxy-report. To assess gastrointestinal symptoms in children, the Rome Foundation establishes questionnaires especially for gastrointestinal functional disorders (13). The PedsQL Gastrointestinal Symptoms Module was established and validated to use several scales to report the quality of life of children, such as symptoms scale, worry scale, medication scale, and communication scale (14). It can assess functional gastrointestinal disease or organic disease (15). The PedsQL currently has subsections which relate to gastric dysfunction. Questions on stomach pain and discomfort after eating, limitation of the child's ability to eat certain foods, early satiety, nausea, vomiting, sensation of "bloating," and abdominal distension, all give information on the presence of gastric dysfunction in the PedsQL. However, the difficulty in gastric dysfunction is that the symptoms are non-specific, and especially in

an OA–TOF patients, in whom GORD, eosinophilic oesophagitis, and oesophageal dysmotility may result in similar symptoms.

INVESTIGATIONS OF GASTRIC FUNCTION

Diagnosing abnormal gastric function in children, including those with OA–TOF, is challenging as several modalities are available, and each of them may provide a different physiologic answer.

Gastric function can be studied by evaluating gastric emptying (GE), gastric smooth muscle function, and gastric myoelectrical activity. GE can be assessed by scintigraphy or octanoic acid breath test. Gastric smooth muscle function can be studied by gastric manometry, and surface electrogastrography (EGG) can evaluate the gastric myoelectrical activity. We will also describe the oral glucose tolerance test (OGTT) that can be used to determine the presence of dumping syndrome.

GE—Gastric Emptying Scintigraphy (GES)

Gastric emptying scintigraphy is an objective physiologic non-invasive test that provides a quantitative measurement of the GE. Even though it represents a standard method to measure GE, GES has several limitations such as the standardization of the meals used and the duration of the imaging. In 2008, the Society of Nuclear Medicine, American Gastroenterological Association, and Neurogastroenterology and Motility Society (16) described in a consensus statement the standardized measurement of GE in adults, mainly based on the work of Tougas et al. (17). In this study, the recommended low-fat meal consists of white bread, egg-white, jam, and water, and they recommend that the images be taken at 0, 1, 2, and 4 h after its ingestion. In 2015, Wong et al. (18) retrospectively examined this protocol in a pediatric population. They documented the difficulty for some children to finish the standard meal and the importance of documenting anthropometric factors (lower weight, height, and body surface area) and age which could influence the results of the GES.

Jolley et al. (19) were the first to investigate GE in 25 children with repaired OA–TOF. Only 20 of the 25 had GES. The aim of the study was not only to evaluate GE but also to see whether there was an association between GORD diagnosed *via* pH monitoring and gastroesophageal scintiscan and delay GE documented in GES. GE was slower in OA–TOF patients who had documented GORD on gastroesophageal scintiscan ($p < 0.005$). The main limitation of this study is that they used a liquid meal to assess GE, and the analysis was limited to the GE at 30 min (17); also, no definition of delayed GE was given. Furthermore, gastroesophageal scintiscan is not recommended for routine evaluation of pediatric patients with suspected GORD (20). This study also showed that slow GE was present in a subset of patients with GORD, diagnosed via a reflux score which was determined by pH monitoring. However, a reflux score, rather than an acid reflux index, was correlated with GE. The only factor associated with higher incidence of significant GORD and slow GE was an excessive tension at the anastomotic site ($p < 0.005$), potentially due to a decrease of the intra-abdominal oesophageal length and alteration of the configuration of the gastroesophageal junction.

In addition to this study, for the first time, Montgomery et al. evaluated 11 OA–TOF patients (age 5–10 years, median 7.5 years) and 10 healthy controls with a GE using a solid meal and a symptom questionnaire (21). All the GE parameters measured, such as the half-emptying time, lag phase (time-point when 90% of the marker remained in the stomach), and corrected half-emptying time (half-emptying time minus the lag phase), were significantly prolonged in OA–TOF patients when compared to controls. Also, in OA–TOF patients, the retention values at 60 and 90 min were increased and the emptying rates (percentage of emptying per hour) were reduced in OA–TOF patients. Twenty-seven percent of OA–TOF children (3 over 11) had a delayed GE (e.g., retention values at 60 and 90 min above 2 SDs). Regarding their clinical findings, there was no statistical difference in the GE studies in patients with or without symptoms (abdominal complaints and reflux symptoms).

In summary, although GES can be used to assess GE, here is, however, a dearth of data on normal values in children due to its low but non-negligible radiation risk. There is also a lack of standardization of the type (liquid vs. solid and caloric content) of meals used and the duration of the study. None of the studies mentioned above on OA–TOF patients followed the protocol recommended by Abell et al. (16) and Tougas et al. (17).

GE—13 C Octanoic Acid Breath Test (OBT)

Due to the drawbacks associated with the scintigraphy methods (mentioned previously), alternative techniques of assessing GE have been recently developed. ^{13}C octanoic acid breath test OBT is a radiation-free method used to determine the GE rate of solid (22) and liquid meals in children or adults. This test assumes a normal absorption of the octanoic acid in the small bowel and normal lung function to determine the ratio of $^{13}CO_2/^{12}CO_2$ in exhaled breath. Three mains parameters are calculated: the GE half-time (GE $t1/2$), the lag phase (T lag), and the gastric emptying coefficient (GEC). Most of the studies have found a significant linear correlation with GE as determined by scintigraphy with respect to the GE half-time time and the lag phase (22–25). The GEC is specific for OBT.

Van Wijk et al. (26) were the first to combine multichannel intraluminal impedance–pH monitoring as a measure of GORD, oesophageal manometry as a measure of oesophageal motility and function, and GE *via* OBT as a measure of GE to evaluate the mechanisms underlying GORD in this cohort. They recruited 10 children and 10 adults with OA–TOF. Among them, seven infants and nine adult patients were assessed by an OBT with a liquid and solid meal, respectively. Delayed GE (>90th percentile of age-, meal-, and sex-appropriate normal values) was found in 57.1% of infants (four infants over seven) and 22.2% of adults (two adults over nine). When GE half-life was compared to oesophageal motility or bolus clearance, no associations were found ($R = -0.48$, $p = 0.32$ and $R = -0.56$, $p = 0.23$, respectively). However, the normal values used to assess the delayed GE were not available in the manuscript or referenced as published data. In addition, the choice of defining an abnormal GE half-life being above the 90th percentile may overrepresent the gastric dysfunction.

Gastric Smooth Muscle Function—Gastric Manometry

Conventional manometry and more recently high-resolution manometry have added a new method to assess gastric motility (27, 28). Conventional gastric manometry is not a commonly used method to study gastric motility, and high-resolution manometry needs further investigation to understand its role and compare its finding with other clinical tests. There has been only one study so far which used conventional manometry to study gastric function in OA–TOF patients. Eleven OA–TOF patients, aged from 13 to 23 years, were recruited by Romeo et al. to evaluate their gastric function *via* GES and gastric manometry (29). Like Montgomery et al., they used a solid meal to assess the GE, in contrast to Jolley et al. who chose a liquid meal. Delayed GE was defined as a t½ more than 90 min and was seen in 36% of the patients (4 over 11). Two of them were symptomatic of GORD, and two remaining patients were asymptomatic. All four presented with altered gastric motility at manometry. Also, 45% of patients demonstrated abnormal gastric peristaltic activity and antral hypo motility on manometric testing. This involved an increased duration of the third phase of the interdigestive cycle, reduction of the frequency and reduction of the amplitude of the peristaltic waves. However, like the previous studies, there was poor correlation between manometry results and symptoms, and abnormal gastric motility was also seen in 20% of asymptomatic patients. This work was the first to study gastric function in adult OA–TOF patients and showed that although gastric motility disorder can still be present in adulthood, it may not always be responsible for the GI symptoms. The authors felt that evaluation of gastric function may be useful in dyspeptic older OA–TOF patients.

Myoelectrical Activity—EGG

Electrogastrography is a non-invasive method for the measurement of gastric myoelectrical activity using cutaneous electrodes (30). There is increasing evidence of its validity since the 1990s. EGG chiefly provides information on myoelectrical rhythm and amplitude/power of the stomach. If the recording of the electrogastrogram follows an adequate preparation of the skin and electrode placement, it is an accurate measurement of gastric slow waves (31). There are currently no recommendations regarding a standard meal for EGG. However, the meal composition is important as solid, liquid, or containing a high percentage of fat may result in different postprandial EGG responses (32, 33). Established EGG parameters are derived from the spectral analysis, and used to classify the result of the EGG. The parameters looked at include dominant frequency (frequency appearing with peak power value of spectra), dominant power (the power observed at the dominant frequency), power ratio (ratio between the power in the postprandial period to the fasting period), percentage of normal gastric slow waves [the frequency of normal slow waves is between 2 and 4 cycles per minute (cpm)]. The EGG is described as bradygastria if the dominant frequency is less than 2 cpm and tachygastria if it is higher than 4 cpm and less than 9 cpm. Arrhythmia is defined if no dominant power is documented. Finally, bradygastria, tachygastria, or arrhythmia defines the presence of dysrhythmia. Although dysrhythmia can be found in healthy controls, normogastria (slow waves between 2 and 4 cpm) should represent more the 70% in healthy controls (34). Several studies described a variation in their normative values, increasing the difficulty to compare them.

Cheng et al. (35) were among the first to assess children with OA–TOF *via* EGG. Their study looked at 18 OA–TOF patients and 10 healthy controls, with a mean age of 2.3 years (2 weeks to 12 years) and 2.1 years (1 month to 10 years), respectively. First, the dominant frequency did not differ significantly between the two groups. Even though, the instability coefficient (SD divided by the mean value of frequency) is the best-established parameter to describe the variation of the regularity of the slow waves, the distribution of frequency was used in the study. OA–TOF patients had a significantly wider distribution of frequency than the controls. The authors postulated that this was secondary to either the gastric pacemaker cells not firing at a regular rhythm or due to abnormalities in intrinsic nerves which modulate smooth muscle cells resulting in poor electromechanical coupling and abnormal gastric contraction. Interestingly, none of the four patients with abnormal EGG (two patients with bradygastria and the two patients with tachygastria) were symptomatic. However, no validated questionnaire was used to determine the presence or absence of reflux symptoms.

Yagi et al. (36) evaluated the gastric function using EGG in 13 OA–TOF children, aged from 1 to 17 years old (mean 7.6 years), and compared them with five controls. EEG anomalies were only reported in OA–TOF, and they were present in 38% of them (5 over 13). Yagi et al. defined dysrhythmia when the SD of peak spectral frequencies was larger than 1.3. Even though this definition varies in the literature, it is significant that only OA–TOF patients (38.4%) in this study had dysrhythmia (two only in the postprandial period and three in the fasting and postprandial period). In addition, the power ratio of the controls was significantly higher than that of the OA–TOF patients (7.6 ± 9.0 vs. 2.6 ± 1.7, $p < 0.05$). The power ratio was also significantly lower in OA–TOF patients with dysrhythmia compared to those without and significantly lower even in OA–TOF patients without dysrhythmia compared to controls, which is suggestive of impaired gastric contractility in these patients. However, there was no statistical difference between the power ratio of OA–TOF patients with and without dysrhythmia. OA–TOF patients with dysrhythmias also had significantly higher mean spectral frequencies than patients without dysrhythmias in both fasting and postprandial states ($p < 0.05$). There were no differences in mean spectral frequencies between OA–TOF patients without dysrhythmia and controls, unlike the power ratio. However, currently, there is no data in the literature that describes the role of mean spectral frequencies in an EGG study. Most studies use the parameters described above. All five dysrhythmic patients were asymptomatic. A contrast study, which is neither specific nor sensitive for the diagnosis of GORD, was used to evaluate reflux in this study. Contrast study showed GORD in 3/5 (60%) of the dysrhythmic patients. The authors postulated that the dysrhythmia detected in the OA–TOF patients might be due to deficiency of intrinsic inhibitory innervation or a lack of extrinsic

autonomic inhibition, a theory supported by prior research by Nakazato et al. and Qi et al.

Gastric myoelectrical activity and gastroesophageal disease were also studied in infants with OA–TOF by Bokay et al. (37). Fifteen OA–TOF infants (mean age of 84 days) and 10 controls were investigated *via* EGG and 24 h oesophageal pH monitoring for the OA–TOF infants. A total of 73.3% of the OA–TOF patients had an abnormal pattern when compared to the controls (10%) during the fasting period. The authors used a cutoff of less than 60% of their percentage of normal slow waves (2–4 cpm) to define an abnormal EGG. In the postprandial phase, a significant increase in bradygastria and a decrease in tachycardia were observed in the OA–TOF cohort. No significant difference was found in the dominant power between the two groups, either before or after the meal. The authors postulated the dysrhythmia seen was due to the abnormalities in Auerbach plexus, leading to poor propagation of electrical potential which in turn results in uncoordinated smooth muscle contraction and peristalsis. They felt that the abnormal gastric electrical activity, during the fasting and/or postprandial period, may lead to uncoordinated contraction of the stomach. Among the 15 OA–TOF patients, 9 had pathological 24 h oesophageal pH monitoring values, and 6 had clinical reflux based on symptoms. When comparing the patients with or without GORD, there were no differences in the distribution of myoelectrical waves or the dominant power, either at rest or after the meal. No information regarding the power ratio was available in this study, making it difficult to compare these results with Yagi et al.'s study. Bokay et al. concluded that EGG is a useful non-invasive investigation to document disturbed neuromuscular function, even in infants, and further studies are required to understand the pathophysiology of feeding disturbances in this population.

To summarize, although EGG is an easy to perform, non-invasive tool to investigate myoelectrical activity, the lack of standardization of the EGG parameters described in the various studies, makes it is difficult to compare the studies. Also, in the literature, the test meal is poorly described. The different test meals in these three studies reflect this statement.

Dumping Syndrome—OGTT

Dumping Syndrome is thought to occur when a rapid transit of gastric contents reaches the small bowel; resulting in an early postprandial hyperglycemia, which then, leads to a profound insulin response producing a secondary late hypoglycemia. The symptoms can be non-specific and can present with malaise, lethargy, nausea, retching, failure to thrive, diaphoresis, tachycardia, and watery diarrhea. The gold standard for the diagnosis of dumping syndrome is OGTT. Serial blood sugar measurements are done during a 4-h period following a sugar load (1.75 g/kg, maximum 75 g) to detect early hyperglycemia or late hypoglycemia. The treatment of dumping syndrome is mainly by dietary modification by avoiding simple carbohydrates, supplementation with complex carbohydrates (corn starch, pectin), continuous gastric or transpyloric feeds. Some studies have also reported a benefit with Acarbose (38). Rarely octreotide, diazoxide, prednisolone, or even TPN is needed in severe cases. The increased risk of dumping syndrome in adults after oesophageal, gastric, or bariatric surgery is well established (39). Most the studies focus on post-fundoplication (antireflux surgery) dumping syndrome (40). Holschneider et al. (41) investigated the complications following fundoplication in children with a focus on OA–TOF. The incidence of postoperative dumping syndrome has been reported to be significantly higher (18.3%) in the OA–TOF cohort when compared to children without OA–TOF (1.6%). Michaud et al. (42) were the first group to report two cases of symptomatic OA–TOF children without previous fundoplication or associated microgastria who presented with dumping syndrome diagnosed with OGTT. They suggested that dumping syndrome should be considered in OA–TOF children who present with non-specific gastrointestinal symptoms that cannot be explained otherwise (e.g., anastomotic stenosis, gastroesophageal reflux, oesophageal dysmotility, etc.). Large multicentre prospective studies are required to determine the true incidence of dumping syndrome in OA–TOF patients. Although OGTT is the gold standard for the diagnosis of dumping syndrome, the role of complementary GES (showing accelerated GE) remains yet to be determined. In addition, normative values for OGTT have also not been firmly established, especially for all ages for the diagnosis of dumping syndrome. Given these findings, it is important that clinicians consider dumping syndrome in every child treated surgically for oesophageal atresia presenting with digestive symptoms, malaise, failure to thrive, or refusal to eat. Dumping syndrome is often underdiagnosed in this cohort because of the non-specific clinical symptoms and because the GI symptoms are often thought to be due to other more commonly occurring factors, such as strictures, GORD, and dysmotility.

Symptoms Questionnaires

Gastroesophageal reflux is often diagnosed based on non-specific symptoms, which is not ideal especially for the younger child. The NASPGHAN-ESPGHAN guideline for the diagnosis and treatment of GORD in children states that in infants and toddlers, there is no symptom or symptom complex that is diagnostic of GORD or predicts response to therapy (20). This is especially so in the OA–TOF patient in whom symptoms secondary to eosinophilic oesophagitis, anastomotic stricture, and dysmotility could mimic reflux disease. There is also a dearth of validated questionnaires to evaluate GORD in all age groups and to evaluate and diagnose abnormal gastric function vs. GORD. Hence, it is not surprising that none of the studies mentioned above which evaluated gastric function and its correlation with gastrointestinal symptoms used a validated symptom questionnaire.

Although the PedsQL currently has subsections which relate to gastric dysfunction, further studies are needed to establish more specific validated questionnaire for children and their parents regarding the symptoms related to gastric dysfunction. Significantly, none of the studies on GE, myoelectrical activity, and motility found a significant correlation between the abnormalities in gastric function and symptoms. This lack of correlation might well be due to not only the small sample sizes but also the lack of a validated symptom questionnaire for gastric function.

TREATMENT OF ABNORMALITIES IN GASTRIC FUNCTION

Role of Prokinetic

The studies investigating the use of prokinetic in OA–TOF patients are scarce. Most of them evaluate the benefits of prokinetics in OA–TOF patients with oesophageal dysmotility or GORD. No study so far has specifically looked at the role of a prokinetic on gastric function in OA–TOF patients. Ideally, the effectiveness of the prokinetic drug should be evaluated not only on pathophysiologic changes in EGG and GE but also on patient-related outcomes with validated symptom questionnaires. Prokinetic drugs can improve gastric motor function/emptying by accelerating rate of GE, and by their effect on gastric peristalsis.

Cisapride increases the motility of the upper gastrointestinal tract by acting directly as a serotonin 5-HT_4 agonist and indirectly as a parasympathomimetic. Its action on the serotonin receptors increases the release of acetylcholine in the enteric nervous system, improving the GE. Tegaserod has a similar mechanism by being a 5-HT_4 receptor agonist. However, both cisapride and tegaserod presented significant side effects, mainly cardiac, leading to a withdrawl of their use (43, 44).

Domperidone is a peripheral dopamine antagonist with affinity for D2-receptors that increases motility and GE (45). It works by antagonizing the effects of dopamine on the gastrointestinal tract, but has no cholinergic activity. It does this by inhibiting fundal relaxation, and by increasing amplitude and peristalsis of the gastric antrum and duodenum. Studies show mixed results regarding symptomatic improvements. Its efficacy was mainly investigated in diabetes gastroparesis, with reduction in nausea and vomiting. However, the trials were small and had methodological limitations (46). Domperidone has been shown to improve gastric dysrhythmia in diabetic gastroparesis (47, 48). Three aspects should be considered when prescribing domperidone. First, it has the propensity to increase the QT interval on electrocardiogram, potentially leading to arrhythmia. Therefore, baseline and follow-up electrocardiogram are recommended, and Domperidone should be discontinued in case of age-related prolonged corrected QT interval (49). Second, domperidone increases prolactin and can result in mild lactation. Third, it alters the function of the cytochrome P450 2D6, theoretically increasing the risk of drug interaction.

Erythromycin, in a sub-antimicrobial dose, has been used in gastroparesis. It mimics the effect of motilin in the proximal gastrointestinal tract, provoking migrating motor complexes and contractions in the antrum and duodenum *via* cholinergic actions (50, 51). Several studies have documented an accelerated GE both in healthy controls and with patients with gastroparesis (52, 53). However, the results were not consistent with some studies showing a poor response (54). Erythromycin also leads to downregulation of the motilin receptor, inducing a tachyphylaxis. Some studies documented a drop of the response after 4 weeks of treatment (55). As with domperidone, erythromycin interacts with other drugs metabolized by the cytochrome P450 3A4. Like Domperidone, it can also be associated with the development of prolonged corrected QT interval, which necessitates close monitoring during its use.

Role of Gastric Pacing

Gastric pacing, or gastric electrical stimulation, is a surgical treatment option. It has been evaluated in patients with refractory gastroparesis (56). After the placement of the electrodes into the muscle layer of the stomach, several modalities of stimulation are available, of which, high-frequency/low-energy stimulation with short pulse stimulation is the one most often described. There are currently no studies that have evaluated the effect of gastric pacing in the OA–TOF cohort. However, there might potentially be a role for gastric pacing in OA–TOF patients with significant feeding difficulties and vomiting not responding to conventional therapy who have documented abnormalities in GE and myoelectrical activity.

CONCLUSION

Due to the substantial reduction of mortality in patients with oesophageal atresia and TOF, the aim of clinicians looking after OA–TOF patients has shifted to improvements of patient-related outcomes and reduction of the morbidity of gastrointestinal disease affecting them. In the past, the literature has focused on GORD, oesophageal dysmotility, and feeding difficulties. However, the evidence that abnormalities in gastric function can contribute to symptoms such as vomiting, dyspepsia, and feeding difficulties is increasing. This review provides an overview of the pathophysiology of abnormal gastric function in this cohort, and the armamentarium of investigations available to gastroenterologists to diagnose abnormal gastric function. The standardization of the methods, especially the test meals and the establishment of rigorous standards, are mandatory to determine normal values for GE and EGG in children.

Even with limited literature currently available on this topic, this review highlights the importance of being aware of the risk of gastric dysfunction in oesophageal atresia and TOF patients. We have described the investigation of gastric function with objective tests, such as GES or OBT to evaluate GE, EGG to evaluate gastric myoelectrical activity, and OGTT to exclude dumping syndrome. Potential treatment modalities for these abnormalities in gastric function have also been described.

Although most of the studies described had small cohorts, they all showed abnormalities in GE and myoelectrical activity in a significant proportion of OA–TOF patients. However, none of the studies could conclusively show a significant correlation between the abnormalities in gastric function and symptoms, although that might well have been due to small sample sizes and lack of a specific validated symptom questionnaire.

FUTURE DIRECTIONS

Several countries have launched a national plan for rare diseases, thus, increasing the awareness of conditions, such as OA–TOF, such as NORD in the United States, or EURORDIS in Europe. Recently, members of the European and North American

Society of Pediatric Gastroenterology, Hepatology and Nutrition developed uniform consensus guidelines for the management of gastrointestinal complications in children with OA–TOF (3). This illustrates the need for collaborations in the field of rare diseases. To improve our understanding of gastric function in OA–TOF, multicentre collaborative prospective trials are needed. Only such large multicentre studies will help determine whether treating abnormalities in GE and myoelectrical activity improves GORD, dyspepsia and feeding difficulties in OA–TOF patients.

Patient-related outcome instruments, including the development of validated patient symptom, and parent-proxy questionnaires are essential in the development of treatment modalities, assuring therapeutics benefits to the patients.

AUTHOR CONTRIBUTIONS

GD reviewed the current literature, elaborated a plan for the review, and wrote the manuscript. UK provided additional help for the review and wrote and corrected the manuscript.

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REVIEW
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Anastomotic Strictures after Esophageal Atresia Repair: Incidence, Investigations, and Management, Including Treatment of Refractory and Recurrent Strictures

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Improved surgical techniques, as well as preoperative and postoperative care, have dramatically changed survival of children with esophageal atresia (EA) over the last decades. Nowadays, we are increasingly seeing EA patients experiencing significant short- and long-term gastrointestinal morbidities. Anastomotic stricture (AS) is the most common complication following operative repair. An esophageal stricture is defined as an intrinsic luminal narrowing in a clinically symptomatic patient, but no symptoms are sensitive or specific enough to diagnose an AS. This review aims to provide a comprehensive view of AS in EA children. Given the lack of evidence-based data, we critically analyzed significant studies on children and adults, including comments on benign strictures with other etiologies. Despite there is no consensus about the goal of the luminal diameter based on the patient's age, esophageal contrast study, and/or endoscopy are recommended to assess the degree of the narrowing. A high variability in incidence of ASs is reported in literature, depending on different definitions of AS and on a great number of pre-, intra-, and postoperative risk factor influencing the anastomosis outcome. The presence of a long gap between the two esophageal ends, with consequent anastomotic tension, is determinant for stricture formation and its response to treatment. The cornerstone of treatment is endoscopic dilation, whose primary aims are to achieve symptom relief, allow age-appropriate capacity for oral feeding, and reduce the risk of pulmonary aspiration. No clear advantage of either balloon or bougie dilator has been demonstrated; therefore, the choice is based on operator experience and comfort with the equipment. Retrospective evidences suggest that selective dilatations (performed only in symptomatic patients) results in significantly less number of dilatation sessions than routine dilations (performed to prevent symptoms) with equal long-term outcomes. The response to dilation treatment is variable, and some patients may experience recurrent and refractory ASs. Adjunctive treatments have been used, including local injection of steroids, topical application of mitomycin C, and esophageal stenting, but long-term

studies are needed to prove their efficacy and safety. Stricture resection or esophageal replacement with an interposition graft remains options for AS refractory to conservative treatments.

Keywords: esophageal atresia, anastomotic strictures, esophageal dilation, bougie dilators, balloon dilators, refractory and recurrent strictures, adjuvant treatments, esophageal stenting

INTRODUCTION

Since the original description of successful repair and primary anastomosis in 1943 (1) improved intensive care treatment, anesthetic techniques, and surgical techniques have dramatically raised survival rates in esophageal atresia (EA). Therefore, the long-term morbidity in children, adolescents, and adult EA patients has become a common challenge for clinicians (2). Anastomotic strictures (ASs) are still the main complication after repair of EA in neonates (3, 4). Despite the identification of multiple risk factors for ASs, such as long-gap EA with consequent anastomotic tension, postoperative anastomotic leak, and gastroesophageal reflux disease (GERD) (3, 5–11), prevention strategies with intraoperative techniques and/or postoperative treatments have failed to decrease the incidence of ASs over time (12). Traction and growth surgical techniques are considered a good system to induce esophageal growth and elongation, therefore facilitating anastomosis with less tension (13). The possible role of these procedures in preventing AS formation has to be clarified. Currently, the burden of ASs in the postoperative care of AE patients is still high and requires improvement of treatment strategies, especially for refractory and recurrent strictures.

The European Society for Pediatric Gastroenterology Hepatology and Nutrition (ESPGHAN) and the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN) recently published the first Guidelines for the evaluation and treatment of gastrointestinal and nutritional complications in children with EA, including indications for diagnosis and management of ASs (14). Nonetheless, prospective studies are still required to optimize strategies to prevent, investigate, and effectively manage patients with ASs after EA repair (12). This review evaluates the recent literature surrounding ASs, with particular focus on refractory and recurrent strictures. We analyzed and compared selected studies, based on existing theories, models, and experts' opinion. Given the lack of evidence-based data on AS in EA children, in order to provide a comprehensive view of the topic, we also critically discussed results coming from adult literature or from studies on esophageal strictures caused by different etiologies.

DEFINITION AND DIAGNOSIS

Anastomotic stricture is defined as a narrowing at the level of the esophageal anastomosis, detected by barium contrast study and/or endoscopy, and associated with significant functional impairment and symptoms (14). Gastrointestinal symptoms include feeding and swallowing difficulties, drooling, regurgitation and vomiting, foreign body impaction, and poor weight gain. Respiratory symptoms include cough, oxygen desaturation during feeding, aspiration, and recurrent respiratory infections (14).

Diagnostic techniques include esophageal contrast X-ray and endoscopy, with different advantages of the two techniques. Radiological images show the esophageal morphology and may detect associated anomalies (i.e., congenital esophageal stenosis) and pulmonary problems, while endoscopy allows combined diagnosis and treatment (14). Measurements are easier on the static radiologic images, while the endoscopic view may induce errors due to prospective effects; nonetheless, they can be minimized by shooting an instant view when endoscope lens is at a given distance (i.e., 2 cm) proximal to the identified AS (15). Simultaneous visualization of a probe with known diameter (guide wire or plastic tube) may help in measuring the degree of luminal narrowing.

There is no consensus about the fluoroscopy or endoscopy definitions for AS in pediatrics. The reduction of luminal diameter must be compared to an age-related normal esophagus (16). Said et al. proposed the stricture index, SI = $D-d/D$, where D is the esophageal diameter of lower pouch and d is the stricture diameter (17). Although the SI has already been used in some studies to assess the degree of ASs by radiographic (18) and endoscopic measurements (15), its clinical usefulness and impact must be confirmed in larger series. More recently, Sun et al. proposed the Esophageal Anastomotic Stricture Index (EASI), as a predictor of the development and severity of ASs after EA repair (19). The EASI was generated after fluoroscopic evaluation of the upper gastrointestinal tract in the early postoperative period (postoperative days 5–10). The equation is a ratio between the diameter of the stricture and the diameter of the upper (U-EASI) and lower (L-EASI) pouches: EASI = (lateral d/D + anteroposterior d/D)/2, where D is the esophageal diameter of upper or lower pouch and d is the stricture diameter. The average between anteroposterior and lateral diameters is considered. The result expresses the diameter of the anastomosis as a percentage of the diameter of the patient's normal esophagus. The authors conclude that EASI is a simple, reproducible tool to identify patients at risk of ASs, to guide the frequency of follow-up visits as well as the scheduling of contrast studies or upper endoscopy, to correlate the severity of strictures with the efficacy of various treatment methods, and to compare anastomotic techniques in patient registries (19). Further studies are needed to validate its usefulness and reproducibility.

The timing for the first screening or assessment of suspected AS is not universally accepted. It is true that most surgeons perform a baseline barium swallow about 5–10 days postoperatively to rule out the presence of an anastomotic leak, thus giving an early postoperative picture of esophageal lumen (19). Nevertheless, a varying degree of "physiological" stenosis can

be found on the first esophagram as a normal healing process from the surgical procedure, without relation to the development of a clinically relevant stricture (15). Early routine screening for ASs, starting 1 month after surgery, has been proposed (15). Recent guidelines, according with the majority of authors, recommend that AS should be excluded only in symptomatic children and those who are unable to achieve feeding milestones (14, 20).

Concerning clinical signs and symptoms, it is worth to underline that in EA children gastrointestinal and respiratory manifestations secondary to AS may overlap with other pathologic conditions, such as esophageal dysmotility, recurrent tracheoesophageal fistula, GERD, tracheomalacia, laryngeal clefts, and vocal cord dysfunction (12). Clinicians must be aware that these conditions may coexist and exacerbate AS symptoms. Moreover, the degree of esophageal narrowing does not correlate with symptoms. Therefore, patients with EA should be evaluated regularly by a multidisciplinary team to rule out the presence of other comorbidities (14).

Once an AS has established, the cornerstone of treatment is endoscopic dilation, whose primary aim is to achieve symptom relief (14). Unfortunately, some patients may experience symptoms persistency or recurrence despite multiple dilation sessions. A definition for both refractory and recurrent strictures has been proposed by Kochman et al. for adults, based on lumen diameter: refractory stricture refers to the inability to successfully remediate the anatomic problem to a diameter of 14 mm over five sessions at 2-week intervals, while recurrent stricture is the inability to maintain a satisfactory luminal diameter for 4 weeks once the target diameter of 14 mm has been achieved (21). A definition for pediatric patients has been proposed using the SI, with refractory stenosis defined as the persistence of SI > 10% after five dilation sessions, and recurrent stenosis in case of recurrence of symptoms or SI > 50% once that SI < 10% has been achieved (12). Expert opinion by the working group of ESPGHAN–NASPGHAN Guidelines for EA patients is that recurrent AS may be defined as ≥3 episodes of clinically relevant stricture (14). More recently, based on Kochman criteria, the ESPGHAN–ESGE Guidelines on diagnostic and therapeutic endoscopy in pediatrics suggests the following definitions: "inability to successfully remediate the anatomic problem to obtain age-appropriate feeding possibilities after a maximum of 5 dilation sessions with maximal 4-week intervals" for refractory stricture; "inability to maintain a satisfactory luminal diameter for 4 weeks once the age-appropriate feeding diameter has been achieved" for recurrent stricture (20).

Refractory and recurrent ASs are a major challenge in the postoperative management of AE patients, and a better understanding of risk factors is essential for prevention strategies, as well as the improvement of therapeutic approaches.

INCIDENCE AND RISK FACTORS

The normal process of wound healing after creation of the esophageal anastomosis involves tissue remodeling and wound contraction, promoted by fibroblasts. Wound contraction in the setting of a circular end-to-end anastomosis creates narrowing. Therefore, it is quite natural to see a degree of narrowing at the site of the esophageal anastomosis after EA repair (22).

Reported incidence of AS after AE repair ranges from 32 to 59% in the majority of recent studies (3, 4, 7, 9, 23–25), but also lower and higher incidence has been reported, up to 5% (26) and 80% (27), respectively. This variability relies in different definitions of AS and in a great number of pre-, intra-, and postoperative risk factor influencing the anastomosis outcome. These risk factors may affect stricture formation as well as its response to treatment, leading to recurrent and refractory ASs.

Preoperative Risk Factors

Gestational age, AE type and associated malformations, and length of the gap have been proposed as preoperative risk factors.

A relationship between stricture formation and prematurity or low birth weight, as well as VACTERL association, has been reported in retrospective cohorts (7, 8), but not confirmed in other series (5). The stricture rate seems to be unaffected by sex and intrauterine growth retardation (7). The role of tracheomalacia is controversial, since some authors reported its association with anastomotic complications (5), while others did not (7).

The type of EA may affect the incidence of AS, due to the different length of upper and lower esophagus, which are manipulated and mobilized during surgery (28). Indeed, vascular compromise affects especially the lower esophagus, which has a segmental blood supply from the aorta or the intercostal blood vessels. Mobilization of the lower esophagus may risk devascularization, ischemia at the esophageal ends, and stricture formation. Conversely, mobilization of the upper esophagus can be performed without vascular compromise, as this segment has a good blood supply coming from the inferior thyroid artery (28).

Long-gap EA is considered a significant predictive factor for developing early and late ASs, defined as strictures occurring less or more than 1 year after surgery, respectively (3). However, it is worth to point out that there is no univocal definition of long gap. It can be measured in centimeters or vertebral bodies. Some authors define 2 or 3 or 3.5 cm as a cutoff point; others classify the gap into short (1 cm), intermediate (2.5–3 cm), and long (>3 cm); others recommend an esophageal replacement if the gap exceeds the length of six vertebral bodies (13).

Intraoperative Risk Factors

Intraoperative risk factors for ASs include tension of the anastomosis, degree of ischemia, and type of suture.

The surgical attitude toward AE repair has changed over the last decades, with an increased rate of early primary esophageal repair and a respective reduction of delayed primary repair and esophageal replacement (29). This changing may be attributed to several factors: improved neonatal care allows children to be in a better condition to survive early definitive surgery; moreover, increased understanding and specialized training of neonatal surgeons has made primary esophageal reconstruction achievable in most long-gap patients (13). A direct consequence of primary anastomosis in long-gap AE is anastomotic tension, which in turn contributes to AS, as widely reported in retrospective

analysis (5–11). Nonetheless, with meticulous handling of the esophageal ends, preservation of the blood supply, and care to include the mucosa in each and every suture of the anastomosis, strictures can be kept to a minimum (24). Surgical techniques of esophageal lengthening, which have been used to achieve a primary anastomosis, may facilitate the reduction of anastomotic tension (13). The Kimura advancement technique may be applied only to the upper esophageal pouch and consists on multistage extra thoracic esophageal elongation of the proximal esophagus by moving the cutaneous stoma progressively further down the anterior chest wall (13, 30). Foker technique involves extensive mobilization of both upper and lower pouches and the placement of sutures in both segments, which are brought out to the skin surface and progressively pulled in the following days until a primary repair is possible (13, 30–32). Further prospective studies are required to investigate the possible protective role of these techniques against AS development.

The type of suture may influence AS formation (28): ASs have been reported to be less frequent when absorbable sutures are used for the initial repair, although this was not confirmed in experimental studies; interrupted sutures are used to potentially reduce the risk of stricture; two-layered or the Haight anastomosis and end-to-side anastomosis are associated with an increased incidence of stricture.

Incidence of ASs seems not to be influenced by thoracoscopic approach versus thoracotomy (33–36).

Postoperative Risk Factors

Anastomotic strictures' formation is influenced by postoperative risk factors, including anastomotic leak and GER. Anastomotic leakage is reported to be more frequent in long-gap AE (8) and to predispose to AS (10, 11). The role of GERD has been diffusely investigated. Mobilization of the distal esophagus and superior displacement of the esophagogastric junction promote GERD (9) and the exposure of the anastomotic area to acid secretions may enhance the reparative response and facilitate stricture formation as well as recurrence or resistance to treatment. Retrospective series reported an increased incidence of ASs in children with GERD (3, 4). AS is reported as a possible complication also in the 8–15% of adult AE patients; as these strictures most likely arise as a result of prolonged acidic reflux, the far-reaching significance of GERD in these adult patients is further underlined (37). However, a multivariate analysis showed the absence of an association between GERD and subsequent stricture formation, probably due to the prescription of a systematic proton pump inhibitor (PPI) (7). An extensive description of GERD diagnosis and management has been reported in the cited ESPGHAN–NASPGHAN Guidelines, including medical and surgical treatment (14). Even if evidence of the beneficial role of prophylactic PPI therapy is lacking in retrospective studies (38), the panels suggest a systematic routine treatment with PPI for 1 year after surgical correction, also in asymptomatic patients. It will be interesting to investigate whether this routine practice will decrease the stricture formation in the future (9).

Duration of intubations after AE repair was associated with increased risk of AS in some patients (8), but not in other cases (7).

TREATMENT

Management of ASs implies a multistep and multidisciplinary approach. Endoscopic dilations are the mainstream of the conservative approach and may benefit from other adjuvant strategies for refractory and recurrent ASs (14, 20). Treatment of comorbidities is essential for the global care of each patient. Surgical approach must be reserved to extremely selected patients (39, 40).

Esophageal Dilation

By exerting expansible forces within the lumen of the stenosis, dilations result in an increased esophageal diameter. Since the first pediatric description approximately 30 years ago (41), esophageal dilation has become the recommended first-line treatment for AS following EA repair (14).

The primary goal of esophageal dilation is to achieve symptom relief, permit maintenance of age-appropriate oral nutrition, and reduce the risk of pulmonary aspiration.

Two main categories of dilators are used in gastrointestinal endoscopy: fixed-diameter push-type dilators (bougie dilators) and radial expanding balloon dilators (42).

Bougie Dilators

Several bougies, varying on designs, calibers, and lengths, are available, but they may be further subdivided into two main categories: weighted (tungsten-filled) or wire-guided bougies.

Flexible tungsten-filled bougies do not accommodate a guidewire and are generally passed blindly without fluoroscopic assistance. Patients may be instructed to use for self-dilation at home. Hurst (Milwaukee, WI, USA) and Maloney dilators (Milwaukee, WI, USA) are the most commonly used non-wire-guided bougies and differ by their tips. The former has a rounded blunt tip, whereas Maloney dilators have an elongated tapered tip. The blind passage of non-wire-guided bougies may lead to a higher risk of perforation and to the incorrect passage of a dilator into the trachea (42, 43).

Wire-guided dilation provides assurance that the dilator is following the line of the esophageal lumen, so they are generally preferred (44).

The most popular guidewire-assisted mechanical bougies are the polyvinyl Savary–Gilliard dilators (Cook Medical, Bloomington, MN, USA). They have a long-tapered tip and a radiopaque band at the beginning of the widest portion of the dilator to allow fluoroscopic guidance. After the tip of the guidewire is endoscopically placed across the stricture, the endoscope is withdrawn, and dilator is passed over the wire. All steps may be monitored with fluoroscopic aid, especially if the endoscope does not traverse the stricture (42).

Fixed-diameter bougie dilators exert radial forces and also cause a shearing effect that generates longitudinal forces as they are passed across the stenosis. The dilation is achieved by using gradually increasing dilator diameters. The selection of the initial size of dilator is based on an estimation of the stenosis diameter. Dilation is considered to have been performed when there is a moderate or significant amount of resistance. Contrarily to balloon dilation, bougie dilation is a tactile technique, meaning that the operator may feel the amount of resistance encountered with

passage through the esophagus and apply the correct force to overcome the stenotic area.

Although there are no definite evidences, it is generally accepted that the risk of perforation could be minimized if the "rule of three" is applied, meaning that, after moderate resistance is encountered, no more than three dilators of progressively increasing diameter should be passed in a single session (20, 45). However, especially in pediatrics, operator experience plays a pivotal role in the choice of the optimal dilator size. Endoscopic assessment of the tissue damage is advised after each dilation, to guide decision-making (40). Bougies are more cost-effective than balloon dilators because they are reusable.

Balloon Dilators

Balloon dilators only exert radial forces when expanded within a stenosis. In contrast to what occurs with bougies, if the balloon is longer than the stricture, the force is delivered simultaneously over the entire length of the stenotic segment rather than progressively from its proximal to its distal extent (42).

Balloon dilators designed for single use only are available in an array of designs, lengths, and calibers. Dilations can be performed under endoscopic guidance with or without fluoroscopy in the operating room or under fluoroscopic guidance in the radiology suite. Through-the-scope (TTS) balloon dilators (Boston Scientific, Marlborough, MA, USA) are currently by far the most frequently used. They are designed to pass with or without guidewire. TTS balloon dilators are passed through the endoscope working channel, which enables the procedure to be performed under direct vision. The balloon is placed across the stenosis and expanded with water or contrast by using a handheld inflation device. The hydraulic pressure can be monitored manometrically. Newer TTS are designed to produce three distinct diameters at three separate pressures during *in vivo* dilation. Despite there are no data on the optimal time the balloon should remain inflated, in practice the inflation pressure is maintained for approximately 30–60 s or until there is a sudden drop in manometric pressure. If fluoroscopy is used, successful dilation is detected by the obliteration of the "waist" on the balloon, representing the stricture. A drawback for TTS balloons is that they require a 2.8-mm working channel and then they are not compatible with small-caliber pediatric endoscopes. In younger children, the balloon can be positioned over a guidewire under fluoroscopic guidance.

The serial incremental size of TTS balloon dilators per single session can follow the "rule of 3," as described earlier for bougie dilators (20).

Bougie versus Balloon Dilators: Outcome and Comparative Data

Despite advances in endoscopic equipment and dilators have improved the safety of esophageal dilation, the procedure may lead to complications even in the most experienced hands. The most frequently reported complications of esophageal dilation include perforation, hemorrhage, and bacteremia. In adults, the overall perforation rates vary between 0.1 and 0.4% (44, 46).

Long-term outcomes are influenced by the underlying condition; stricture diameter and length are established factors that influence the number of dilations required for symptom relief and the need for additional dilations (47). Children with long-gap EA and postoperative anastomotic leak are more prone to develop more severe AS.

A systematic review, including 5 studies (17, 48–51), has looked at the outcomes of balloon dilation (fluoroscopic and/or endoscopic) in children with EA (139 children with a total of 401 balloon dilation sessions), reporting a success rate ranging from 70 to 100%, with approximately 3 dilation sessions per child and a perforation rate of 1.8% (52). Alshammari et al. analyzed a series of 49 children who underwent esophageal balloon dilation for different etiologies; among 24 EA children they reported a median of 2 dilatations per patient, with a perforation rate of 8% (2 patients) (53). In a study aimed to retrospectively evaluate efficacy and complications of esophageal dilatations with Savary–Gilliard bougies in 23 children with EA, dilation was successful in 87% of patients, stricture resolution occurred after a mean of 3.2 dilatations per patient, and no complications were observed during or after the dilatation sessions (7). Moreover, in a large study, 107 children with benign esophageal strictures underwent Savary–Gilliard bougie dilations, the procedure was successful in 104 patients (93.7%), and perforations occurred in 6 cases during 648 dilation sessions (0.9%). In this study, only 12 children had AS secondary to EA, while most patients had caustic strictures (54).

Two retrospective studies involving EA children compared the two techniques. Lang et al. reported that children with EA who had undergone balloon dilation (16 patients) required fewer procedures than the bougie group (12 patients) (2.0 versus 8.5, respectively), while perforations (2 cases) occurred only after balloon dilation (52). Jayakrishnan and Wilkinson reported that fluoroscopic balloon dilatation (125 procedures) had fewer perforations than surgical bouginage (88 procedures) (1.6 versus 5.7%, respectively) in 37 children with esophageal strictures (24 with EA) (55).

Currently, there are no randomized controlled trials comparing efficacy and safety of hydrostatic balloon with bougie dilator for treatment of AS in EA children. Data coming from controlled trials in adults found no significant differences between bougie and balloon dilators in terms of efficacy and safety while treating benign esophageal strictures (46, 56).

Therefore, due to the lack of strong evidences, the choice between balloon dilation and bougie is only based on the endoscopist's experience and level of comfort. Indeed, more than the technique itself, a trained operator is required to reduce complications following esophageal dilations. Based on experts' opinion, ESPGHAN–NASPGHAN Guidelines for children with EA only recommend the use of guide wire-guided dilators (bougie or balloon) (14).

Timing of Dilations: Prophylactic versus Selective Dilatations

Definitely, the degree and duration of the effect of dilation, as well as and the need for repeating the procedure, are dependent on the length and diameter of stenosis, which are in turn linked to the baseline and underlying condition, such as long-gap AE and the presence of severe GERD.

However, there is currently no definitive evidence to support the ideal interval between the dilatation sessions. Based on single institutional experience, various "philosophies" have been adopted in clinical practice, but two main approaches exist: (1) prophylactic routine dilation/calibration to prevent symptoms developing (51) and (2) selective dilatations only when the symptoms arise (7). The rationale of the first approach, performing dilations systematically even in the absence of symptoms, is to ascertain an adequate caliber of the esophagus in all patients and thus avoid complicated strictures and long-term functional problems. The purpose of the second approach, "wait and see," is to reduce the number of invasive procedures and thus the risk of dilation-related complications. In 2009, Koivusalo et al. retrospectively compared the effect of the two approaches and concluded that the policy of selective dilatations resulted in significantly less dilatations than routine dilation with equal long-term outcomes in terms of dysphagia, nutritional status, and respiratory symptoms (57).

Recent ESPGHAN–NASPGHAN recommendations state that there is no evidence supporting the use of the more invasive strategy of routine dilations; therefore, the presence of AS should be excluded and treated only in symptomatic children (14). However, a close follow-up should be undertaken during the first 2 years of life, with special attention to weaning phase. Patients with long-gap EA and postoperative anastomotic leak need a close follow-up to avoid development of a severe AS.

Refractory and Recurrent Strictures: Adjuvant Treatments

Despite dilation treatment, some patients may experience symptoms relapse or persistency. The cause of recurrent and refractory AS is not fully understood. As previously discussed, numerous baseline conditions, as well as intra- and postoperative risk factors, concur to the stricture outcome. The dilation procedure itself may be partially responsible, because of intense fibrogenesis during healing process after the dilation procedure. Iterative dilations increase the risk of complications and may cause psychological problems in children. Nevertheless, once a stricture becomes refractory to esophageal dilation, conservative approach is preferable before the patient is candidate to surgery (39). Despite the absence of specific controlled trials, different non-surgical adjuvant treatments can be used in clinical practice for refractory and recurrent esophageal AS.

Intralesional Steroid Injection

Intralesional corticosteroid injection as an adjunct to dilatation has been proposed to prevent stricture recurrence approximately 50 years ago (58). However, in the last two decades, there has been a growing interest in the use of this therapy for refractory benign esophageal strictures of various etiologies (59).

Despite this long experience, the real mechanism of action of this treatment remains poorly understood. It is believed that steroid injection may reduce collagen synthesis, fibrosis, and chronic scarring processes, by inhibiting the transcription of certain matrix protein genes (59).

The most used steroid for intralesional injection is triamcinolone acetate or acetonide; betamethasone and dexamethasone preparations have been also used (59).

Triamcinolone acetate (dose 10 or 40 mg/mL; volume per injection ranging from 0.5 to 2.8 mL) is usually injected with a standard sclerotherapy needle in four quadrants of the esophagus at the upper border of the stricture before dilatation (59–61).

Two small-sized randomized trials in adult with recalcitrant esophageal stricture showed that local steroid injections resulted in a decreased need for multiple dilations and a longer average time to repeat dilation. In these series, all but 4 patients (from the Altintas' study) who underwent steroid injection of the stricture had peptic injury (25 patients in total) (61, 62). The efficacy of steroid injection as adjunctive treatment remains unclear in other types of benign strictures (63). Apart from encouraging results reported in uncontrolled studies (59), well-designed studies showed mixed findings. Hirdes et al., in a multicenter double-blind placebo-controlled trial, failed to find any statistical significance in patients with benign esophagogastric ASs (64). Later, Pereira-Lima et al., in a double-blind randomized trial, reported a significant improvement or resolution of dysphagia with complex esophagogastric anastomotic treatment-naive strictures (65). Camargo et al. found no difference in dilation frequency or recurrent dysphagia in patients with caustic strictures treated by steroid injection or placebo (66). Conversely, Nijhawan et al., treating 11 patients with refractory corrosive esophageal strictures, showed a significantly improved periodic dilation index (number of dilatations per month) and dysphagia score from pre- to postintervention period (67).

Concerning AS in EA children, Gandhi et al. described 12 patients, among which 5 were EA survivor, how received intralesional steroid injections combined with dilations reporting a long-term remission of symptoms (68). Holder et al. and Zein et al. also reported good outcomes in three and one EA children, respectively (69, 70). Even though other centers probably use intralesional steroid injection in clinical practice (15, 22, 71), evidences in EA children are lacking.

Potential complications of esophageal injections of steroid injection include adrenal suppression, perforation, intramural infection, candida infection, mediastinitis, and pleural effusion (71).

Concluding, since studies exploring efficacy and safety of intralesional steroid treatment are small, uncontrolled, and heterogeneous, it is difficult to draw definitive conclusions regarding the benefit of intralesional steroids in reducing recurrent stricture formation in EA patients (14, 71). The ESGE–ESPGHAN Guidelines for pediatric gastrointestinal endoscopy do not support the routine use of intralesional steroids for refractory esophageal stenosis in children (20).

Systemic Steroid Therapy

The use of systemic steroids associated with endoscopic dilation has been reported only in anecdotal cases. Hishiki et al. described the case of a boy with EA, who developed refractory AS and underwent surgical resection of the stenotic lesion with reanastomosis. A secondary AS was again impossible to treat with dilations, but ultimately resolved after two short courses of intravenous dexamethasone (1 mg/kg) (72). Morikawa et al. reported the use of high-dose methylprednisolone in a patient with refractory AS who was a candidate for surgical intervention.

A scheme with gradual tapering (daily 25, 15, 10, 5, and 2 mg/kg for 4 days each) was administered intravenously after balloon dilation with intralesional steroid injection and followed buy oral prednisolone (daily 2, 1, and 0.5 mg/kg for 1 week each). This treatment finally resolved the AS (73).

Evidence is currently lacking to suggest systemic steroids in AS (14).

Mitomycin C (MMC)

Mitomycin C is a natural antitumor antibiotic isolated from the broth of *Streptomyces caespitosus*. MMC can be administered intravenously, to treat upper gastrointestinal cancers (e.g., esophageal and gastric carcinoma), pancreatic adenocarcinoma, and other types of solid cancer. It may also be administered also topically, to treat bladder and intraperitoneal tumors.

In addition to its antineoplastic properties, it has been shown that MMC may inhibit wound healing by downregulating the gene expression for extracellular matrix proteins and then it acts as an antiproliferative agent by decreasing collagen synthesis and scar formation (74). Over the past years, MMC has gained wide acceptance as adjunctive treatment in the field of ophthalmology for reduction of scar formation in glaucoma filtration or pterygium surgery (75). In a study on human Tenon's capsule tissue, MMC caused almost complete inhibition of fibroblast proliferation. Nonetheless, several factors may influence its efficacy. These factors include the dose delivered to the tissues (which is concentration dependent), volume, duration of exposure, preparation method, administration, and tissue-related factors (76). Following these observations, the use of MMC was extended to the treatment of laryngeal and tracheal stenosis (77) and then esophageal stricture (78).

The delivery method of MMC is an important aspect to be considered; in fact, the application should be targeted precisely to the stenotic segment, while potentially dangerous exposure to the surrounding healthy mucosa should be avoided. Different application techniques have been described, the most frequent was local application *via* a cotton pledget soaked in MMC solution under direct endoscopic visualization (79). Several techniques to protect the mucosa from contact with the pledget have been reported, such as the use of an overtube or a sheath, and frontloading of the pledget in a standard cap used for band variceal ligation. The use of a drug-eluting microporous polytetrafluoroethylene catheter balloon positioned across the stricture under fluoroscopic guidance was also described (80). Spraying onto the stricture is another possible technique (81). A further alternative, previously reported only in adult studies, involves injection of MMC directly into each quadrant of the stenosis after dilation (82, 83).

Mitomycin C was mostly reported to be freshly prepared immediately before the application. A recent systematic review showed that concentrations of MMC ranged from 0.1 to 2 mg/mL (median and mean values of 0.4 and 0.5 mg/mL, respectively). The number of MMC applications varied between 1 and 12 with a mean of 2 and 2.6 in pediatric and adult patients, respectively, although the majority [67 children (79%) and 24 adults (63%)] required only 1 to 2 applications. When MMC was applied more than once, intervals ranged from 1 week to 13 months, with a median of 4 weeks (84). To date, no study compares the effectiveness of different concentrations and dosages of MMC; the concentration of 0.4 mg/mL is the most commonly used and appears to be effective.

Most data on MMC efficacy in treating persistent esophageal stricture are coming from studies involving patients with caustic esophageal injury (79, 84).

El-Asmar et al., in a double-blinded, randomized, placebo-controlled trial involving children with caustic esophageal strictures, showed a significant reduction of the number of dilatation sessions needed to alleviate dysphagia in patients undergone MMC application compared to controls. During the study period, 80% of strictures in the MMC group got completely resolved compared to only 35% in the placebo group (85). Berger et al. systematically reviewed pediatric studies, showing that in 27 of the 31 children published (87.1%) results were either excellent or good. A complete relief of symptoms was achieved in 21 children (67.7%), partial relief in 6 (19.4%), and no benefit in 4 (12.9%). Importantly, no adverse effect was found in any case. Only 7 out of 31 were EA children, and all but 1 had a good outcome (79). However, the results of a more recent retrospective study involving EA children contradicted these promising results. Chapuy et al. compared the outcome of 11 EA children who received topical application of MMC with 10 EA historical controls who underwent 3 or more dilations. The final outcome was similar in the two groups, with the stricture disappearing in the majority of children. Furthermore, the median number of dilations, although not statistically significant, was smaller in the historical cohort than in the MMC group [3.7 (range 3–7) and 5.4 (range 3–11), respectively]. Author concluded that in EA children adjuvant MMC treatment does not confer a real benefit compared with repeated dilations alone (86).

Potential side effects of systemic MMC include bone marrow, pulmonary, and renal toxicity; however, topical application has not been described to cause severe side effects so far. Nevertheless, being MMC a cytostatic agent, there is a hypothetical risk of secondary malignancy. Indeed, given the rapid cell turnover of the gastrointestinal epithelium, the activity of MMC on esophageal mucosa may lead to dysplastic transformation especially with repeated applications (79). To date, only in one case series, a *de novo* gastric metaplasia at the site of stenosis has been revealed in two out of six patients (39). For this reason, great caution should be taken and a long-term endoscopic follow-up program with esophageal biopsies at the site of MMC application is recommended (39, 79).

Concluding, encouraging data about local MMC are mostly derived from caustic refractory strictures. Several questions have no answers yet, and larger prospective studies are needed to better define optimal application technique, dosage, concentration, duration, and number of MMC applications. Despite contrasting reports exist, MMC can be considered as potential adjuvant treatment for the management of recurrent strictures in EA patients, as stated by the ESPGHAN–NASPGHAN Guidelines (14, 20).

Incisional Therapy

Endoscopic electrocautery incisional therapy (EIT) has been used as an alternative option for the treatment of Schatzki's ring and

refractory ASs (87). The basic principle of EIT is the disruption of the fibrotic tissue of the stricture to gain satisfactory lumen diameter with a needle-knife electrocautery. Different EIT techniques have been described with or without dilatation, including electrocautery combined with argon plasma coagulation, or endoscopic scissors, but standard needle knives have been applied most often (88).

Standard needle knife is constituted by a diathermy wire that is pushed out from the tube by a handle mechanism. Insulated-tip knife, consisting of a conventional diathermy needle knife with a ceramic tip, which permits cutting only at the side of the knife, seems to be preferable to minimize the risk of perforation (89). EIT technique consists of multiple radial incisions parallel to the longitude of the esophagus at the stricture site followed by endoscopic balloon dilation. All the steps of the procedure are performed under direct visualization (90). A variation of this technique has been developed by Muto et al. who described a radial incision and cutting method in radial incisions are followed by cutting away of the fibrotic tissue between the incisions (91). Lee et al. described a modified method consisting of the use of a transparent hood attached to the scope tip to reduce unintentional injury during incision (92).

Data on safety and efficacy of EIT are primarily derived from reports in adult patients. EIT therapy has shown exciting results in the treatment of both naïve (as a first-line treatment) (92–95) and refractory strictures (90, 91, 96). In a randomized, prospective study, Hordijk et al. demonstrated that EIT and Savary bougienage were equally efficacious as a primary therapy for previously untreated ASs in adults (95). Muto et al. found that EIT resulted in significantly higher patency rates than repeated dilations in the management of refractory AS (after ≥3 dilation sessions) at 6 and 12 months' follow-up (91). Patients with long-segment (>1 cm) strictures showed a worse outcome in terms of reoccurrence of the stricture and need of repeated treatments to achieve dysphagia-free status (90, 92). Importantly, EIT has shown a good safety profile; no complications occurred in all (90, 92, 94–96) but one of the studies where all 2 out of 54 patients experienced a pinhole perforation who have been treated conservatively (91).

Very limited data on EIT are available in pediatrics. In retrospective series of seven AE children with refractory AS underwent EIT alone (four patients) or in association with esophageal stenting (three patients), sustained symptom improvement was achieved in all patients, in five of them after a single treatment while an additional treatment was needed in two cases. No severe complications were observed (97).

In summary, despite very limited, especially in children, current evidences suggest that EIT could be considered as an alternative treatment in patients AS, particularly in those with a relatively short length stricture.

Esophageal Stenting

Esophageal stent placement is the most frequently used method for palliation of dysphagia from esophageal cancer. Over the last years, temporary stent placement has increasingly been used for refractory benign esophageal strictures in adults (98). Despite there is no specifically designed stents for children, this technique has also gained wide acceptance in pediatrics for the management of refractory and recurrent stricture when medical and endoscopic treatments fail (40, 42).

The rationale of esophageal stenting for refractory strictures is that continuous radially oriented pressure over a long period allows the esophagus to maintain luminal patency while simultaneously stretching the stricture. Remodeling of scar tissue may occur while the stent is in place, which can result in persistent luminal patency and reduced risk of recurrent stricture formation.

As for many of the other treatments, even for esophageal stents, experiences primarily derived from the adult literature. Currently, different designs of esophageal stents are commercially available but they can be divided into three main categories: self-expandable metal stents (SEMSs), self-expandable plastic stents (SEPSs), and biodegradable stents (BDSs) (99, 100).

Self-expandable metal stents consist of woven, knitted, or laser-cut metal mesh cylinders that exert self-expansive forces until their maximum fixed diameter is reached. They are composed of nitinol, a nickel, and titanium alloy. To prevent tissue ingrowth through the stent mesh, SEMs can be fully or partially covered by a plastic membrane or silicone (99). Partial or fully covered SEMs are currently recommended for palliation of malignant dysphagia, only fully covered stent designs can safely be removed after a prolonged time of stenting (98).

Self-expandable plastic stents are constituted by a woven polyester skeleton completely covered with a silicone membrane. Radiopaque markers positioned at the middle and ends of the stent to guide the placement under fluoroscopy (99).

Both SEPS and SEMS are generally deployed *via* a delivery device catheter over a guidewire under fluoroscopic guidance. In contrast to most SEMSs, which are sold in a constrained fashion, the SEPS requires mounting onto the delivery catheter just before use (99).

Biodegradable stents are made from a biodegradable polymer that is slowly absorbed so that, contrarily to SEMSs and SEPSs, BDSs does not need to be removed. BDS maintains its integrity and radial distensile force for approximately 6 weeks and disintegrates in 11–12 weeks after deployment (101). Despite all stent types have been used for the treatment of refractory benign esophageal stricture in adults, only the SEPSs received formal approval for this indication in adults (98).

As commercially available esophageal stents are often inappropriate in size for pediatric patients, airway or biliary stents could be used for children. Airway stents are more rigid than traditional esophageal stents, so the risk of complication is increased, but are available in different size (diameter from 8 to 20 mm and lengths from 2 to 8 cm). Biliary stents are more flexible but are available only in small size (caliber of 8 and 10 mm of and lengths of 4, 6, and 8 cm) (22, 102–104).

In order to overcome these limits, a customized stent has been developed. The "dynamic stents" consists of a plastic or silicon tube, customized in different length and diameter according with the stricture size and level, affixed to a nasogastric tube. The main difference with the other expandable stents is that foods, instead of passing within the lumen of the stent, pass between the stent and the esophageal wall allowing for the long-term improvement

of esophageal patency. Intraluminal customized stent is passed under fluoroscopic guidance after stricture dilations (105, 106).

No studies have compared different strategies in terms of stenting duration, so no ideal stenting time has been determined yet. Adults guidelines suggests that fully covered SEMSs or SEPSs should remain in place for at least 6–8 weeks and no more than 12 weeks, to maximize success and to minimize the risk of hyperplastic tissue reaction and stent embedment (98). In pediatric series, the range varies from 7 to 133 days but is more typically 4–6 weeks (104). Complications include potentially life-threatening events such as perforation, hemorrhage, and airway compression but also migration (which is the most frequent complication), granulation tissue, gastroesophageal reflux, and aspiration pneumonia (99). More significantly, massive esophageal bleeding has been reported after stent placement as a cause of arterioesophageal fistulae in two cases of EA children (one death). It is important to underlying that, compared with the general population, EA patients have higher incidence of aortic arch and great vessel anomalies, and consequently they may be more prone to develop this catastrophic complication. Thus, cross-sectional imaging is warranted to evaluate the proximity of great vessels (with or without possible aberrancy) to minimize the risk (107).

In adults, the use of removable stents to treat benign esophageal strictures has yielded contrasting results as summarized in a recent systematic review and meta-analysis. The pooled clinical success rate was 40.5% (95% CI 31.5–49.5%) with no significant differences between patients treated with SEPS and SEMS ant those treated with BDS. The overall adverse event rate was 20.6% (95% CI, 15.3–28.1%) with no significant difference between the three types of stents (108).

Overall, pediatric data on stricture resolution are scarce and heterogeneous, reported success rates ranging from 26 to 86% (103, 105, 109, 110). Data on EA patients are even scarcer. Manfredi et al. in 23 EA patients underwent a total of 40 stenting sessions, reported a success rate of 39 and 26% at ≥30 and at ≥90 days after stent removal, respectively. Both SEPS (14 patients) and fully covered SEMS (26 patients) were used. The mean duration of stent placement was 9.7 days (range 2–30 days) (110).

In a series of predominantly small children (median age 1-year-old child), Best et al. reported that esophageal stenting using and airway stent treatment was successful in all patients, five out of seven had long-gap EA (103). Using the customized "dynamic stent," the group of Bambino Gesù Children's Hospital all reported an overall success rate of 89% in a series of 79 children, mostly with caustic strictures. Esophageal stenting (≥40 days of duration of stent placement) was successful in 17 out of 21 children with EA (81%). High-dose systemic steroid therapy (dexamethasone 2 mg/kg/day for 3 day) was administered in all children after stent placement (105, 106).

In conclusion, esophageal stenting is a promising tool for the treatment of recurrent and refractory ASs. Advantages include prolonged maintenance of luminal patency and better oral feeding. Nonetheless, patients' tolerance may not be optimal and migration may occur, as well as other possible complications. The long-term efficacy and safety must be demonstrated by prospective trials.

ERCP Guidewires and Catheters As Adjunct Tools

In select cases, when the stenosis is so severe that the lumen cannot be identified and passed, guidewires used for can be used (111). After preloading, a standard ERCP catheter with a 0.035″ guidewire, the floppy tip can be used to gently probe the stricture. Once the lumen has been identified and passed, confirmation of the final guidewire tip location should be monitored with fluoroscopic guidance. Then, the guidewire may be left in place and used for dilations with Savary–Gilliard polyvinyl or ERCP dilators.

SURGICAL MANAGEMENT

Although conservative treatment is preferable for ASs (39), children who fail to respond to all conservative strategies require a surgical intervention.

Despite the difficulties in the management of refractory and recurrent ASs, the number of reported patients who require resection of the stricture is remarkably small, ranging from 3 to 7% (12, 112). No large data are available about long-term outcomes of these patients, since cohorts are small and data are always retrospective.

Stricture Resection with Direct Anastomosis

Resection and esophageal anastomosis is the most common surgical intervention for refractory ASs (112, 113). Although mediastinal scarring complicates reoperation, by this time the esophageal ends are in apposition and better vascularized, increasing the likelihood of success (114). Nonetheless, patients treated with a second end-to-end anastomosis may still require postoperative dilatation, as well as a second operative revision (12).

Esophageal Replacement

Interposition graft placement for the treatment of AS (as opposed to the primary treatment of long-gap EA) is exceedingly rare in the recent literature (12).

The decision to abandon the native esophagus and perform replacement surgery is an important one and needs to be a well-informed decision, made by experienced surgeons in discussion with a multidisciplinary team (114). The morbidity associated in the long and short term with esophageal replacement may be significant, but the benefits are also easily seen in those patients with a long and complicated previous surgical history (114).

The choice of graft (gastric transposition, colon interposition, jejunal interposition, and gastric tube) is determined by individual and institutional expertise. Outcomes of the different approaches must be prospectively evaluated. A recent review aimed to describe *pros and cons* of each technique, regardless of the indication (115).

CONCLUSION

With better survival from improved surgical techniques and preoperative/postoperative care, we are increasingly seeing children with EA experiencing significant short- and long-term

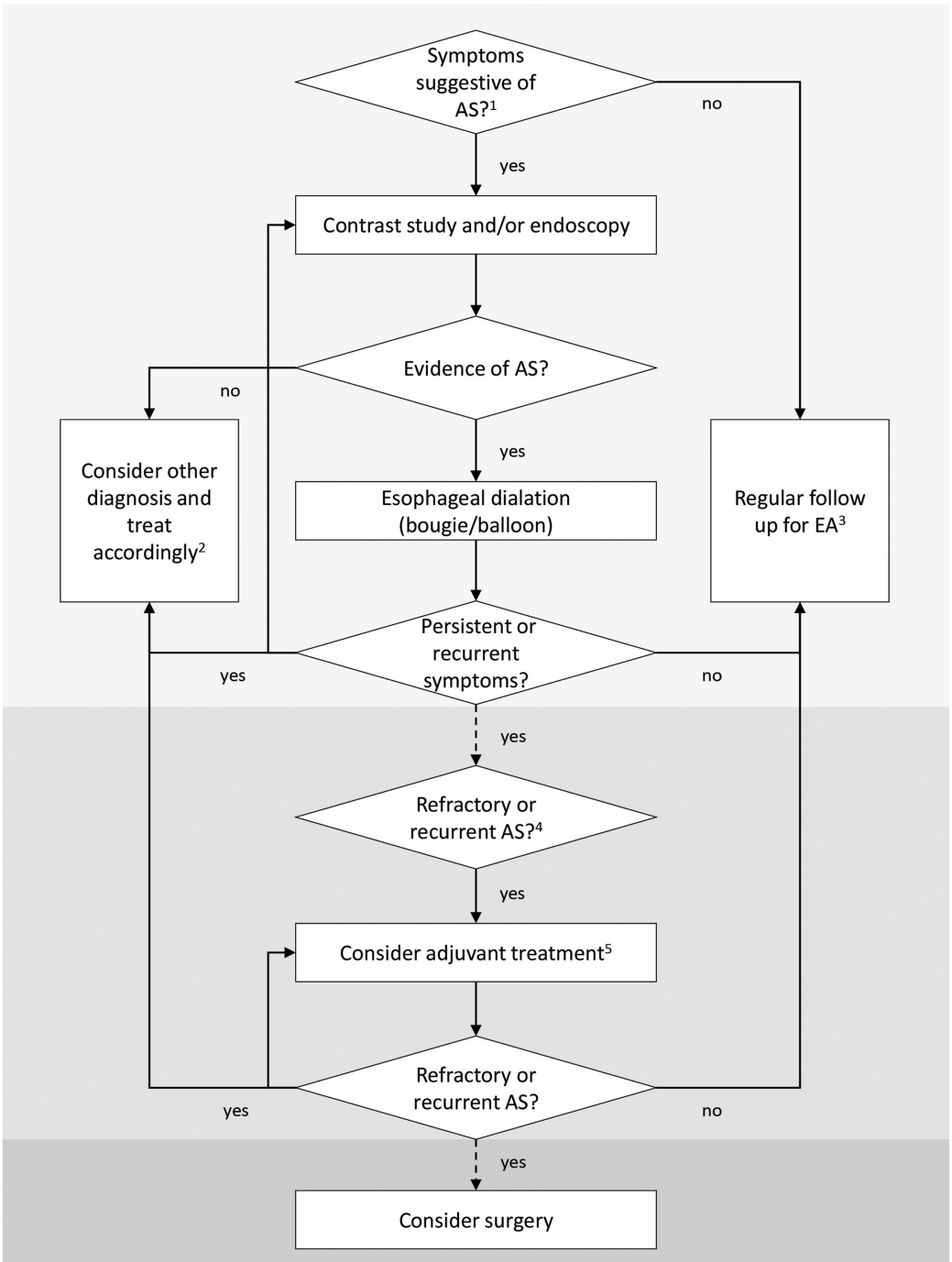

FIGURE 1 | **Simplified algorithm for diagnosis and treatment of anastomotic strictures (ASs) after esophageal atresia (EA) repair**. [1]Symptoms suggestive of AS depend upon the age of the child and the type of food ingested (liquid or solid) and include feeding and swallowing difficulties, regurgitation and vomiting, mucus or food impaction, cough, drooling, recurrent respiratory infections, foreign body impaction, and poor weight gain. In EA patients, these symptoms may overlap with other pathologic conditions, and none of them alone is sensitive or specific enough to diagnose an AS (14). [2]Other diagnosis includes esophageal dysmotility, recurrent tracheoesophageal fistula, gastroesophageal reflux disease, tracheomalacia, laryngeal clefts, and vocal cord dysfunction; these conditions may coexist and exacerbate AS symptoms. Patients with EA should be evaluated regularly by a multidisciplinary team (14). [3]EA children in the first 2 years of life (with special attention during the introduction of solid food) and patients with long-gap EA and postoperative anastomotic leak need a closer follow-up (14). [4]Recurrent AS: ≥3 episodes of clinically relevant stricture relapses after dilations (14) or inability to maintain a satisfactory luminal diameter for 4 weeks once the age-appropriate feeding diameter has been achieved (20). Refractory AS: inability to successfully remediate the anatomic problem to obtain age-appropriate feeding possibilities after a maximum of five dilation sessions (refractory) with maximal 4-week intervals (20). [5]Potential adjuvant treatments may include intralesional and/or systemic steroids, topical application of mitomycin C (MMC), stents, and an endoscopic incisional therapy (14). Temporary stent placement or application of topical MMC following dilation is suggested as a first-line adjunctive treatment in children (20).

gastrointestinal morbidities. Despite the real incidence is still undetermined, AS is the most common complication following EA operative repair. Despite the efforts to identify possible pre-, intra-, and postoperative risk factors, incidence of ASs does not seem to be changed over time. Limited evidence exists regarding diagnosis and treatment, and there is still a lack of uniform and systematic approach for the care of these patients. By virtue of this, over the last year, the working group of International Network on Esophageal Atresia, including members from ESPGHAN and NASPGHAN, published the first evidence-based Guidelines for the management of children with EA.

It is strongly recommended that ASs are investigated and treated only when symptoms occur as opposed to routine screening and dilatation. The diagnosis can be done by either contrast study or endoscopically. The mainstay of stricture management is serial esophageal dilatation. No clear advantage of either balloon or bougie dilator has been demonstrated; therefore, dilation should be carried out using the technique with which the operator is most skilled and experienced. Despite several dilation sessions, AS persistency or recurrence may be experienced. In these cases, conservative approach should be preferred before considering any surgical treatment. Different non-surgical adjuvant treatments have been used to minimize the risk of stricture reoccurrence. Although data are scarce and heterogeneous, especially in EA patients, temporary stent placement or application of topical MMC following dilation are suggested as a first-line adjunctive therapy.

Even though recent Guidelines from ESPGHAN and NASPGHAN have provided an essential help for the management of EA patients in clinical practice, there is still an overall lack of evidence-based indications and several questions have no answers yet. Large, prospective, multicenter studies are needed to better understand AS pathophysiology and to determine the optimal treatment strategy, especially in patients with refractory and recurrent AS. A simplified algorithm for diagnosis and treatment of AS in EA patients shown in **Figure 1** is based on current knowledge.

AUTHOR CONTRIBUTIONS

RT and GA performed the literature search, analyzed the data, and drafted the manuscript. LD and PA designed and coordinated the work and critically revised the manuscript for important intellectual content. FT, TC, VB, AC, ER, FR, SF, and GFA contributed to literature search and data interpretation and critically revised the manuscript. All the authors approved the final version of the manuscript.

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REVIEW
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Feeding Problems and Their Underlying Mechanisms in the Esophageal Atresia–Tracheoesophageal Fistula Patient

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Feeding difficulties such as dysphagia, coughing, choking, or vomiting during meals, slow eating, oral aversion, food refusal, and stressful mealtimes are common in children with repaired esophageal atresia (EA) and the reasons for this are often multifactorial. The aim of this review is to describe the possible underlying mechanisms contributing to feeding difficulties in patients with EA and approaches to management. Underlying mechanisms for these feeding difficulties include esophageal dysphagia, oropharyngeal dysphagia and aspiration, and aversions related to prolonged gastrostomy tube feeding. The initial diagnostic evaluation for feeding difficulties in a patient with EA may involve an esophagram, videofluoroscopic imaging or fiberoptic endoscopic evaluation during swallowing, upper endoscopy with biopsies, pH-impedance testing, and/or esophageal motility studies. The main goal of management is to reduce the factors contributing to feeding difficulties and may include reducing esophageal stasis, maximizing reflux therapies, treating underlying lung disease, dilating strictures, and altering feeding methods, routes, or schedules.

Keywords: esophageal atresia, tracheoesophageal fistula, feeding difficulties, oropharyngeal dysphagia, impedance testing, aspiration, videofluoroscopic swallow study

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INTRODUCTION

Children born with esophageal atresia (EA), with or without tracheoesophageal fistula (TEF), experience various gastrointestinal and respiratory complications and these complications often manifest with feeding difficulties; up to 75% of patients report difficulties with eating and the reasons for this are often multifactorial (1–7). Despite the high prevalence of these issues, the literature focused on feeding difficulties in these children is limited. While the focus of many studies is on esophageal abnormalities as the source of feeding difficulties, it is also important to consider oropharyngeal dysfunction and aerodigestive abnormalities as well (8). The aim of this review is to describe the nature of feeding difficulties in patients with EA, to discuss possible mechanisms for abnormal feeding, and highlight approaches to management in these patients.

THE PREVALENCE OF FEEDING DIFFICULTIES IN CHILDREN WITH EA

A number of feeding problems have been described in children with EA, including dysphagia, liberal fluid intake during meals to help clear food boluses, coughing, choking, or vomiting during meals,

Abbreviations: EA, esophageal atresia; VFSS, videofluoroscopic swallow study; TEF, tracheoesophageal fistula.

slow eating, oral aversion, food refusal, and stressful mealtimes (9–11). In a study of 124 children with repaired EA, Puntis et al. characterized feeding difficulties and found that, compared to healthy controls, children with EA were significantly more likely to eat slowly, refuse meals, cough or choke during eating, and vomit with meals (9). In a recent review of 75 children (ages 0–16 years) seen in a multidisciplinary EA clinic, 79% had at least one problematic mealtime behavior with 54% of patients unable to consume age/developmentally appropriate textures, 29% with extremely selective eating behaviors, and 25% with lengthy mealtimes (10). While these feeding difficulties decreased with age, these rates are still extremely high (10, 11). While patients who have undergone primary repair of long-gap EA have delayed onset of feeding and significant variability in individual results, overall the major feeding milestones occurred in a similar pattern to normal infant controls (12).

Given the high prevalence of feeding difficulties in children with EA, providers should be aware of these issues and discuss feeding concerns with caregivers. Compared to normative sample controls, caregivers report significant feeding difficulties on validated feeding difficulty questionnaires: 17.5% of children with EA scored 1 SD above the mean and 6.7% scored 2 SDs above the mean (13). Even when present, the feeding difficulties were classified as mild in the majority of patients. Children with non-type C EA and those who were premature were more likely to have scores in the severe range (13). In a survey of 128 parents participating in an EA support group, 68% of parents reported that their children struggled with feeding difficulties including pain with eating, regurgitation of food, vomiting, burping, and avoidance of tough/bulky foods (14). Food impactions are also common in this population and 69% of parents reported that their child had at least 1 food impaction following their repair. Despite the widespread prevalence of feeding difficulties in patients with EA, few patients raise these concerns with their medical team; in a study by Puntis et al., only 11% of parents reported discussing feeding concerns during a medical visit (9). This suggests that targeted feeding questions should be included on all medical intake questionnaires and added to every follow-up clinical visit. While recognizing the problem is important, Ramsay and Birnbaum (15) took the recommendations a step further and recommended early involvement of a multidisciplinary team comprises occupational therapy, nutrition, and psychological support to assist families with feeding-related difficulties, and this recommendation has been supported by recent EA guidelines (16).

MECHANISM OF ABNORMAL FEEDING IN CHILDREN WITH EA

Esophageal Dysphagia

Esophageal dysphagia is common in patients with EA and causes include dysmotility, anatomic abnormalities, esophageal outlet obstruction, and esophagitis. While older children may present with complaints of food getting stuck, the presentation is often more challenging to discern in younger children. Symptoms in younger children include feeding difficulties, respiratory symptoms, vomiting, or poor growth (16). Dysphagia is present in 38–85% of patients with EA (1, 6, 7, 11, 17–19). Connor et al. found, in a systematic review and meta-analysis, an overall pooled estimated prevalence of 50.3% (3). Evaluation of dysphagia in a patient with EA may involve a number of diagnostic studies including (1) an upper GI contrast study assess for strictures or esophageal pooling, (2) videofluoroscopic swallow study (VFSS) to assess for aspiration and other causes of oropharyngeal dysphagia, (3) upper endoscopy to assess for esophagitis, and (4) esophageal motility testing to measure esophageal peristalsis and assess for bolus stasis if paired with impedance (8). Recent ESPGHAN–NASPGHAN guidelines recommend that all EA patients with dysphagia undergo at minimum an evaluation with an upper GI contrast study and esophagoscopy with biopsies for the evaluation of dysphagia, though in centers with motility capability, high-resolution esophageal manometry is helpful (16).

Esophogram

Barium imaging of the esophagus is helpful to identify esophageal strictures (congenital, peptic, or anastomotic), recurrent or missed fistulae, or pooling in the proximal esophageal pouch, all of which can contribute to feeding difficulties. Upper GI contrast studies are particularly helpful in patients with EA who have undergone fundoplication, where the fundoplication has the potential to create an esophageal outlet obstruction in the setting of esophageal dysmotility; in these patients, it is important to check delayed films to look for retained barium in the esophagus. Furthermore, following the barium into the stomach allows for imaging of slipped or herniated fundoplications. Holschneider et al. reported higher rates of postoperative dysphagia in children with EA who underwent fundoplication (17.2%) compared to those who underwent fundoplication for other indications (6.5%) (20). While there are no studies that directly address the role of fundoplication in feeding difficulties specifically in this population, patients with fundoplication can present with dysphagia, retching, volume intolerance during feeding, recurrent respiratory infections, and coughing after feeding, all of which have the potential to contribute to feeding difficulties.

Endoscopic Evaluation

Esophagitis is not uncommon in patients with EA and may be implicated as an underlying cause for dysphagia. In a study of 45 patients with EA undergoing upper endoscopy, Castilloux et al. found that although 31% of patients had histologic evidence of esophagitis, there was no association between symptoms of dysphagia and either gross or microscopic esophagitis (17). Sistonen et al. found similar results; while 25% of patients had esophagitis on histology, there was no relationship between inflammation and dysphagia (18). In another study by Deurloo et al., patients with dysphagia were more likely to have abnormal esophageal manometry studies, although there was no association between a reported symptom of dysphagia and a histologic diagnosis of esophagitis (21). While food impactions are often attributed to esophagitis, 38% of patients with EA who experienced food impactions actually had normal esophageal biopsies (17). This suggests that dysmotility may play a role in the pathogenesis of

food impactions even in the absence of inflammation. All of these studies suggest that while treating esophagitis may be important, feeding issues are rarely a result of esophageal inflammation and setting realistic expectations for symptomatic improvement after acid suppression therapy for families is important.

Recently, there has been a growing body of literature on increased rates of eosinophilic esophagitis in children with EA. Dhaliwal et al. found a 17% incidence of eosinophilic esophagitis in a review of 103 patients with EA at a single center (22). This is higher than the incidence of eosinophilic esophagitis in the general population, which is estimated to be approximately 55/100,000 (23). Eosinophilic esophagitis should be a consideration in children with EA who have persistent symptoms despite appropriate antireflux therapy, progressive dysphagia, or recurrent strictures. However, because rates of recalcitrant reflux esophagitis may be higher in patients with EA because of the inability of a dysmotile esophagus to clear acid or because of inadequate acid suppression dosing, it is critical to determine if persistent esophagitis is incompletely treated reflux or eosinophilic esophagitis (16, 24–26). This evaluation may include additional testing with pH–MII to not only test for the amount of acid reflux but, if performed on therapy, also to assess for medication efficacy.

Multichannel Intraluminal Impedance with pH

While gastroesophageal reflux disease (GERD) is frequently reported in children with EA and objective diagnostic testing detects pathologic reflux in up to 67% of patients, recent literature suggests that feeding difficulties are not consistently associated with reflux events (24–29). In a study of 35 patients with EA who underwent pH–MII testing, Tong et al. found that only 19% of all dysphagia symptoms reported during pH–MII testing were associated with reflux events (24). Pedersen et al. studied 59 patients with EA and 25 controls who underwent pH–MII testing (26). Despite the fact that 70% of patients with EA reported dysphagia (compared to 20% of controls), there were no significant differences in any pH- or MII-parameters aside from the total number of acid reflux episodes that was actually higher in controls. In a study of 24 patients with repaired EA who underwent pH–MII testing, Fröhlich et al. found, using a standardized questionnaire, dysphagia with liquids in 13% of patients and dysphagia with solids in 58% of patients (28). However, there was no significant correlation between total symptom score based on questionnaire responses and either the reflux index (percentage of recording time with pH < 4) or the bolus index (percentage of recording time with esophageal exposure to a refluxate) on pH–MII testing. If pH–MII testing is considered in the evaluation of children with dysphagia or feeding difficulties, it must be analyzed not only by the software but also manually; baseline impedance values can be 75% lower than controls, so therefore software may underestimate reflux burden and symptom correlations (24, 28).

Esophageal Manometry

Low amplitude or absent esophageal peristalsis have been reported in many studies of esophageal motility in children with EA (18, 21, 30). In a study of 101 adult patients with EA, only 20% of patients had normal propagating peristalsis (18). Similar manometric findings were described by Deurloo et al.; 70% of subjects had low amplitude esophageal contractions and retrograde contractions were observed in 35% of subjects (21). Those patients who reported dysphagia were more likely to have abnormal esophageal motility along with significantly lower scores on health-related quality of life scales. For centers where manometry is not routinely performed, even radionucleotide esophagram studies reveal significantly longer esophageal transit times in patients with long-gap EA compared to those with non-long-gap EA, suggesting that imaging may be a potential adjunctive tool to help identify dysmotility (31). This suggests that distal esophageal dysmotility, rather than pooling over the anastomosis, may be a bigger contributor to feeding difficulties in many children and supports imaging to understand the pathophysiology of dysphagia first before dilation or other more aggressive interventions. From a prognostic perspective, there may be some improvement in esophageal peristalsis based on manometric studies as patients get older, although this needs additional validation using high-resolution manometry (32).

Standard manometry is limited because of the wide spacing between sensors that leave larger areas of the esophagus unmapped including areas of possible dysmotility and the lower esophageal sphincter. To overcome these limitations, high-resolution manometry catheters, which have up to 36 closely spaced sensors, allow for improved characterization of motility abnormalities in patients with EA. In a study of 40 children with repaired EA who underwent high-resolution manometry, Lemoine et al. found that 38% of patients had aperistalsis and 15% had evidence of pan esophageal pressurization (33). Both gastroesophageal reflux and pulmonary symptoms were more common in the aperistalsis group. However, it is critical to understand that symptoms often thought to be reflux-related are not, in fact, a result of increased numbers of reflux episodes but rather poor clearance of whatever reflux is present or retrograde movement of retained swallowed esophageal contents. Kawahara et al. reported absent mid-esophagus peristalsis in all 29 out of 29 patients studied with repaired EA; 17 out of these 29 patients also had absent contractions in the distal esophagus (30). This lack of peristalsis translates into poor bolus transit when compared to controls (28). Esophageal dysmotility may not be an entirely postoperative phenomenon and may not be unique to those with EA. Lemoine et al. reported esophageal dysmotility, with abnormal high-resolution manometry studies, preoperatively in two patients with isolated unrepaired tracheoesophagela fistula (34). These observations suggest that there may be abnormal development of the esophageal innervation and smooth muscle that contributes to the dysmotility seen in these patients.

Oropharyngeal Dysphagia and Aspiration

One of the other contributors to feeding difficulties is oropharyngeal (rather than esophageal) dysphagia with resultant aspiration. Patients can present with food refusal, back arching, watery eyes, cyanotic spells, chronic respiratory infections, chest rattling, or noisy breathing before, during, or after feeding. The differential diagnosis for this oropharyngeal dysphagia includes laryngeal clefts, vocal cord paralysis or paresis, neuromuscular

dyscoordination, or developmental delays in swallowing function. Hörmann et al. studied 25 VFSSs in 19 children with repaired EA (35). In this cohort, 16% of patients had nasopharyngeal regurgitation, 5% had had residue in the pharynx, 10% had laryngeal penetration, and 37% had aspiration. In a study of VFSS in 12 children with repaired EA, Coppens et al. found that 36% of patients had abnormal oral phases and 75% of children had abnormalities in the pharyngeal phase (36). Oropharyngeal dysphagia/aspiration is also an important factor in the long-term nutritional outcomes for children with EA; children who are at risk for aspiration are significantly more likely to be malnourished compared to children without aspiration that may be a combination of inadequate oral intake and increased metabolism related to recurrent respiratory infections and tachypnea (10). Once aspiration or penetration is diagnosed on VFSS, the following differential diagnoses should be considered to help predict prognosis.

Vocal Cord Paralysis or Paresis

Vocal cord paralysis is reported in 3–17% of patients with EA and may result from a combination of postoperative recurrent laryngeal nerve damage and prolonged or traumatic intubation (37–39). Morini et al. studied 174 patients with treated EA/TEF and found that 7 (4%) of patients had vocal cord paresis. Risk factors for vocal cord paresis in these patients included longer duration of time intubated, cervical esophagostomy, long-gap EA, and anastomotic leakage (37). Pediatric patients have high rates of recovery; in patients with vocal cord paralysis following cardiac surgery, for example, 35% of patients ultimately recovered vocal cord function with a median time to recovery of 6.6 months (40). The clinical implications are important because if vocal cord function is suspected to improve, placement of enteral feeding tubes may not be needed.

Laryngeal Cleft

Laryngeal clefts are included in the differential diagnosis of aspiration. In a recent study of children with EA undergoing rigid bronchoscopy and laryngoscopy, 26% of EA patients had a laryngeal cleft (41). In a case series of 183 pediatric patients diagnosed with laryngeal clefts, 22 (12%) patients had a TEF (39). Half of these patients presented with aspiration and 18% had feeding difficulties. Only 17 of the 22 patients with laryngeal clefts and TEF required surgical repair. Postoperative modified barium swallow studies showed resolution of aspiration following cleft repair (39). Again, the implications are important because if a laryngeal cleft can be repaired, enteral feeding tubes are not needed, and potential long-term feeding aversions can be avoided.

Neonatal Swallowing Dysfunction

The differential diagnosis for aspiration in a neonate includes neonatal swallowing dysfunction. Aspiration of thin liquids was observed in 68% of former preterm neonates referred for VFSS in a study of 148 patients done by Davis et al. (42). However, many of these patients eventually had improvements in their swallow function and ultimately went on to pass a repeat VFSS after a median of 3.4 months. While there are no studies assessing improvements in swallowing function over time in neonates with EA, the findings in the general neonatal population suggest that clinicians should consider repeating a swallow study to assess for improvement in swallowing before considering surgical interventions such as gastrostomy tube placement or fundoplication. Additionally, determining the natural history of this developmental condition in children with EA is critical to avoid unnecessary surgeries.

DIAGNOSING ASPIRATION DURING SWALLOWING

Oropharyngeal dysphagia with resultant aspiration can be diagnosed by several different diagnostic tests. While there is no true gold standard test for aspiration, all testing modalities are considered complementary to one another. Studies comparing diagnostic testing modalities have found poor agreement between different studies. In a study of 63 children with cerebral palsy who underwent barium videofluoroscopy, salivagram, and milk scan for evaluation of aspiration, Baikie et al. found poor agreement between tests, with a maximum kappa of 0.20 (43). These results suggest that if aspiration is suspected, several different diagnostic modalities should be considered (8). The sensitivity of these tests in patients with EA is not known.

Videofluoroscopic Swallow Study

The VFSS allows for visualization of the oral and pharyngeal phases of swallowing. Oropharyngeal aspiration diagnosed on VFSS is common in children. One large study of 300 symptomatic pediatric patients with feeding disorders undergoing VFSS found oropharyngeal aspiration in 34% of children (44). Of these patients, 81% had silent aspiration. Children with neurologic impairment (OR 4.65), developmental delays (OR 4.62), aspiration lung disease (OR 3.22), and enteral feeding (OR 2.03) were more likely to have silent aspiration. Weir et al. studied pneumonia risk in 150 children with swallowing dysfunction diagnosed on VFSS to determine if the results of VFSS predicted clinical outcome (45). On univariate analysis, the risk of pneumonia was significantly increased in patients with aspiration of thin liquids (OR 2.4) and in those with post-swallow residuals (OR 2.5), although there were no significant differences on multivariate analysis. Aspiration of consistencies other than thin liquids was not associated with any increased risk of pneumonia. However, the spectrum of pulmonary symptoms extends beyond just pneumonia and additional studies are needed to correlate findings on VFSS with other pulmonary manifestations. Another advantage of VFSS studies is that they can accurately identify primary, missed, or recurrent TEFs in addition to the primary swallowing dysfunction (46).

Salivogram

In contrast to a VFSS that detects aspiration of a food bolus, aspiration of oral secretions can be detected using radionucleotide scintigraphy, and this may provide some insight into the severity of oropharyngeal dysphagia. In a study of 129 pediatric patients with suspected oropharyngeal dysphagia, Simons et al.

found that aspiration was identified on 21% of studies (47). Factors associated with positive salivagram results included developmental delay (OR 2.8), chronic respiratory infections or pneumonia (OR 2.6), reactive airway disease exacerbations (OR 2.8), and use of H2 blockers or proton pump inhibitors (OR 2.7). Drubach et al. found a similar frequency of positive salivagrams (25%) in 222 children, with high agreement (kappa = 0.891, $P < 0.0001$) between salivagram and chest X-ray findings (48). In a study of developmentally normal children with recurrent lower respiratory tract infections, Somasundaram et al. found positive salivagrams in 39% of infants and 16% of children aged 1–2 years (49). There was no aspiration noted in children over the age of 2 years.

Fiberoptic Endoscopic Evaluation of Swallowing (FEES)

Fiberoptic endoscopic evaluation of swallowing visualizes the pharynx and larynx during swallowing using a transnasal flexible fiberoptic laryngoscope, and this technique can be used to diagnose aspiration in both children and adults (50–54). FEES is the only study that can assess swallowing in infants while breastfeeding and is safe and effective in this population (55). Studies comparing FEES to VFSS have found low agreement between the two studies. In a study of 30 children undergoing both VFSS and FEES, da Silva et al. found low agreement overall between the two the studies, although laryngeal penetration and aspiration on FEES were associated with higher positive predictive value and specificity for abnormal VFSS (52). Kelly et al. studied 15 symptomatic adults who underwent simultaneous FEES and VFSS (51). Fifteen independent investigators from several sites reviewed the images and scored aspiration or laryngeal penetration. There was higher agreement between experts for the FEES images compared to VFSS. In a study of 126 adults with dysphagia, Aviv randomized participants to receive testing with either FEES or VFSS and monitored outcomes (54). Neither the incidence of pneumonia nor the pneumonia-free interval was significantly different between the two groups.

High-Resolution Manometry

High-resolution manometry can also be used as part of the diagnostic approach to suspected aspiration. Omari et al. compared assessment of swallow function using high-resolution manometry with impedance (HRM-I) to VFSS in 20 adults with suspected aspiration and 10 healthy controls (56). The swallow risk index (SRI) was calculated from automated analysis of combined manometric and impedance variables. The authors found that the SRI could be used to predict aspiration on fluoroscopy. These findings suggest that measurements taken during HRM-I can be used in the diagnosis of aspiration and offer the benefit of no radiation. In a HRM-I study of 20 children with oropharyngeal dysphagia, higher SRI, elevated upper esophageal sphincter pressure, and longer impedance flow intervals predicted risk of aspiration on VFSS, suggesting this technology also holds promise for use in children (57). The added benefit of this technology in children with EA is that both the upper and lower esophagus can be simultaneously assessed to determine aspiration risk, the quality of peristalsis, and the degree of esophageal stasis, all of which can contribute to feeding difficulties.

Cervical Auscultation

Cervical auscultation involves audible detection of breathing and swallowing sounds by using a microphone, stethoscope, or accelerometer placed over the neck. It offers an advantage over instrumental assessments of swallowing in that it is non-invasive and does not involve exposure to radiation. A recent randomized controlled trial studied the utility of cervical auscultation in children referred for suspicion of aspiration (58). Children were randomized to either a clinical feeding evaluation plus cervical auscultation group or to a clinical feeding evaluation only group. The ability to predict aspiration, using VFSS as a reference, was studied. The sensitivity for cervical auscultation plus clinical feeding evaluation was 85%, whereas the sensitivity for clinical feeding evaluation alone was 63%. The utility of this in children with EA is not known and may be complicated by the tracheomalacia sounds frequently heard in these children.

MANAGEMENT OF OROPHARYNGEAL DYSPHAGIA-ASSOCIATED FEEDING DIFFICULTIES

There are many causes for feeding difficulties, and the main goal of management is to reduce the factors contributing to these difficulties. This may include reducing esophageal stasis by dilating fundoplications, maximizing reflux therapies, treating underlying lung disease to improve cough, posttussive emesis and tachypnea (all of which can affect swallowing), dilating strictures, and switching formulas. Sometimes changing feeding schedules or adding cyproheptadine (both as an appetite stimulant and to improve gastric accommodation) improves oral intake by maximizing hunger, allowing for greater gastric volumes, and drying up oral secretions. Many causes of oropharyngeal dysphagia improve over time, and thus management decisions regarding feeding should be made in the context of the likelihood of improvement. Although there are no studies directly addressing the management of aspiration in children with EA, the available literature in other populations may offer useful insight into managing aspiration in these children.

Thickened Oral or Gastric Feeds to Reduce Aspiration during Swallowing and Aspiration of Gastric Contents

Thickening may serve many roles including reducing aspiration during swallowing, reducing full column reflux, and reducing retching. From a reflux perspective, Wenzl et al. studied 14 healthy infants with reflux who underwent intraesophageal impedance measurement and pH monitoring while being fed alternating thickened feeds and standard formula (59). The frequency and amount of regurgitation were significantly lower when infants received the thickened formula. Horvath et al. found a similar improvement in regurgitation in a systematic review of 14 randomized controlled trials evaluating the efficacy of thickening for

management of infant GER (60). However, as was seen in the Wenzl et al. study, thickening had no effect on the frequency of acid GER episodes, the number of reflux episodes lasting >5 min, or the reflux index. Given these results, thickening may serve an important role in the aspirating child when trying to prevent formula from entering the mouth.

A second benefit of thickening may relate to a direct impact on the stomach. Patients with gastrostomy tubes and fundoplications may have less retching and gagging with thickened feeds. In a study of 33 children, Pentiuk et al. found that more than half of patients studied had over a 75% reduction in retching and gagging when given a diet of pureed foods *via* gastrostomy tube (61). Similar findings were reported by Nishiwaki et al. in adult patients with percutaneous endoscopic gastrostomy tubes; patients who received a semisolid diet had a significantly lower percentage of GER when compared to those receiving a liquid diet (62). Differences in gastric emptying time did not appear to be a significant driver of these findings.

Finally, thickening helps with oropharyngeal dysphagia. Studies in both children and adults have shown that thicker liquids alter the temporal characteristics of swallowing, especially closure of the true vocal cords, and lengthen deglutition time (63, 64). In a retrospective study of 546 infants, children with silent aspiration had fewer acute respiratory infections requiring admission or emergency room visits when receiving thickened feeds than those without thickening (65). In a study of 15 infants with respiratory syncytial virus bronchiolitis, 9 were found to have abnormal VFSS studies (laryngeal or tracheal penetration or aspiration) with thin barium. However, repeat studies with thickened barium improved these abnormalities in all but one patient (66). In adult patients with neurogenic dysphagia, increasing bolus viscosity significantly improves the safety and efficacy of deglutition (67). While thickening improves swallow mechanics in many patients, its role in changing the timeline for full oral feeding or role as a caloric supplement to improve weight gain is not known.

Bolus versus Continuous Feeds to Reduce the Risk of Aspiration of Gastric Contents

Clinicians often alter the type of feeding to try to reduce reflux burden and change the feeding interval to improve oral feeding. However, there is limited data to support this practice in pediatric patients, and most data come from studies in preterm infants. Corvaglia et al. (68) studied cardiorespiratory outcomes in 33 preterm infants who each received both bolus and continuous feedings *via* orogastric tube. The continuous feedings were associated with more total apneic periods, more apneic periods lasting >20 s and more hypoxic episodes when compared to bolus feedings. In a randomized trial of intermittent bolus or semicontinuous nasogastric tube feedings in 246 low birth weight preterm infants, Rövekamp-Abels et al. found significantly lower mean daily gastric residual volumes in the bolus group (69). However, gastroesophageal reflux, respiratory complications, and time to full oral feeds were not assessed as outcomes in this population. The impact of feeding type in EA patients is not known.

Changing Feeding Schedule or Formula to Reduce Discomfort or Reflux That May Impair Oral Feeding

There is no data in children with EA though there is limited pediatric data in other populations. From a reflux perspective, while patients are conventionally told that small, more frequent meals are better in reducing reflux, there is no pediatric data to support this. In fact, the feeding frequency has more to do with the type of refluxate. Children fed more frequently have predominantly non-acid reflux, whereas a longer period of time after initiation of a feed is associated with more acid reflux events (70, 71).

While breastfed and formula-fed infants do not differ significantly with respect to reflux characteristics, the formula type may be important (70, 72). In a crossover study of 17 children with suspected GERD and cow's milk allergy who underwent pH–MII testing while fed 24 h of amino acid-based formula and then 24 h of cow's milk, the authors found a significantly higher total number of reflux episodes and also a significantly higher number of weakly acid episodes when infants were being fed the cow's milk (72). Similar results have been reported in adults. Horiuchi et al. found more rapid gastric emptying and fewer episodes of aspiration in adults with gastrostomy tubes who were given an elemental diet versus a standard liquid diet (73).

Finally, there may be a role for significantly reducing gastrostomy tube feeds in order to stimulate hunger and wean from gastrostomy tube feeds. In a recent prospective randomized controlled study of children with gastrostomy tubes initially placed for feeding difficulties, those assigned to a hunger provocation program with reductions in tube feeding by 50% had significantly more success weaning entirely off tube feedings than controls who had reductions of only 20–25% (86 versus 9%, $P < 0.001$) (74). Despite the desire of families to have their children on oral feeding, there is a significant lack of resources to facilitate this transition. In a study by Gardiner et al., this lack of resources results in significant practice variation in transitioning patients to oral feeding, and this is a critical step for all infants including those with EA (75).

Transpyloric Feeding

Transpyloric feeding may be helpful in some children with EA as it has the potential to help reduce reflux burden, reduce retching, and allows for safe nighttime feeds. Because the rates of reflux are similar in children who receive transpyloric feeding and those who had a fundoplication (76, 77), transpyloric feedings can be used as a fundoplication alternative until the feeding difficulties or reflux improve. This feeding method allows for infant and toddler growth without permanently obstructing the lower esophagus (with a fundoplication), which may be of great benefit in children with EA who have absent esophageal motility and are therefore at risk for stasis over the fundoplication. Transpyloric feedings have been shown to reduce risk of pneumonia in adults and children. Metheny et al. described significantly fewer pneumonias in a cohort of 428 critically ill adults when feeds were introduced distal to the second portion of the duodenum (78). Srivastava et al. compared outcomes in 366 children with neurologic impairment and

GERD who underwent management with either fundoplication (323 children) or gastrojejunal tube feedings (43 children) (79). The authors found that overall survival and pneumonia-free survival was similar between the groups during the follow-up period (median 3.4 years).

Fundoplication to Improve Feeding Tolerance

Fundoplications are commonly performed in children with EA, with reported rates between 39 and 59% of all patients with EA (5, 6, 17, 80). The recent ESPGHAN–NASPGHAN guidelines list refractory anastomotic stenosis, long-gap EA, poorly controlled GERD despite maximal medical therapy, long-term dependency on transpyloric feeding, and cyanotic spells as indications to consider antireflux surgery in children with EA (16). There are very few studies that address the role of fundoplication on feeding tolerance in patients with EA. In a recent study, Menzies et al. found that EA patients who underwent fundoplication had significantly poorer growth compared to those who did not have a fundoplication (10). This suggests that altering the anatomy with fundoplication may actually worsen dysphagia and volume tolerance into the stomach, contribute to feeding difficulties, and subsequently impair growth. Levin et al. found that EA patients who underwent fundoplication had higher rates of dysphagia postoperatively, compared to preoperative symptoms, regardless of surgical fundoplication technique (81). There were no significant differences in the rates of poor growth in the preoperative and postoperative settings in this cohort. Because of the relatively high rate of fundoplication in this population, additional studies on the impact on feeding are critical. Children with EA who are being considered for fundoplication should be evaluated with a barium contrast study, endoscopy with biopsies, and reflux testing preoperatively as well as esophageal motility testing whenever possible (16).

CONCLUSION

Feeding difficulties are common in patients with repaired EA, and this review highlights possible underlying mechanisms for abnormal feeding. Esophageal dysphagia, due to esophageal dysmotility, musical inflammation, or anatomic abnormalities such as strictures, is well described in patients with EA. Oropharyngeal dysphagia with resultant aspiration can also contribute to feeding difficulties in these patients and can be under recognized as symptoms often mimic other conditions such as reflux. There are many diagnostic tests that can aid in diagnosis of dysphagia, and patients with EA often require multiple tests to arrive at the correct diagnosis. Management centers on reduction of underlying factors contributing to feeding difficulties while recognizing that many causes of esophageal and oropharyngeal dysphagia improve over time. Clinicians caring for patients with EA should have a high index of suspicion for feeding difficulties in their patients and management with a multidisciplinary team is recommended for optimal care.

AUTHOR CONTRIBUTIONS

LM and RR each contributed to the draft of the manuscript and approved the final draft submitted.

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REVIEW
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Aspiration Risk and Respiratory Complications in Patients with Esophageal Atresia

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Chronic, long-term respiratory morbidity (CRM) is common in patients with a history of repaired congenital esophageal atresia, typically associated with tracheoesophageal fistula (EA/TEF). EA/TEF patients are at high risk of having aspiration, and retrospective studies have associated CRM with both recurrent aspiration and atopy. However, studies evaluating the association between CRM in this population and either aspiration or atopy have reported conflicting results. Furthermore, CRM in this population may be due to other related conditions as well, such as tracheomalacia and/or recurrent infections. Aspiration is difficult to confirm, short of lung biopsy. Moreover, even within the largest evidence base assessing the association between CRM and aspiration, which has evaluated the potential relationship between gastroesophageal reflux and asthma, findings are contradictory. Studies attempting to relate CRM to prior aspiration events may inadequately estimate the frequency and severity of previous aspiration episodes. There is convincing evidence documenting that chronic, massive aspiration in patients with repaired EA/TEF is associated with the development of bronchiectasis. While chronic aspiration is likely associated with other CRM in patients with repaired EA/TEF, this does not appear to have been confirmed by the data currently available. Prospective studies that systematically evaluate aspiration risk and allergic disease in patients with repaired EA/TEF and document subsequent CRM will be needed to clarify the causes of CRM in this population. Given the prevalence of CRM, patients with repaired EA/TEF should ideally receive regular follow-up by multidisciplinary teams with expertise in this condition, throughout both childhood and adulthood.

Keywords: esophageal atresia with or without tracheoesophageal fistula, respiratory aspiration, tracheoesophageal fistula, esophageal atresia, gastroesophageal reflux

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INTRODUCTION

Repaired esophageal atresia, typically associated with congenital tracheoesophageal fistula (EA/TEF), is commonly associated with long-term respiratory morbidity, including recurrent respiratory tract infection, chronic cough, persistently abnormal pulmonary function, and reported asthma (1, 2). There are many potential causes for respiratory complications in this population. Clinically significant tracheomalacia may occur in up to 78% of EA/TEF patients. In infants, tracheomalacia may lead to cyanotic spells (2). In children and adults, tracheomalacia may cause reduced airway clearance, leading to persistent bacterial bronchitis (3, 4). Patients with repaired EA/TEF have

multiple, and sometimes interrelated risk factors for aspiration. Aspiration can be due to esophageal dysmotility, which is present in up to 75–100% of EA/TEF patients (2) or esophageal stricture. Gastroesophageal reflux disease (GERD) can also cause lung disease due to aspiration of gastric contents, and 35–58% EA/TEF patients have been reported to experience GERD. Recurrent TEF may arise in about 9% of EA patients. Laryngeal clefts (particularly types 1 and 2) and unilateral or bilateral vocal cord paresis or paralysis appears to be frequent in EA/TEF patients, and often leads to aspiration (5, 6). Vocal cord paresis or paralysis may be, in at least some cases related to EA/TEF corrective surgery (7). Thoracic large vessel malformations such as aberrant right subclavian artery also appear to be abnormally common in EA/TEF patients, and may worsen tracheal and esophageal function, leading to dyspnea, dysphagia, and aspiration (8). Recent studies indicate that other esophageal diseases that impair esophageal function may also be commoner in patients with repaired EA/TEF, further increasing the risk of aspiration, including eosinophilic esophagitis, congenital esophageal stenosis, and heterotopic gastric mucosa in the esophagus (9, 10). Patients with repaired EA/TEF may also develop other respiratory conditions, such as atopy and asthma (2, 11); potentially due to altered gastrointestinal mucosal immunity, they may actually be at increased risk for these conditions. At present, the extent to which chronic respiratory morbidity (CRM) is due to aspiration early in life is unclear. This paper will attempt to summarize current knowledge of the degree to which aspiration is responsible for CRM in these patients.

ASPIRATION

Aspiration may be defined as the "inhalation of oral, gastric contents into lower respiratory tract." Its effect depends on whether the aspirate originates in the pharynx or stomach, whether it is liquid or solid, its pH, the presence of bacteria, and, importantly, its volume and the chronicity of the aspiration. There is evidence that at least 50% healthy adults aspirate small volumes oropharyngeal secretions while asleep, but this is cleared by airway clearance including cough, and by the immune system, leaving no sequelae (12). Aspiration is a general term used to describe a spectrum of acute lung syndromes such as aspiration pneumonitis, aspiration pneumonia, and foreign body aspiration, as well as chronic pathology including diffuse aspiration bronchiolitis, bronchiectasis, organizing pneumonia, and *bronchiolitis obliterans* syndrome (12, 13). Aspiration pneumonitis (Mendelson's syndrome) is due to regurgitation of gastric contents in the presence of reduced consciousness such as anesthesia, leading to acute lung injury and/or acute respiratory distress syndrome. The aspirated fluid is typically sterile, at least initially, unless the gastric pH had previously been iatrogenically elevated (12). Aspiration pneumonia is caused by the aspiration of infected oropharyngeal secretions in patients who are at risk for aspiration. It is typically a patchy bronchopneumonia that, classically, is in the dependent lobes. Aspiration may lead to necrotizing bronchopneumonia and lung abscess formation (13).

Several research groups have described the pathology and radiology of chronic aspiration. Mukhopadhyay and Katzenstein reported the lung biopsy findings in 59 adults with aspiration pneumonia due to aspiration of particulate matter. Their mean age was 57 years, and, of interest to EA/TEF patients 32% of the cases had esophageal disease or a hiatus hernia. All of the specimens contained alveolar foreign material, including vegetable matter in 92% of cases, and giant cells were present. Eighty-eight cases had cryptogenic organizing pneumonia (*bronchiolitis obliterans* organizing pneumonia) with intraluminal fibroblast plugs in the small bronchioles and alveolar ducts, mainly associated with foreign body-type suppurative granulomas, and foci of bronchopneumonia. A few cases had interstitial foreign material with fibrosis (14). Cardasis et al. reported 25 adult patients with occult aspiration. Their mean age was 62 years. Ninety-six percent had GERD, 32% had a hiatal hernia, and 40% had other esophageal diseases. Biopsies revealed poorly formed granulomas near the bronchioles with evidence of chronic inflammation, and foreign body giant cells and lipoid pneumonia was common. On computerized tomography (CT) imaging, bronchial wall thickening, centrilobular nodules, and tree-in-bud opacities were observed. These were evident mainly in the lower lungs. A few cases had ground glass opacity, interstitial lung disease, or traction bronchiectasis (15). Pereira-Silva described an older patient population, consisting of 13 patients with chronic microaspiration. Their mean age was 71 years. Sixty-nine percent had GERD, 46% had a hiatus hernia, and 23% had esophageal dysfunction. CT scanning demonstrated centrilobular nodules and focal areas of ground glass opacity in all of the patients, and in 85%, these findings were present in the dependent lung regions. Branching (tree-in-bud) opacities were common, and bronchiectasis was evident in 54% (16). It has been reported that on pulmonary function testing (PFT), patients with chronic aspiration commonly have restrictive defects and a low diffusing capacity for carbon monoxide (DLCO) (17).

Aspiration is believed to contribute to a number of chronic lung diseases. Bronchiectasis is believed to be caused by aspiration in 4–18% of patients with non-CF bronchiectasis. El-Serag et al. studied 1,980 neurologically normal children with GERD and 7,920 controls. They reported that the odds ratio (OR) for bronchiectasis was 2.3 ($p < 0.0001$), and pneumonia was 2.3 ($p < 0.02$), among children with GERD (18). By contrast, Piccione et al. reported that in 66 patients with bronchiectasis diagnosed in a specialized Aerodigestive Clinic, aspiration-associated bronchiectasis was strongly associated with severe neurologic impairment. Bronchiectasis was also associated with parental report of GER, but not with the results of esophageal impedance studies or prior fundoplication (19). However, in this population with severe neurologic impairment, CRM may have been predominantly due to chronic aspiration of saliva (20), and the findings may be of less relevance to populations with aspiration predominantly due to other causes. In patients with *bronchiolitis obliterans* syndrome post-lung transplant, GERD appears to play an important role in worsening lung function, and lung function improves with fundoplication (21). In idiopathic pulmonary fibrosis, lung function is possibly worsened by GERD, particularly in scleroderma patients, who may also have esophageal dysfunction. In pulmonary fibrosis patients, there is some evidence that medical anti-reflux therapy may slow the decline in lung function (13).

CLINICAL FEATURES OF ASPIRATION

Clinically, the diagnosis of aspiration may be obvious in the case of massive or witnessed choking, but often is under-recognized when due to subclinical microaspiration and misattribution of chronic cough, wheeze, and/or dyspnea.

DIAGNOSING ASPIRATION

Confirming whether aspiration is occurring remains medically challenging. Several tests are available, and they tend to have widely varying reported sensitivity and specificity.

The presence of aspiration is confirmed by lung biopsy showing evidence of a foreign body or foreign body granulomas (*vide supra*), a bronchoscopy demonstrating particulate matter, or when particulate matter is found in the bronchoalveolar lavage (BAL) fluid. Lipid from aspirated food or drinks is ingested by alveolar macrophages, and the presence of lipid-laden macrophages in the BAL has been proposed as evidence of aspiration. The latter may also be quantified as the BAL lipid-laden macrophage index (LLMI). This requires evaluation of 100 macrophages in the BAL, each of which is scored from 0 (no lipid) to 4 (completely opacified). The total is summed and can potentially range from 0 to 400. A value over 100 has been considered as evidence of GERD with aspiration. However, necrosis of alveolar lining cells as a result of severe pneumonia also releases lipid from cell membranes into the BAL. As a result, while the LLMI has "been associated with chronic aspiration" its reported sensitivity varies from 57 to 100%, and its specificity from 57 to 89% (21). Borrelli et al. observed that the LLMI was significantly higher in children with recurrent lung consolidation than in children with asthma ($p < 0.05$), and that the LLMI correlated with the number of reflux and non-acid reflux episodes, and number of episodes reaching the proximal esophagus ($p < 0.01$) on pH-multichannel intraluminal impedance testing. The LLMI also significantly correlated with the number BAL neutrophils ($p < 0.01$) (23). By contrast, Rosen et al. found that in 50 children with a mean age of 6 years, the LLMI was not associated with pH-impedance findings, endoscopic esophagitis, or clinical improvement following fundoplication (24). While BAL pepsin or bile acids have been proposed as markers of aspiration, they require further study (21). Exhaled breath condensate (EBC) was investigated by Fitzpatrick et al. as part of a study of lansoprazole in 110 children with asthma. They found no association between EBC and esophageal pH probe results. Moreover, EBC acidity did not change with lansoprazole and the investigators concluded that EBC does not appear to be useful in the evaluation of the respiratory effects of GERD (25).

Bacterial culture of the BAL fluid may be a surprisingly useful marker of aspiration. Rosen et al. observed that in 46 children with chronic cough or wheezing, with a mean age 74 months, 26% had a positive BAL culture. Cultures grew mainly *Streptococcus pneumoniae* and *Haemophilus influenza*. The presence of a positive BAL culture was predicted by the amount of non-acid reflux or full-column GER on a pH-impedance study, but not a history of pneumonia in previous 6 months. The presence of bacteria in the BAL may also reflect the effectiveness of mucociliary clearance of any aspirated material (26).

In the future, examination of the lower airway microbiome (ribosomal 16 s rRNA ecosystem) may be helpful. The lower airways of healthy people have been reported to have low levels of mainly oral bacteria such as *Prevotella* and *Veillonella* (27), but the microbiome of individuals with chronic aspiration has not been investigated to date.

DETERMINING THE SOURCE OF ASPIRATION

When there is convincing evidence of aspiration, determining its source may be difficult, and different tests may provide conflicting results.

Swallowing dysfunction can be demonstrated by videofluoroscopic swallowing study or, less commonly, fiberoptic endoscopic evaluation. Weir et al. reported that aspiration of thin liquids or post-swallow residue, seen on videofluoroscopic swallowing study, was associated with pneumonia in a broad group of pediatric patients (28). These types of studies have demonstrated that aspiration due to abnormal swallowing is common in EA/TEF patients (29, 30). Esophageal dysfunction can be diagnosed by an upper gastrointestinal (UGI) series or manometry. High-resolution manometry, demonstrating aperistalsis in EA/TEF patients, has been associated with CRM (29). Video manometry, particularly to evaluate a lack of coordination between pharyngeal contraction and relaxation of the upper esophageal sphincter, may also be helpful (31). Recent studies suggesting that laryngeal clefts and vocal cord paresis or paralysis are common in patients with EA/TEF indicate that careful otolaryngologic evaluation of the upper airway should be performed in EA/TEF patients suspected as having aspiration (5, 7). As thoracic vascular malformations may also compromise esophageal function in EA/TEF patients, complete cardiac evaluation of thoracic vessels should also be considered (8). A recurrent or persistent TEF is most often diagnosed by UGI with pull-back study. Many tests are available to diagnose GERD, including UGI, endoscopy, scintigraphy, and impedance/pH probe.

Borrelli et al. used pH-multichannel intraluminal impedance to study 21 children, with a mean age of 4.1 years. They found that 49% of events were non-acid, 74% reached the proximal esophagus, and 80% of the episodes were liquid. The number of reflux episodes, non-acid reflux episodes, and non-acid reflux episodes reaching proximal esophagus were all significantly higher in children with recurrent lung consolidations than in children with asthma ($p < 0.01$) (23). Condino et al. performed these studies in 24 children with asthma and GERD, with a mean age of 33 months. They reported that 51% of events were non-acid. However, there was a low association with symptoms; for example, only 8% of events were associated with cough (32).

Ravelli et al. performed nuclear scintigraphy studies in 51 neurologically normal children with a median age of 6.5 years. GER to the upper 1/3 of the esophagus was detected in 27% of the patients. Delayed gastric emptying (over 90 min) was seen in 53%, and aspiration on a 20-h delayed scan was observed in 49% of children. However, this investigation correlated poorly with other tests. The number of reflux episodes did not differ in

children with normal or abnormal pH studies. Seventy-five percent of the children who had aspiration on the delayed scan had a normal pH study, and few of them had histologic esophagitis. Aspiration was associated with CRM, with aspiration seen in 62% of children with recurrent pneumonia and all the infants with apnea. They felt that the sensitivity of the delayed scan was limited by the relatively short half-life of the technetium (33).

GERD AND ASTHMA

The largest repository of data regarding the association of aspiration with CRM concerns the possible link between GERD and asthma, with over 1,600 studies published. The possible relationship between GERD and asthma is potentially bidirectional, with asthma increasing the risk of GERD, and GERD increasing the severity of asthma. GERD may worsen asthma through a reflex mechanism, with stimulation of vagal nerves in the esophagus by acid, since some of these afferents end in same region of nucleus of the solitary tract where respiratory sensory nerves terminate (34), or through microaspiration, leading to bronchoconstriction and airway inflammation. Non-acid GER may be particularly harmful, as it would likely stimulate airway protective reflexes less. These relationships appear to be complex, with studies showing differing effects of reflux on asthma outcomes. For example, in one study of adults with asthma, omeprazole had no effect on methacholine challenge but did reduce cough sensitivity to capsaicin challenge in the patients who had pH probe-evidence of reflux (35). By contrast, another study observed a correlation between the number of esophageal reflux episodes and airway reactivity as evaluated by methacholine challenge (36).

In a systemic review, Thakkar et al. found that the prevalence of asthma in children with GERD was 13 versus 7% in controls (37). A systemic review in adults noted that the prevalence of GERD, using the Montreal definition, in adults with asthma was 58%, compared to 38% in controls, giving an OR for GERD in adults with asthma of 5.5, and the OR for asthma in patients with GERD was 2.7 (36).

Several studies have evaluated whether GERD is associated with indicators of asthma control. In adults with poor asthma control, abnormal distal or proximal esophageal pH was associated with oral steroid use, and proximal reflux was associated with worse quality of life, but neither was associated with FEV_1, asthma control, or methacholine challenge (38). By contrast, Kwiecien et al. noted that in 66 children with asthma with a mean age 10 years, night asthma symptoms were associated with a longer time spent at night with an esophageal pH below 4 (39).

Multiple studies have examined whether treating reflux improves asthma outcomes, although the results are contradictory. A study of esomeprazole in 828 adults with asthma and a positive GERD score resulted in very small, but statistically significant improvements in FEV_1 and quality of life, but not in peak flow, exacerbations, or symptoms (40). In another, study of 207 adults with asthma and GERD symptoms, lansoprazole improved quality of life and reduced exacerbations needing prednisone, but had no effect on lung function or symptoms (41). In a Cochrane systematic review (mainly involving adults), anti-GERD therapy had no consistent effect on peak flows or symptoms (42). Reducing gastric acidity does not appear to be effective in children or adults with asthma and no GERD symptoms (38, 43).

It is important to recognize that proton pump inhibitors do not treat non-acid GER. Rothenberg and Cowles described a series of 235 children with asthma on prednisone who underwent laparoscopic Nissen fundoplication. Ninety percent reduced or stopped their steroids, 90% of children with night symptoms improved, and in the 56 children who underwent PFTs, FEV_1 improved 26% (44). However, this was a non-controlled, non-blinded study.

In summary, anti-GER therapy appears to improve asthma to some extent in patients with asthma and symptomatic GERD, although the outcomes which improved vary between studies. Some of the variation may be related to differences in how GERD was defined. It is unclear why a treatment effect was seen only in patients with symptomatic GERD.

ASSOCIATIONS WITH RESPIRATORY MORBIDITY IN PATIENTS WITH REPAIRED EA/TEF

Recurrent infection, aspiration, and atopic disease have been associated with CRM in EA/TEF patients. In 68 patients with type C EA/TEF, respiratory complications including recurrent pneumonia were associated with GERD in 74% of patients, with recurrent TEF in 13%, and with esophageal strictures in 10% (45). Recurrent TEF has been associated with cough and with recurrent pneumonia (46). Bronchitis and pneumonia have been associated with dysphagia in 20 children with repaired EA/TEF (47). Shah et al. recently observed that early esophageal stricture formation was associated with recurrent pulmonary infections. GERD was associated with the subsequent performance of an aortopexy to treat severe tracheomalacia (9). A variety of studies have observed that PFT obstructive defects are associated with history of reported GERD (but not results of a 2-h pH probe), as well as choking spells during infancy, and pneumonia during the first 4 years of life (48–50).

Several studies have specifically examined the relationship between GERD and CRM in patients with repaired EA/TEF. However, several of these studies were likely limited by variability in the objective assessment of GERD. In addition, research to date has been retrospective and may underestimate GERD early in life. Peetsold et al. examined the effect of anti-GERD surgery as a marker of past, chronic GERD (51). They reported that neither exercise capacity nor PFT restrictive defects were associated with anti-GERD surgery, but prior surgery was associated with a lower FEV_1. Using prior anti-GERD surgery as a marker of chronic GERD may be problematic. Anti-GERD surgery is clearly performed because of ongoing, incompletely controlled GERD. However, surgery may prevent GERD from leading to CRM. Furthermore, depending on the degree to which esophageal function is impaired, fundoplication may actually worsen aspiration by causing retention of swallowed material in the esophagus, and oropharyngeal aspiration. Malmström found that in 23 adolescent EA/TEF patients, while 78% had a positive histamine challenge (used as a marker of airway reactivity), airway reactivity was not associated with esophageal symptoms, prior fundoplication, the number of previous reported pneumonias,

the results of allergy testing, or physician diagnosis of asthma. Furthermore, airway reticular basement membrane thickening was not associated with gastrointestinal symptoms, esophageal biopsies, atopy, histamine challenge, or exhaled nitric oxide. In addition, PFT restrictive changes were not associated with current esophageal symptoms or past fundoplication (52). Similarly, Legrand et al. found that PFT abnormalities among 57 children with repaired EA/TEF were not associated with GERD symptoms or the results of objective testing, or with prior fundoplication (53). A small study of 26 7-year olds with repaired EA/TEF had similar results, with no association between "esophageal symptoms" and PFT abnormalities, including lung clearance index (as a measure of small airway function). Furthermore, the results of 24-h pH probe were not associated with respiratory symptoms. Olbers et al. also noted that PFT abnormalities in this population could be due to tracheomalacia (54). Pedersen et al. did not find a significant association between abnormalities of esophageal function (determined by endoscopy and pH probe) or a history of recurrent pneumonia, and either obstructive or restrictive PFT defects (55). Sistonen et al. performed histamine challenges in 101 adult patients with repaired EA/TEF. Forty-one percent were positive, and, as expected in individuals with asthma, a positive challenge was associated with atopy or an elevated serum IgE. Unexpectedly, an elevated exhaled nitric oxide was not associated with atopy. While a positive histamine challenge was not associated with esophageal metaplasia on esophageal biopsy, PFT restrictive defects were (56).

Atopic disease, including asthma, may be commoner in EA/TEF patients than in the general population. It is conceivable that chronic aspiration and/or recurrent lower respiratory infection early in life results in persistent airway inflammation and a risk of asthma and other airway diseases later on. In addition to the effects of chronic aspiration, it is possible that altered mucosal immunity in the gastrointestinal tract changes cellular immunity and increases the risk of atopy. Whether asthma in EA/TEF patients is secondary to the effects of aspiration or primary, asthma may cause chronic respiratory symptoms in older patients with EA/TEF. In 334 adult EA/TEF patients, persistent respiratory symptoms were associated with allergies or a family history of allergy (50). In children with EA/TEF and wheezing, 2/3 had a history of atopy (47). Allergies appear to be common in EA/TEF patients. Malmström et al. reported that 15% of children with repaired EA/TEF had allergic rhinitis, and 54% had positive allergy skin tests (52). In adults with repaired EA/TEF, 42% had allergies, 37% had positive allergy tests, and 20% had a high serum IgE. Moreover, these findings were associated with current respiratory symptoms (56). Another smaller study of 28 adults with repaired EA/TEF found that increased airway reactivity, measured using methacholine challenge, was associated with serologic evidence of allergies and with elevated exhaled nitric oxide [generally an indicator of allergic airway inflammation (57)]. However, all of these tests were poorly associated with reported physician-diagnosed asthma (58). By contrast, while Robertson et al. found that methacholine challenge was positive in 48% of 18 EA/TEF patients, it was not associated with symptoms of atopy (59). Similarly, Pedersen et al. did not find that the frequency of allergies (measured by skin prick testing and by serum IgE), abnormal airway reactivity (measured by a mannitol challenge test), or abnormal exhaled nitric oxide differed between EA/TEF patients and a control group being evaluated for GERD (55).

Bronchiectasis is a potentially devastating long-term complication of EA/TEF (22). Using CT scanning, rates of bronchiectasis in EA/TEF survivors may be as high as 27% (4, 55). While neither DeBoer et al. (4) nor Cartabuke et al. (60) examined potential associations with bronchiectasis (59), bronchiectasis in this population has generally been associated with massive aspiration, including patients with gastric or colonic interposition in a selected referral population (22), longstanding GERD (61), massive TEF pouch secretions, trisomy 21 (62), undiagnosed TEF (63), or broncho-esophageal fistula (64, 65).

SUMMARY

In the general population, bronchiectasis has been clearly associated with GERD and cryptogenic organizing pneumonia can result from chronic aspiration. The relationship between GERD and asthma is unclear, with various studies reporting conflicting asthma morbidities associated with GERD. In patients with repaired EA/TEF, GERD has been inconsistently associated with a low FEV_1 and with PFT restrictive defects. Early studies have suggested that aspiration early in life in EA/TEF patients is associated with subsequent CRM. However, in more recent studies, while airway reactivity has been at least inconsistently associated with atopy in patients with repaired EA/TEF, increased bronchial hyper-reactivity has not shown to be associated with GERD. Based on a number of case reports and a small series, there is compelling evidence that bronchiectasis in patients with repaired EA/TEF is typically due to massive, chronic aspiration. The lack of consistent evidence that aspiration leads to CRM in patients with repaired EA/TEF almost certainly reflects the variety of ways in which aspiration can be diagnosed, the retrospective nature of research to date, which may well underestimate the severity and chronicity of prior aspiration events, and the effects of previous treatment of aspiration, such as fundoplication. Ideally, prospective studies will be needed carefully documenting esophageal function and GERD, and subsequent CRM. This would likely be the most effective way of quantifying the extent to which aspiration influences subsequent pulmonary morbidity in this population. Research is also required to determine the best methods of diagnosing aspiration, assessing the effects of aspiration on the lower airway microbiome, and assessing whether altered gastrointestinal mucosal immunity affects atopy in these patients. Given the strong association of aspiration with cryptogenic organizing pneumonia and evidence that restrictive pulmonary defects are relatively common in EA/TEF survivors, evaluation by CT and/or biopsy is needed to determine whether at least some of the restrictive impairments seen in patients with repaired EA/TEF are due to cryptogenic organizing pneumonia.

Until additional data are available, there is a compelling need for long-term follow-up of these patients, ideally by multidisciplinary expert teams, both during childhood *and* during adulthood (4, 66). Respiratory follow-up should include serial PFTs including spirometry, measurement of lung volumes, and, possibly, evaluation of bronchodilator responsiveness (67, 68).

Chest radiography may be useful (59), and exercise testing and methacholine challenge should be considered when clinically indicated. If bronchiectasis is suspected, it is best diagnosed by CT of the chest. When bronchiectasis is confirmed, urgent evaluation of potential causes of aspiration should be carried out. Based on the evidence currently available, patients with repaired EA/TEF who have CRM should be evaluated for clinically significant tracheomalacia, as well as for aspiration due to swallowing dysfunction, GERD, and/or a recurrent or persistent TEF.

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REVIEW
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The Management of Cyanotic Spells in Children with Oesophageal Atresia

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Cyanotic spells, also known as blue spells, dying spells, or apparent life-threatening events, refer to a bluish tone visible in the mucosal membranes and skin caused by an oxygen decrease in the peripheral circulation. Although this decrease may be transient and benign, it may also be indicative of a severe underlying problem that requires immediate intervention. Children with oesophageal atresia (OA) are at risk for a number of coexisting conditions that may trigger cyanotic spells. This current article will focus on the management of cyanotic spells both in children with innominate artery compression and those with tracheomalacia.

Keywords: oesophageal atresia, oesophageal atresia/tracheoesophageal fistula, cyanosis, pediatric, other, tracheomalacia

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INTRODUCTION

Cyanotic spells, also known as blue spells, dying spells, or apparent life-threatening events, refer to a bluish tone visible in the mucosal membranes and skin caused by an oxygen decrease in the peripheral circulation. Although this decrease may be transient and benign, it may also be indicative of a severe underlying problem that requires immediate intervention. If a high level of vigilance is not maintained and appropriate measures are not taken in a timely manner when cyanotic spells are severe and prolonged, they may lead to bradycardia, cardiorespiratory arrest, and ultimately death.

Children with oesophageal atresia (OA) are at risk for a number of coexisting conditions that may trigger cyanotic spells. In an early study (1963), Fearon and Shortreed (1) described episodic reflex apnea as the physiologic mechanism thought to cause these spells and maintained that they were sometimes associated with tracheobronchial compression secondary to a double aortic arch or an anomalous innominate artery. They presumed that reflex apnea was triggered when vagal afferent nerve fibers were stimulated. They also believed that swallowing and other forms of transient intrathoracic pressure increase could trigger a reflex type respiratory arrest (2).

The association between OA and cyanotic spells in children with tracheomalacia has also been recognized for the past several decades (3, 4). Children with OA are at risk for various comorbidities in addition to either innominate artery compression or tracheomalacia. They are prone to a number of conditions such as oesophageal dysmotility with slow transit and risk of bolus obstruction, gastro-esophageal reflux, aspiration, risk of anastomotic strictures and proximal dilatation of the oesophageal and pouch, and diverticulum. They also have high incidence of concurrent airway pathology such as laryngeal cleft and vocal cord paralysis (5).

In view of the well-established clinical associations between OA and both innominate artery compression and tracheomalacia, our discussion will focus on the management of cyanotic spells in children with these conditions.

INNOMINATE ARTERY COMPRESSION

Gross and Neuhauser were the first group to describe anterior tracheal compression by an innominate artery arising on the left side of the trachea (6). The innominate artery normally crosses the anterior aspect of the trachea from left to right about 1 cm above the carina (7, 8). When it arises more downstream along the aorta on the left, it may lead to anterior compression of the tracheal cartilages. Three other explanations (9) accounting for tracheal compression have also been described. The innominate artery may be tauter than normal, leading to compression of the trachea. Also, tracheal cartilages may be unusually compliant and more easily compressed. Finally, dilation of other structures such as the heart, esophagus, or thymus can cause mediastinal crowding, thus causing the innominate artery to compress the trachea (9). In all of these clinical scenarios, the innominate artery creates an indentation in the trachea. Although the indentation is visualized endoscopically in many children, it is clinically important only when it significantly compresses the trachea (2).

Symptoms related to innominate artery compression appear during the early months of life and may range from exceedingly subtle to obvious. In the former clinical setting, the problem may be misdiagnosed and treated for years as resilient asthma or croup. Recurrent pneumonia and bronchitis are also a possible presentation of innominate artery compression. These patients are prone to recurrent chest infection because they have difficulty in passing secretions through the narrowed segment of the trachea (10) Moreover, during coughing, the tracheal lumen may be collapsed at this site, leading to further entrapment of secretions (10). Cyanotic episodes generally begin after 2 to 3 months of age and characteristically occur during or after a meal or during coughing or crying (3, 11, 12). During feeding, bolus transfer compresses the posterior wall of the trachea at the malacic site (13). The most dramatic consequence is cardiorespiratory arrest (3, 4). These events are often unpredictable and can occur without other respiratory symptoms.

TRACHEOMALACIA

Tracheomalacia (either primary or secondary) is the most common congenital tracheal anomaly, and most children are either asymptomatic or minimally symptomatic. This anomaly is characterized by an abnormally compliant trachea displaying dynamic collapse during the respiratory cycle or when coughing. Either the entire trachea or specific portions of the trachea (i.e., the anterior and/or posterior walls) can be involved. Tracheoesophageal fistula (TOF) is a commonly associated abnormality (4).

Although tracheomalacia can either be the result of abnormal embryologic development of the trachea or occur following the repair of OA and TOF, these two etiologies are not mutually exclusive and may coexist. When the cause is primarily embryologic, it is the result of a disproportion between the cartilaginous and membranous components of the trachea. When tracheomalacia is observed in children with OA after TOF repair, the trachea retains an abnormal configuration, with a wide membranous portion rather than the normal C-shape (12). This predisposes to collapse. The interval between OA repair and the appearance of respiratory symptoms could be less than 30 days (8). As with vascular compression, these symptoms may range from exceedingly subtle to obvious; in the former clinical scenario, it can be misdiagnosed and treated for years as resilient asthma or croup (**Table 1**).

There is no accepted classification of tracheomalacia; however, classifying this anomaly as mild, moderate, or severe assists with clinical management. Mild tracheomalacia is characterized by respiratory difficulties associated with infectious processes such as croup or bronchiolitis. Moderate tracheomalacia typically presents with stridor, wheezing, recurrent respiratory infections, and cyanosis associated with infection. Severe tracheomalacia is characterized by upper airway obstruction, trapping of secretions with pulmonary infection, cyanotic spells, and sometimes death. Shah et al. reported that patients with severe tracheomalacia were significantly more likely to experience cyanotic spells, with an odds ratio of 180 (14). Although mild tracheomalacia is watched expectantly and anticipated to improve with time (15), more severe symptoms warrant intervention. When cyanotic spells occur, prompt intervention is essential. Events such as infections, general anesthesia, or extubation may precipitate and exacerbate symptoms (16, 17).

Cyanotic episodes generally begin after 2–3 months of age and characteristically occur during or after a meal or during coughing or crying (4, 12). Feeding and coughing increase intrathoracic pressure, leading to further tracheal compression (12). As in children with innominate artery compression, the most dramatic consequence of cyanotic spells in children with severe tracheomalacia is cardiorespiratory arrest (4, 12).

OESOPHAGEAL ATRESIA AND TRACHEOESOPHAGEAL FISTULA

Respiratory symptoms are common in patients with repaired OA and TOF, and tracheomalacia that precipitates life-threatening cyanotic spells has been reported to be the most frequent serious problem following OA and TOF repair (4). It is, however, difficult to distinguish between symptoms caused by tracheomalacia and those caused by problems such as recurrent pneumonia and aspiration (18). Although tracheomalacia is reported to be present in 75–90% of pathologic specimens, it is clinically significant in only 10–30% (19, 20), with the lower half of the trachea being affected in the region of the TOF, most likely due to the malformation and deficiency of the tracheal wall at that site (21). Patients with OA without TOF often have a normal trachea and no airway symptoms (22).

TABLE 1 | Symptoms of tracheomalacia.

Asymptomatic
Dyspnea (at rest or with exertion)
Cough (brassy type)
Sputum retention
Wheezing/stridor
Recurrent pulmonary infection
Bronchitis
Cyanotic spells

DIAGNOSTIC EVALUATION

All children with OA who have a cyanotic spell require prompt diagnostic assessment (**Figure 1**). Initially, it is essential to rule out a missed or recurrent TOF. The latter occurs in approximately 10% of patients (21). Other airway conditions such as laryngeal cleft, vocal cord pathology, tracheal diverticulum/pouch should be evaluated and treated accordingly. Flexible or rigid bronchoscopy is the gold standard of investigations. Bronchoscopy provides valuable information regarding vascular compression and tracheal collapse. It is performed under light general anesthesia with the child spontaneously ventilating.

Flexible and rigid bronchoscopy are complementary diagnostic tools, with each having advantages and disadvantages (**Table 2**). At Cincinnati Children's Hospital, experts on the pulmonary and otolaryngology team evaluate the airway with both flexible and rigid bronchoscopes. We perform rigid endoscopy with a telescope only rather than through a rigid ventilating bronchoscope to lessen distortion of anatomy. Flexible bronchoscopy requires less sedation than rigid endoscopy and allows clinicians to appreciate dynamic collapse while the child is spontaneously breathing. In smaller or less specialized pediatric centers, rigid bronchoscopy may be more readily available and is therefore a widely used alternative. The rigid telescope is often less obstructive than the flexible scope and may be better tolerated by the patient; however, it requires a deeper level of anesthesia and may falsely stent the anterior or posterior tracheal wall, thus obscuring visualization (**Figure 2**). In both rigid and flexible endoscopic approaches, adequate anesthesia is crucial. If anesthesia is too light, it may induce vigorous respiratory efforts and cause more pronounced malacia. If anesthesia is too heavy, it may mask malacia because the patient is not breathing independently, thus limiting the extent of dynamic collapse. Tracheomalacia can also be masked by positive pressure during insufflation. When performing an endoscopy, the clinician should estimate the percentage of airway collapse. Generally, an anteroposterior collapse of 75% with a cough or expiration is considered to be severe (4). In children with innominate artery or other vascular compression, anterior or anterolateral extrinsic pulsatile compression of the airway can be visualized (9).

Imaging studies provide useful information regarding tracheal anatomy and compression of the trachea. High-resolution chest computed tomography (CT) with contrast and magnetic resonance imaging (MRI) are valuable in delineating innominate artery or other vascular compression or cartilaginous anomaly (23). When vascular compression is suspected, the imaging test of choice is MRI, as it also better demonstrates mediastinal vasculature and lower airway anatomy (9). Chest CT can be combined with 3D reconstruction and unlike MRI may not require sedation to acquire the images if the child is compliant. This allows exploration of regions inaccessible with endoscopy, such as areas distal to severe luminal obstruction. Similar to endoscopy, CT and MRI images are highly dependent on the level of sedation and respiratory effort of the patient.

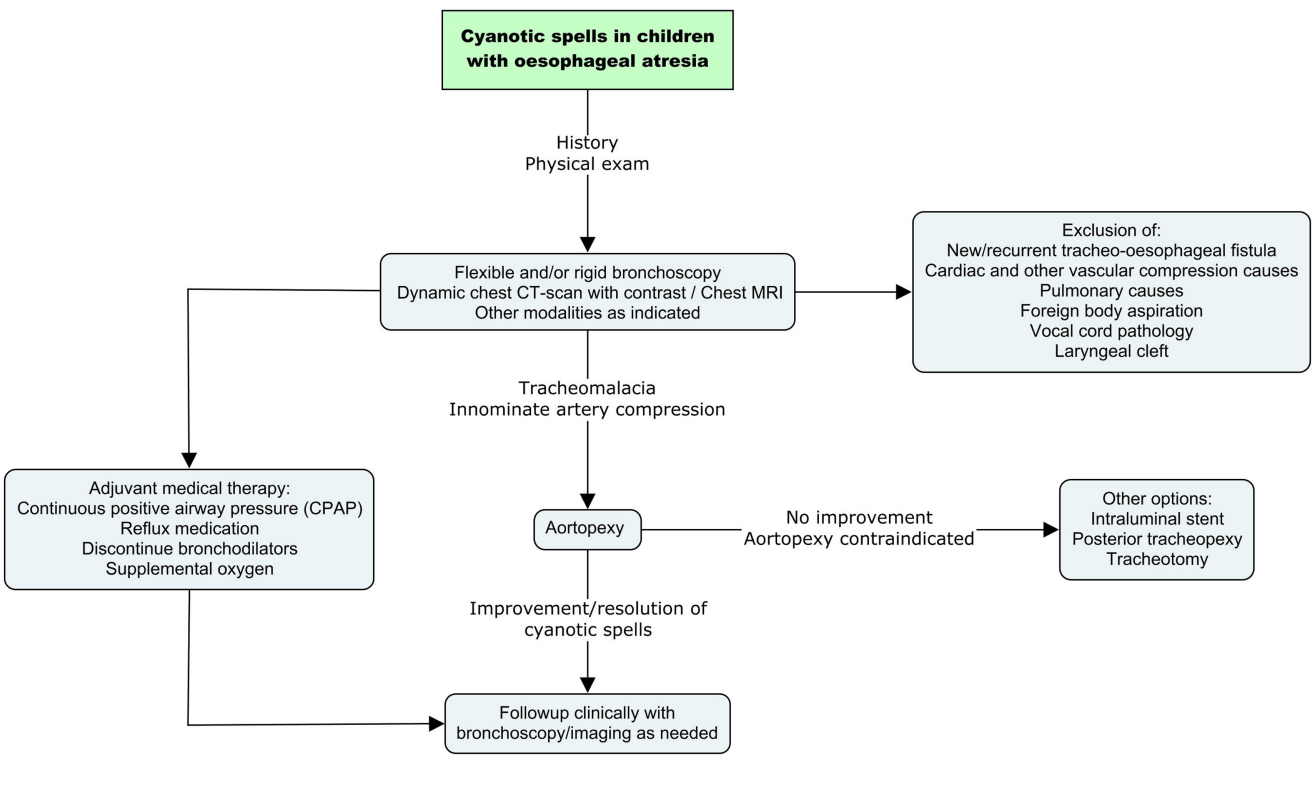

FIGURE 1 | **The management of cyanotic spells in children with oesophageal atresia**.

TABLE 2 | Confounding factors associated with the bronchoscopic assessment of tracheomalacia.

Factors that underestimate the severity of tracheomalacia	• Stenting effect of rigid bronchoscopy • Positive pressure • Paralytic agents • Patient is too heavily sedated
Factors that overestimate the severity of tracheomalacia	• Engaging the suction channel during flexible bronchoscopy • Patient is too lightly sedated

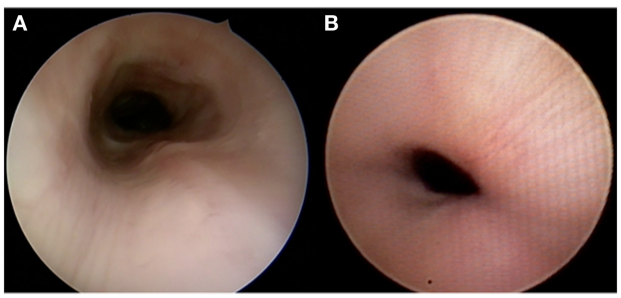

FIGURE 2 | Different appearances of tracheomalacia as seen with rigid bronchoscopy using a telescope only (A) and flexible bronchoscopy (B).

Dynamic CT scan is a newer modality that provides dynamic images of the airway during the respiratory cycle. Images are taken when the patient is breathing or coughing. The patency of the lumen of the tracheobronchial tree is evaluated. The normal decrease in caliber during tidal breathing in children is around 30%. A collapse ranging from 30 to 75% may be monitored, depending on the severity of clinical symptoms (24). A collapse of more than 75% is likely to be considered significant and may require intervention (24). Dynamic CT can be performed without sedation and without contrast; the radiation dose is equivalent to that associated with a high resolution CT scan.

Airway fluoroscopy has also long been used to diagnose vascular compression and tracheomalacia, and it remains an alternative when the previously discussed diagnostic modalities are not available. However, a small study ($n = 22$) published in 2012 demonstrated that fluoroscopy has poor sensitivity (23.8%) but high specificity (100%) when used as a diagnostic tool for tracheomalacia (25). It is primarily used to diagnose OA or TOF. To assess these two conditions, fluoroscopy and/or oesophagogastroscopy could provide valuable information along the other previously described investigations about the site of the fistula and the extent of the atresia (26). Complete esophageal investigation could also include manometry and pH monitoring when judged relevant (26, 27).

A chest X-ray or high-resolution CT of the chest can be performed to assess the impact of recurrent infections, chronic aspiration, or the possible presence of a mediastinal mass. Pulmonary function testing (PFT) is used to show a reduction in peak expiratory flow and is typically abnormal in patients with tracheomalacia or innominate arterial compression; nevertheless, this is not a finding specific to tracheomalacia or innominate artery compression. PFT can be difficult to perform and interpret in young children who are uncooperative and has a positive predictive value of only 74% for tracheomalacia (9). Overnight polysomnography may be useful to quantify the impact of the obstruction and to plan decannulation for children in whom a tracheotomy has been placed (28).

MANAGEMENT

Cyanotic Spells Secondary to Innominate Artery or Other Vascular Compression

When cyanotic spells are secondary to innominate artery or other vascular compression, a number of medical and surgical management options are currently used. Prior to surgical management, children with cyanotic spells must be optimized. Pneumonia and bronchitis should be managed with a course of antibiotics. If necessary, supportive continuous positive airway pressure (CPAP) and oxygen should also be used.

The mainstay of surgical management is aortopexy (29). In the setting of anterior wall tracheal collapse, this procedure can be performed either thoracoscopically or by using an open approach (**Figure 3**). The goal of this operation is to treat the airway collapse by ventral suspension of the trachea (30). Sutures are placed in the pericardial reflection over the aortic root and in the adventitia of the aortic arch and then tied to the underside of the sternum. As the aorta is pulled forward, fibrous attachments between the aorta and the trachea ensure that the front wall of the trachea is pulled forward, opening the lumen. Preoperative imaging enables the clinician to evaluate the size of the thymus and determine the amount of space available to move the aorta forward. When performed by thoracoscopy or left lateral thoracotomy, the surgery consists of thymectomy and subsequent minimal dissection of the lateral and posterior aorta prior to suspending the aorta to the posterior sternum. Intraoperative endoscopy is valuable and allows the surgeon to note improvement of the airway lumen. However, the endoscopic appearance of the trachea may not immediately change and the trachea may appear to be relatively malacic even several months after surgery (31). Complete response rates vary; however, they are reportedly as high as high as 100%, depending on the definition of response (32).

Although both reimplantation of the innominate artery and ligation and division of the innominate artery have historically been described, they are rarely performed. Literature pertaining to these procedures is scant, and success rates are not as high as those achieved with aortopexy (29). Management of other vascular compression such as double aortic arch and vascular ring require specific treatment. This includes various surgical techniques, primarily surgical division of these anomalies (33). The placement of intratracheal stents is not advised.

Cyanotic Spells Secondary to Tracheomalacia

Once a bronchoscopic assessment has been performed, the clinician should know the severity and location of the malacia, particularly the possible presence of associated bronchomalacia,

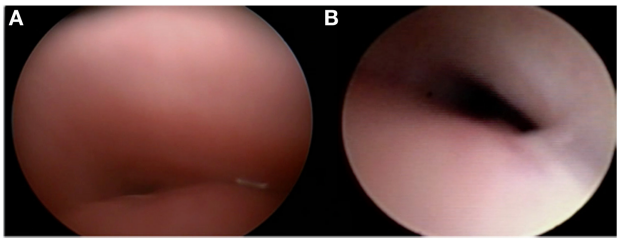

FIGURE 3 | Tracheomalacia before (A) and after aortopexy (B).

and be able to determine whether positive pressure support improves the malacia (34).

The same preoperative medical options described for innominate artery compression are used to address cyanotic spells in children with tracheomalacia. It is, however, important to note that management is symptom driven, not based on bronchoscopic appearance (34). When CPAP is specifically indicated, a tracheostomy may be required. Bronchodilators are not indicated, as they decrease posterior wall rigidity and may exacerbate tracheomalacia. If used, however, they must be discontinued prior to surgery. The use of airway smooth muscle stimulants such as bethanechol are sometimes helpful (35). Gastroesophageal reflux is commonly seen in children with tracheomalacia. Treatment with a proton pump inhibitor is an essential part of preoperative optimization (36). Other options include H2 antagonists, low-dose erythromycin, and fundoplication for refractory cases (37).

Surgical therapy depends on the area affected (anterior and/or posterior wall) and its location (extrathoracic trachea versus intrathoracic trachea). Surgical interventions that should be considered include aortopexy, intraluminal stenting, tracheotomy, posterior tracheopexy, external scaffold, and cartilage grafts. Regardless of the intervention, parents should be made aware of the possibility that surgery may not result in a complete response. For those cases, parents should undergo further counseling and basic life support training to decrease anxiety. Moreover, children may benefit from various interventions, such as texture modification with pacing and proper positioning during feeding, use of annual influenza vaccination, chest physiotherapy, reduction in childcare attendance, no exposure to passive smoking, and maximization of anti-reflux measures including fundoplication if appropriate (38).

Aortopexy

Aortopexy (described above) represents the first line of treatment. In the case of anterior wall tracheal collapse, this procedure can be performed either thoracoscopically or by using an open approach. It is ideally suited for children with isolated symptomatic tracheomalacia that is most severe in the mid-tracheal region. It is not appropriate if severe bronchomalacia coexists, as it would not resolve distal collapse. Preoperative imaging allows evaluation of the size of the thymus and determination of the extent of space to move the aorta forward. When performed by thoracoscopy or left lateral thoracotomy, the surgery consists of thymectomy with subsequent minimal dissection of lateral and posterior aorta prior to suspending the aorta to the posterior sternum. Intraoperative endoscopy is valuable and allows the surgeon to visualize improvement of the airway lumen. However, as stated previously, the endoscopic appearance of the trachea may not change immediately. Postoperative recurrence rates necessitating revision range from 10 to 25% (30). Overall, few complications have been reported and the operation is usually well tolerated.

Intraluminal Stenting

Intraluminal stenting for tracheomalacia should be reserved for highly selective cases (39) and is considered a last resort under special circumstances. This approach should be avoided in children with tracheomalacia and concurrent bronchomalacia since stenting of the distal bronchus is difficult and rarely successful. Stenting can be either temporary or permanent and a large variety of stents exist. Intratracheal metal stents may be an appropriate choice as a temporizing measure in that they expand enough to grip but not integrate with the mucosa. Ideally, they should be removed within a few weeks. Silicone stents are also a temporary measure and their use is limited to older children. There are reports of migration if not secured appropriately, creation of intraluminal biofilm leading to infection, and granulation tissue at either end of the stent (40, 41). If available, biodegradable airway stents may offer a better option, as they do not require removal and spontaneously disintegrate with time. Although data regarding their use are scant, no major complications have been reported to date (42).

Tracheotomy

Although tracheotomy is not curative and has inherent risks in a child, it may be used as a temporizing measure with the expectation that improvement will occur over time. When a tracheotomy is placed, the customized inner shaft length must bypass the malacic segment of the trachea; this sometimes requires a cannula that is specifically fashioned for an individual patient. If necessary, CPAP and oxygen can be provided through the cannula. In older children in whom the tracheomalacia has improved, it generally takes longer to wean and decannulate than in children without a history of malacia. Moreover, the tracheotomy itself may create an area of tracheomalacia and suprastomal collapse by weakening the cartilage where it was previously inserted.

Other Options and Experimental Modalities

Posterior tracheopexy, a technique developed at Boston Children's Hospital, has been reported to stabilize the posterior membrane (43). This procedure can be performed with aortopexy to synergistically relieve anterior tracheal compression. In children with significant tracheomalacia associated with OA and/or TOF, the main component of the airway collapse is often the posterior tracheal membrane causing the posterior trachea to protrude into the tracheal lumen during exhalations—thus resulting in airway obstruction (**Figure 4**) (44). This technique can be performed concurrent with esophageal surgery.

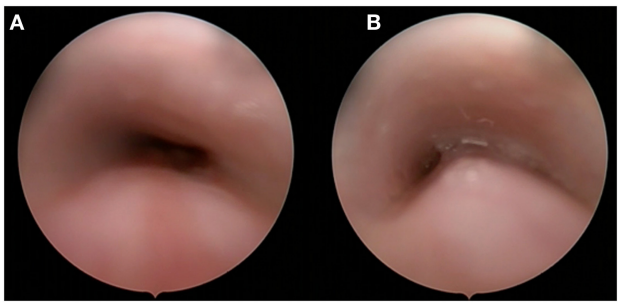

FIGURE 4 | Rigid endoscopy with telescope only at inspiration (A) and expiration (B).

Although extratracheal scaffold stents have been studied, they are rarely used because they will not grow and cannot be expanded or easily removed. Cartilage grafts, which can replace the weaker area of the trachea, are also rarely used (44). In addition, several projects using 3D printing of the trachea have been undertaken (45), though few have yielded results consistent with acceptable clinical standards.

POSTOPERATIVE FOLLOW-UP

The fact that bronchoscopy early in the postoperative period may not reveal a significantly different appearance of the trachea cannot be overemphasized. Similarly, in some children, more time is required for symptom improvement. Patience is paramount and follow-up encompassing observation of clinical improvement and serial bronchoscopy or CT scans is essential. Some patients may present severe tracheomalacia on exams, but have virtually no signs and symptoms.

After surgical intervention, tracheomalacia is considered clinically significant when a patient has recurrent pneumonia, recurrent hospitalizations for airway issues, or persistent cyanotic spells. In this setting, revision surgery may be necessary.

CONCLUSION

Cyanotic spells represent a potentially life-threatening condition. For patients with OA and TOF that was previously repaired, the possibility of a recurrent or missed TOF should be eliminated. Primary etiologies of cyanotic spells include severe tracheomalacia and innominate artery compression. Investigations should minimally include an endoscopic exam with flexible and/or rigid bronchoscopy. Imaging studies such as MRI with contrast can help to determine mediastinal anatomy and the presence of a vascular anomaly. Multiple medical and surgical options exist and must be promptly initiated to avoid serious consequences of these cyanotic spells.

AUTHOR CONTRIBUTIONS

MB, AC, and RC: writing, revision, editing, and review of literature.

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REVIEW
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Update on Foregut Molecular Embryology and Role of Regenerative Medicine Therapies

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Esophageal atresia (OA) represents one of the commonest and most severe developmental disorders of the foregut, the most proximal segment of the gastrointestinal (GI) tract (esophagus and stomach) in embryological terms. Of intrigue is the common origin from this foregut of two very diverse functional entities, the digestive and respiratory systems. OA appears to result from incomplete separation of the ventral and dorsal parts of the foregut during development, resulting in disruption of esophageal anatomy and frequent association with tracheo-oesophageal fistula. Not surprisingly, and likely inherent to OA, are associated abnormalities in components of the enteric neuromusculature and ultimately loss of esophageal functional integrity. An appreciation of such developmental processes and associated defects has not only enhanced our understanding of the etiopathogenesis underlying such devastating defects but also highlighted the potential of novel corrective therapies. There has been considerable progress in the identification and propagation of neural crest stem cells from the GI tract itself or derived from pluripotent cells. Such cells have been successfully transplanted into models of enteric neuropathy confirming their ability to functionally integrate and replenish missing or defective enteric nerves. Combinatorial approaches in tissue engineering hold significant promise for the generation of organ-specific scaffolds such as the esophagus with current initiatives directed toward their cellularization to facilitate optimal function. This chapter outlines the most current understanding of the molecular embryology underlying foregut development and OA, and also explores the promise of regenerative medicine.

Keywords: esophageal atresia, tracheo-esophageal fistula, foregut development, stem cell, tissue engineering, enteric nervous system

INTRODUCTION

OA affects approximately 1 in 3,500 live births (1). Surgical correction aims at reconstituting gut continuity and disrupting the connection between the digestive and respiratory systems but despite considerable surgical expertise, including the introduction of minimally invasive approaches, the prognosis remains guarded and quality of life throughout childhood and adolescence poor. Affected

children and adults continue to suffer from severe gastroesophageal reflux (GER), esophagitis, dysphagia, and esophageal dysmotility as well as poor weight gain together with chronic respiratory infections, tracheomalacia, and decreased exercise tolerance (2, 3). Although definitive surgery is carried out early in life, children with OA often require further interventions such as esophageal dilatations.

Surgically, OA is typically classified in two main groups according to the distance of separation between the two esophageal pouches: long gap OA and non-long gap OA. The most used definition of long gap OA is a gap greater than two to four vertebral bodies or 4–6 cm in length, although others have defined it as the inability of joining the esophagus at the first surgery with the result that there has been no unanimous definition for the two groups (4). In the current issue, the International Network of Esophageal Atresia has proposed that any OA that has no intra-abdominal air should be considered as long-gap (see the article by Van Der Zee et al.).

While other classifications are available and discussed in other articles of this special edition, the authors believe that distinguishing long gap OA from other forms is therapeutically important. In this group of patients, repair can present a significant surgical challenge and an esophageal replacement is often used. This can include gastric transposition (often called "gastric pull-up") (5), colonic (6), or jejunal interposition (7). Such interventions are generally reliant on the position and length of the remaining native esophagus. During gastric pull-up procedures, the entire stomach including its vascular supply is moved into the mediastinum and a pyloroplasty is usually performed in an attempt to avoid delayed gastric emptying (8). An esophageal substitute can also be created from the larger curvature of the stomach, without moving the stomach itself [gastric tube esophagoplasty (9)]. In other cases, either jejunum or colon is used as substitute, with sections of these organs moved together with their own vasculature (6–8). More recently, closure of the gap by mechanical lengthening *via* external traction has been attempted by several surgeons (10–12), with Khan et al. reporting preservation, in terms of thickness, of the mural layers of the esophagus after this treatment (13).

Despite these efforts a definitive therapy for OA has yet to be developed. Such efforts have been halted somewhat by a failure in determining the precise etiopathogenesis of OA in human patients. Even with advances in genetic diagnostics, the genetics of OA represents a challenge, as the condition is frequently associated with malformations in other organs, especially congenital defects of the heart and of other endodermal organs. For instance, VACTERL syndrome is characterized by the involvement of defects in at least three body systems from the vertebral, anorectal, cardiovascular, tracheal, esophageal, renal, and limb systems. Tracheo-esophageal fistula (TOF) has been reported to be variably associated with this syndrome in between 50 and 80% of cases (14–16). There is, however, emerging evidence of an important role for genetic factors in the molecular specification of foregut development. Significant evidence has been garnered from multiple transgenic animal models, which are beginning to shed light on possible dysfunctional mechanisms resulting in OA ± associated TOF, which may have translational consequences for clinical diagnostics in human OA.

GROSS DEVELOPMENT OF THE FOREGUT: MODELS FOR THE PATHOGENESIS OF OA/TOF

The gastrointestinal (GI) tract is a complex physiological system comprising the hollow organs of the digestive system (pharynx, esophagus, stomach, intestine, and colon), usually termed the "gut" and the GI tract derivatives (thyroid, thymus, parathyroid, lungs, liver, and pancreas). Throughout the GI tract, each region exists as a sophisticated multi-layered system consisting of a mucosal layer, neural plexuses, and a number of muscle layers. Developmentally, all three germ layers participate in the formation of the gut. The endoderm and mesoderm form the epithelial layer and muscle layers, respectively, with the ectoderm forming the various neural plexuses present throughout the GI tract termed "the enteric nervous system." Initially, the embryonic gut develops as a result of cephalocaudal and lateral embryo folding and incorporation of the endoderm-lined yolk sac. This leads to the formation of two blind-ending endodermal invaginations at the anterior and posterior ends of the embryo, which fuse to give rise to the primitive gut. This primitive gut structure subsequently undergoes significant patterning along the anterior–posterior axis and is delineated into three main areas: the foregut (esophagus and stomach), midgut (small intestine), and hindgut (colon) (17). Anatomically, the foregut can further be divided into two portions, the anterior and posterior foregut, with the former giving rise to the esophagus, trachea, and lungs and the latter to the stomach, pancreas, and liver.

Of particular interest to the development of the foregut is the common origin of both the digestive and respiratory systems. Despite their differing function, the digestive and respiratory systems share a common embryonic origin, deriving from the developing anterior foregut. In mouse, between embryonic (E) days 9.5 and 11.5 (equivalent to weeks 4–6 in human gestation), a compartmentalization process takes place with the formation of the respiratory diverticulum (lung buds) from the ventral anterior foregut endoderm and the gradual separation of the ventral respiratory diverticulum from the dorsal anterior foregut by the esophagotracheal septum (**Figure 1**). This process ultimately results in the development of two independent and separate systems that will form the trachea and the esophagus (17).

The molecular processes that lead to compartmentalization, however, are not fully understood at present, and three main models have been proposed: the Outgrowth model (18, 19), the Watershed model (20), and the Septation model (21, 22).

The Septation model, which is currently the most accepted model of foregut development, suggests that lateral ridges of thickening epithelium, along the dorsoventral midline, make contact across the lumen and fuse together, forming the esophagotracheal septum. Subsequently, this septum moves rostrally to separate the trachea and esophagus (21). Definitive affirmation of this model has been hampered by the paucity of available data on the development of the lateral ridge.

According to the Outgrowth model, the trachea sprouts from the primitive foregut and elongates forming the respiratory tube from the larynx to the lungs, while the foregut itself differentiates

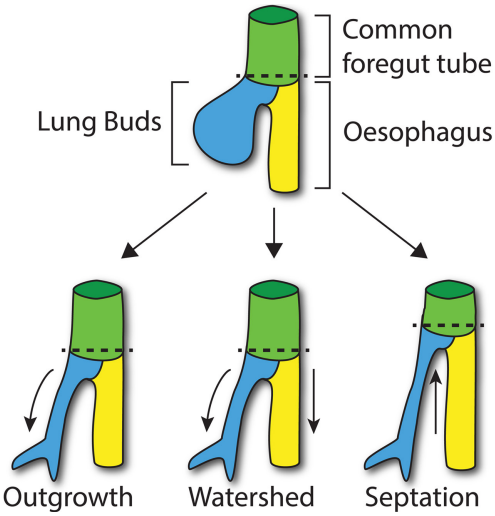

FIGURE 1 | Compartmentalization of the foregut. At E9.5 in the mouse, the lung buds start to arise from the common foregut tube (dashed line; top). According to the Outgrowth model (bottom left), the trachea extends from the foregut tube at the level where lung buds develop (curved arrow). The Watershed model suggests that both developing trachea and esophagus elongate (arrows) from the diverging point (dashed line; middle). According to the Septation model (bottom right), a septum is formed from lateral ridges of mesenchyme, which moves up along the longitudinal axis of the common foregut tube separating the trachea and esophagus (arrow).

into the esophagus (18, 19). By contrast, the Watershed model is based on the concept that a mesenchymal septum blocks elongation at the dorso/ventral midline of the foregut, while both trachea and esophagus elongate on the side (20). However, these two models are not supported by any scientific data. Both models postulate the presence of regions of increased proliferation, which has not yet been proven. For example, in the first scenario, a proliferation "hot-spot" would be expected where the trachea buds from the foregut. Furthermore, these models assume that the common foregut does not elongate while the compartmentalization takes place. Recent data however appear to suggest that the foregut tube actually decreases in length during the compartmentalization process (23). These findings taken together with genetic specification studies of the ventral foregut (24) lend weight to the Septation model.

MOLECULAR SPECIFICATION OF FOREGUT IN DEVELOPMENT AND IMPLICATIONS FOR OA/TOF

During gut development, many molecular pathways control and determine its regional specification. Of critical importance to the establishment of regional specification is the presence of retinoic acid (RA), a derivative of Vitamin A, along the anterior–posterior axis in a concentration-dependent manner, whereby the pharynx is exposed to little RA and the colon to highest concentration of RA (**Figure 2**) (25). This RA gradient induces the expression of various transcription factors in different regions along the gut tube, thus specifying each region in turn. Despite

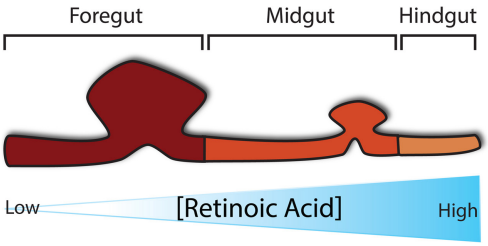

FIGURE 2 | Regional specification of the developing gut. Specification of the developing gut is determined initially by a concentration gradient of retinoic acid along the anterior–posterior axis.

the fact that fetal vitamin A deficiency in humans has not been associated with OA/TOF, it has been reported that mice deficient in RA signaling develop foregut compartmentalization defects (26–28). In particular, the absence of retinoic acid receptors, specifically in mice lacking either all RARA isoforms and RARB2 or all RARB isoforms and RARA1, seems to block the foregut compartmentalization process, leading to the development of an undivided foregut with respiratory epithelium (28, 29). The role of RA in foregut development, along with its importance for pancreatic specification (30), has also been implicated in a mouse model that lacks RA-synthesizing retinaldehyde dehydrogenase 2 (*Aldh1a2*), which results in embryonic death at around E10.5. These mice, if rescued with a short dose of RA, reach birth but develop similar foregut defects together with other cardiovascular anomalies (31). In terms of foregut development, *Sox2* and *Pdx1* expression appear to be vital signaling components for specification of the esophagus and of the stomach and pancreas, respectively (30, 32, 33).

In addition, dorsoventral specification, at the molecular level, in the foregut endoderm may help explain how the compartmentalization process of the trachea and esophagus occurs (**Figure 3**). Specifically, the dorsal foregut endoderm expressing Sox2 gives rise to the esophagus, while the ventral foregut endoderm expressing the transcription factor Nkx2.1 (34) forms the trachea. Both *Sox2* and *Nkx2.1* seem to be crucial factors involved in foregut separation as revealed in transgenic mouse models. *Nkx2.1* null mice display incomplete foregut compartmentalization, resulting in a condition similar to tracheal agenesis with the lungs directly connected with the foregut, ultimately resulting in respiratory failure (34). The exact role of *Sox2* has been more difficult to determine as complete *Sox2* loss-of-function results in embryonic death pre-gastrulation (35). However, investigations using hypomorphic and null alleles of *Sox2* demonstrate that reduction in *Sox2* levels results in an OA with TOF phenotype 60% of the time (36). Moreover, this TOF phenotype displays respiratory characteristics, such as endodermal expression of *Nkx2.1* and the presence of cartilage (36). Therefore, it is clear that these two genes are necessary for organ specification of trachea and esophagus, but their specific role in the compartmentalization process is not proven (37).

Several signaling pathways determine the dorso/ventral patterning of *Sox2* and *Nkx2.1*. On the ventral side of the foregut, NKX2.1 protein expression is established by the production of

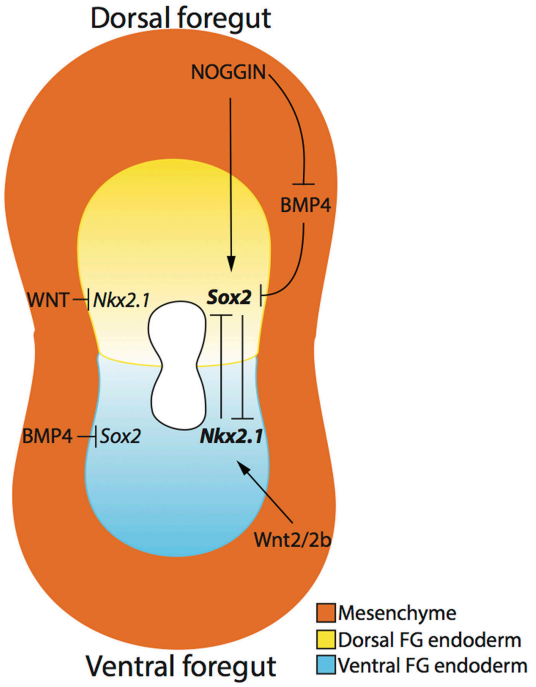

FIGURE 3 | Dorsoventral patterning of the developing foregut endoderm. The dorsal (yellow) and ventral (blue) endoderm express *Sox2* and *Nkx2.1*, respectively. NOGGIN, produced by the surrounding mesenchyme (orange), regulates the expression of *Sox2* in the dorsal foregut endoderm by directly activating *Sox2* expression and indirectly inhibiting BMP4, which in turn inhibits *Sox2*. Ventrally, Wnt2/2b signaling activates the expression of *Nkx2.1* in the ventral foregut endoderm, and WNT signaling also inhibits *Nkx2.1* expression in the dorsal foregut endoderm. The mutual inhibition activity of *Nkx2.1* and *Sox2* create an expression gradient of these two genes, thereby allowing the separation of the two organs.

BMP4 from the surrounding ventral mesenchyme, which acts through the BMP receptors BMPR1a, b in the ventral endoderm. If BMP4 is not produced in the mesenchyme or the endodermal receptors BMPR1a, b are absent, respiratory determination of the foregut will not proceed and tracheal agenesis may occur (38, 39). In this situation, *Sox2* expression appears to expand along the ventral aspect of the foregut, suggesting that BMP signaling is important for repressing ventral *Sox2* expression (37). Using a conditional knockout model of *Bmpr1a, b*, Domyan et al. demonstrated that subsequent suppression of *Sox2* can rescue *Nkx2.1* expression and the tracheal agenesis phenotype, suggesting that BMP signaling does not play a role in *Nkx2.1* specification, but rather in *Sox2* repression (38).

The BMP pathway is also important for dorsal foregut endoderm determination. More specifically, BMP ligands, produced in the ventral foregut mesenchyme, are counterbalanced by a BMP antagonist, NOGGIN, secreted by the dorsal foregut mesenchyme and the notochord (37). NOGGIN binds BMP4 to suppress BMP signaling in the dorsal endoderm (40), therefore allowing the expression of SOX2. Indeed, reduction in BMP antagonism causes OA/TOF as demonstrated by a 75% incidence of OA/TOF in *Noggin* null mutant mice (41). However, Fausett et al. have shown that *Noggin* is not critical for the dorso/ventral patterning of the foregut, which will express *Sox2* and *Nkx2.1* in the absence of *Noggin* as demonstrated *via* investigation of *Noggin* null mice (42).

The initial endodermal patterning of the foregut is subsequently stabilized by interactions between the endoderm and visceral mesoderm adjacent to the gut tube. This interaction is initiated by sonic hedgehog (SHH), a member of the Hedgehog family of morphogens expressed by the endoderm along the length of the gut (43, 44), which subsequently upregulates various transcription factors that are regionally expressed in the visceral mesoderm. These include homeobox-containing transcription factors (*Hox* genes) that are crucial for the morphogenesis and cytodifferentiation that determines structure along the length of the GI tract (44).

Shh ligand acts *via* binding to its receptor and through GLI1, 2, and 3 activating the transcription of target genes (45). For this reason, any deficiency in the downstream SHH pathway can cause disruption, mild to severe, in foregut development. For example, *Gli2* null mice do not exhibit severe problems, with only mild lung defects and hypoplastic trachea and esophagus. By contrast, $Gli2^{-/-};Gli3^{+/-}$ mice present with a more severe lung phenotype including delayed or incomplete separation of the trachea and esophagus (46). Moreover, hedgehog signaling seems to be critical in foregut compartmentalization as demonstrated by the development of abnormal esophageal and tracheal phenotypes in *Shh* null mice. In these mice, under-developed lung buds emerge directly from a single foregut tube connected to the stomach (43).

Another important molecular pathway involved in foregut specification is the WNT/β-catenin signaling pathway. WNT/β-catenin signaling has been proven to be necessary and sufficient for respiratory cell fate of the ventral foregut, provided that *Sox2* expression is repressed by BMP signaling as discussed previously (38). WNTs are secreted glycoproteins that act trough β-catenin (*Ctnnb1*), a cytoplasmic protein that translocates to the nucleus and binds transcriptional repressors ultimately inducing transcription of target genes (47). In terms of foregut development, WNT appears to be necessary for the ventral expression of *Nkx2.1*, with WNT2 and WNT2B, expressed in the ventral foregut mesenchyme, acting as important ligands involved in the compartmentalization process (48). Similar to loss of endodermal receptors BMPR1a, b in the foregut ventral endoderm, mesenchymal loss of WNT2 and WNT2b leads to disrupted endodermal expression of *Nkx2.1* and results in disrupted tracheal formation (48). Similarly, conditional deletion of the WNT signaling mediator β-catenin in mouse foregut mesenchyme and epithelium impedes the compartmentalization of the foregut, resulting in tracheal agenesis (39, 49). Conversely, a significant expansion in *Nkx2.1* expression through foregut endoderm, including the upper stomach epithelium, occurs if *Ctnnb1* is constitutively activated (48) further confirming the importance of WNT/β-catenin signaling.

In addition to the advances in knowledge achieved using transgenic approaches in various animal models, pharmacological studies using Adriamycin administration (50, 51) have provided additional means to study and analyze disruption in foregut development. Adriamycin, also called doxorubicin, is an anthracycline antibiotic and chemotherapeutic agent that, when injected in pregnant wild-type mice or rats before foregut compartmentalization,

causes phenotypes of VACTERL syndrome (21, 24). Doxorubicin acts by interfering with replication and therefore inhibits DNA and RNA synthesis, in this way affecting multiple tissues and organs. Furthermore, doxorubicin also affects the SHH–GLI receptor signaling pathway, giving rise to abnormalities during foregut development as previously described (52). Due to the clinical association of OA/TOF with syndromic malformations such as VACTERL, CHARGE (coloboma, heart defects, atresia of choanae, retardation of growth, and ear abnormalities), and Di George Syndrome, other genetic traits have been investigated for possible association of foregut malformation. T-box genes are a family of transcription factors richly expressed in tissues undergoing active embryonic induction of organogenesis. *TBX1* has been shown to be a major determinant in 22q11 deletion syndromes (22q11DS), including Di George syndrome; hence, the influence of *TBX* gene activity in the developing foregut has recently attracted significant interest. Using both wild-type mice and the aforementioned Adriamycin model, McLaughlin et al. have demonstrated a focal pattern of *Tbx1* gene expression confined to the dorsal and ventral poles of the proximal wild-type esophagus. Altered *Tbx1* foregut expression in Adriamycin treated animals in this study further suggests that *Tbx1* may modulate normal esophageal development (53). Additional *Tbx* genes have been shown to play a role in foregut development. *Tbx4* expression has been demonstrated in the lung buds and mesenchyme surrounding the trachea (54). Furthermore, *Tbx4* has been shown to be specifically expressed in the visceral mesoderm of the developing lung in the chick model, and *Tbx4* misexpression shown to induce disrupted formation of the tracheo-esophageal septum, ectopic budding of the lung and TOF, further confirming the crucial involvement of *Tbx* gene activity in foregut embryology.

DISRUPTION OF THE ENTERIC NERVOUS SYSTEM (ENS) IN OA

Esophageal dysmotility is a very common and well-recognized disorder in children suffering OA (55). Kirkpatrick et al. reported uncoordinated contractile waves in the distal esophagus in 14 patients with OA (56), and others have associated GER with complications due to the surgical procedure, such as excessive tension on the vagus nerve or overt injury to it at the site of the esophageal anastomosis (57, 58). Although esophageal body motility dysfunction has been reported in patients following surgery, Lemoine et al., using high-resolution esophageal manometry before surgical repair in two children with isolated TOF, demonstrated that both had abnormal esophageal motility (hypomotility with distal contraction and complete aperistalsis) (59), suggesting that esophageal dysmotility is likely to be congenital.

This dysmotility is likely to be explained by loss, disruption, and/or dysfunction of the intrinsic innervation (ENS) of the esophagus. The ENS is derived principally from a population of vagal neural crest cells, which enter the foregut in humans at approximately week 4 (E9.5 in the mouse) (60) and migrate in a rostrocaudal fashion starting from the presumptive esophagus to colonize the entire gut by approximately week 7 (E13.5 in the mouse) (61, 62). To enable full gut colonization during embryogenesis, the neural crest cell population displays significant proliferative capacity. This proliferative capacity is tightly coordinated by *Ret*/GDNF signaling (63), while SOX10 and endothelin 3 signaling have been shown to be critical in the maintenance of multilineage ENS progenitors (64). The ENS is organized into two concentric plexuses, the inner submucosal plexus is present in the submucosa and an outer myenteric plexus is present between the circular and longitudinal muscle layers along the length of the GI tract. In the normal esophagus, the ENS is largely present in the myenteric plexus and the submucosal plexus is absent or sparsely present. Nakazato et al. showed that the myenteric (Auerbach) plexus of infants with OA is deficient. Specifically, a lower amount of neural tissue was present in the distal esophagus compared to the proximal end of untreated OA patients and control patients (65). More recently, Boleken et al. suggested that the expression of neuronal markers, such as neurofilaments, specifically found in neuronal cells, and synaptophysin, a calcium-binding protein present in the presynaptic vesicles of neurons, were significantly reduced in the affected part of the esophagus while S100 expression, a marker of glial cells, was increased in the muscular layers and the myenteric plexus (66). Of interest, GDNF expression, an important neurotrophic factor for neural cells, was significantly reduced in these OA patients, suggesting a possible signaling deficiency, which could account for the observed intrinsic innervation deficits (66).

THE ROLE OF STEM CELL THERAPY AND TISSUE ENGINEERING IN THE TREATMENT OF OA/TOF

Despite advances in our understanding of the genetic determinants of foregut development, this knowledge has not translated, as yet, to improved therapeutic interventions in the treatment of OA/TOF. Hence, alternative approaches using novel techniques such as gene and stem cell therapy in combination with advancing tissue engineering protocols may provide alternative routes for treatment of these difficult disorders following standard surgical intervention and pharmacological management. The current limitations of surgical approaches for the treatment of OA and TOF combined with the ongoing post-operative symptoms experienced by patients have provided the impetus to investigate potential cell-based therapies alone or combined with tissue engineering as a means of replenishing missing or dysfunctional cell types or indeed absent sections of esophagus. Alternatively, they may provide a mechanism to treat ongoing foregut dysfunction, post-surgery, in less severe cases.

Arguably, the most promising approach lies in esophageal tissue engineering as a potential replacement of tissue segments. Tissue engineering approaches, using acellular scaffolds derived from animals and humans, or cell-seeded grafts, have recently been investigated (67). In particular, similar to a previous report for the trachea (68), decellularized esophageal scaffolds have been used with good results in both preclinical and clinical studies (69). Significant heterogeneity exists among studies, both with respect to the type of scaffold, and extent of surgery and species used, which partly explains the range of results reported. Badylak et al. laid sheets of small intestinal submucosa (SIS) onto the raw

internal surface of the esophagus following endoscopic submucosal resection in five patients with superficial cancers (69). The scaffold promoted physiological remodeling and decreased the chance of stricture formation. Moreover, a commercially available extracellular matrix was able to promote full-thickness regeneration of the esophagus with stratified squamous epithelium, a normal five-layer wall, and peristaltic motility with bolus transit (70). Decellularized esophageal tissue retains signals, both chemical and structural, which should promote appropriate migration and differentiation of host cells (71–73), which may be unlikely to occur with scaffolds originating outside the esophagus, such as SIS. In an attempt to engineer a complex structure more closely resembling normal esophagus, Nakase et al. developed an elegant method for producing an esophageal construct. Oral keratinocytes and fibroblasts were cultured on human amniotic membrane and smooth muscle cells cultured on PGA. The two layers were rolled into a tube, implanted in the omentum, harvested at 3 weeks and used to replace a partial defect (74). Similarly, circumferential replacement of the cervical esophagus was achieved using a tube-shaped tissue-engineered acellular substitute with autologous skeletal myoblasts covered by a human amniotic membrane seeded with autologous oral epithelial cells. Under the temporary cover of an esophageal endoprothesis, which was removed at 6 months, animals were able to reach nutritional autonomy and at sacrifice the tissue remodeled toward an esophageal phenotype (75).

While significant steps have been made in the ability to expand both epithelial and muscle cells for tissue engineering purposes (68), it will be essential to neo-innervate any potential engineered scaffold to allow for full restoration of function. To this end, major strides have been made in the last decade in the identification and isolation of enteric neural stem cells (ENSCs), which may not only provide an ideal candidate for neo-innervation of tissue-engineered scaffolds but may also provide a mechanism of restoring function in patients where ongoing dysfunction, following surgery, is found to be neuropathic. A number of studies have demonstrated that the human postnatal GI tract contains multipotent cells that upon transplantation can colonize the gut and differentiate into appropriate enteric neural phenotypes (76, 77). The proliferative capacity and multipotent nature of these neural crest derivatives has lead to investigation of the identification and isolation of ENSCs. Recent investigations have sought to utilize such ENSC as a means of replacing lost or absent neurons in a number of GI disease models. Both mouse and human ENSC have been shown to integrate within mouse colonic tissues after transplantation (78–80). Previous studies have also demonstrated that ENSC can colonize aneural colonic tissues *ex vivo* (77). Importantly, both embryonic and postnatal mouse ENSC have been shown to integrate, differentiate into appropriate neuronal subtypes, and form functional neurons *in vivo* in recipient mouse models where the endogenous ENS persists (79). Furthermore, it has more recently been shown that human ENSC have the ability to colonize gut and integrate with the endogenous ENS in wild-type mouse colon, including functional integration of human fetal ENSC (78). These studies provide critical evidence that ENSC may provide a mechanism to restore function in various gut tissues. Significantly, ENSCs have been identified in both human fetal (78) and postnatal tissues (77, 81), demonstrating the possibility of an autologous source of neural stem cells which could be harvested relatively easily *via* endoscopy, from other bowel regions, expanded, and then transplanted *via* tissue-engineered scaffolds or autologous transplantation directly to the esophagus. A significant advantage of this approach would be the ability to circumvent immunological rejection of autologously transplanted cells. It may also be possible to perform heterologous transplantation of ENSC from matched donors; however, such an application is likely undesirable due to the possible requirement of lifelong immunosuppression. Future studies including preclinical evaluation of the ability of ENSC to provide functional rescue of foregut disorders and provide functional innervation within tissue-engineered specimens are required, prior to implementation of any clinical trials in human patients. One significant caveat regarding the use of ENSC is the potential limitation in their expansion characteristics. Transplantation studies, to date, have demonstrated relatively modest expansion and integration of ENSC within transplanted colonic tissues (79, 80), which may impact on their ability to restore function in large-scale human tissues. It remains possible that significant cell numbers will be required for the treatment of OA; therefore, studies of alternative cell sources are additionally required to determine the best cellular source for esophageal neo-innervation.

To this end, there has been significant interest in the potential use of pluripotent stem cell (PSC) populations as a source of regenerative neural cells. Both embryonic stem (ES) cells and induced pluripotent stem (iPS) cells have the capacity to give rise to any cell of the body. Both mouse and human pluripotent stem cells (ES and iPS cells) can be differentiated into "ENS-like" cells (82) with capacity to proliferate limitlessly and therefore may provide an ideal cellular source for neo-innervation studies.

Of particular interest, recent studies have shown that ES and iPS cells can be manipulated *in vitro* to induce a neural crest-like phenotype (83–85). Recent work has demonstrated that human iPS-derived vagal-like neural crest cells can be combined with human pluripotent stem cell-derived intestinal organoids to form functional organoid units complete with neuronal reflexes (83). The ability to source autologous patient-derived iPS cells, which can be subsequently driven toward and ENS phenotype may revolutionize treatments for enteric neuropathies allowing autologous cell therapy without lifelong immunosuppression. However, at present, limited data exist as to their integration and the ability of such cells to functionally rescue gut motility. Interestingly, Fattahi et al. recently suggested that human ES- and iPS-derived enteric neural crest could rescue a mouse model of Hirschsprung disease after *in vivo* transplantation. Transplantation of these human-derived vagal neural crest cells to the colon of EDNRB$^{s\text{-}l/s\text{-}l}$ (SSL/LEJ) mice led to 100% survival; however, no mechanisms regarding the integration of these cells within the host neuromusculature, or the functional rescue achieved at the organ level, were presented (84). Therefore, further work is crucially required to establish the functional integration of PSC-derived neural crest cells after *in vivo* transplantation in a number of model systems.

While the potential expansion and manipulation of pluripotent stem cells provide an exciting proposition above that of ENSC, several issues remain to be addressed prior to their validation as a suitable treatment option. One critical issue regarding the potential

use of pluripotent stem cell sources is the potential introduction of residual pluripotent stem cells, which could be tumorigenic. Furthermore, studies are required to both consolidate and standardize protocols for the derivation of pure enteric neural crest cells and establish safety parameters for such pluripotent protocols, including genetic and epigenetic stability given that such derivations usually require significant culture periods. Such studies will allow for critical determination of the beneficial impacts of these cell replacement sources above that of autologously sourced ENSC.

CONCLUSION AND FUTURE DIRECTIONS

The management of esophageal atresia remains challenging. This stems in part from a failure to understand the precise molecular mechanisms that underlie normal foregut development and the aberrations that lead to disease such as OA. As a result, therapies for OA are limited and designed to palliate rather than cure. Even when primary anastomosis is achieved in OA, the esophagus is often dysfunctional leading to major gastric and respiratory problems associated with poor quality of life. Treatments of complications related to OA are unsatisfactory and may require multiple surgeries. Some strides toward a better understanding of normal and abnormal development of the foregut have been made, but there is still a need for focused research in this area. This could lead to the development of innovative treatments. Regenerative medicine may have a role not only for *filling the gap* when primary anastomosis is not possible but also for ameliorating esophageal dysfunction. Alternatively, such dysfunction may be addressed more simply and directly utilizing the significant advances that have occurred in the field of ENSC biology. The transplantation of such cells may provide an adjunct to surgery to improve outcomes. Either way, the coming decade may well herald exciting prospects for the understanding of the origins of OA and the development of definitive therapies.

AUTHOR CONTRIBUTIONS

NT conceived the work. SP and CM contributed equally to the work and are joint first authors. SP designed and made the figures and together with CM wrote the first draft. NT, OB, and PC helped draft the final manuscript and revised it critically for important intellectual content. All authors critically reviewed the final manuscript.

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