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Oesophageal atresia

Marinde van Lennep[1], Maartje M. J. Singendonk[1], Luigi Dall'Oglio[2], Fréderic Gottrand[3], Usha Krishnan[4,5], Suzanne W. J. Terheggen-Lagro[6], Taher I. Omari[7,8], Marc A. Benninga[1] and Michiel P. van Wijk[1,9]*

Abstract | Oesophageal atresia (EA) is a congenital abnormality of the oesophagus that is caused by incomplete embryonic compartmentalization of the foregut. EA commonly occurs with a tracheo-oesophageal fistula (TEF). Associated birth defects or anomalies, such as VACTERL association, trisomy 18 or 21 and CHARGE syndrome, occur in the majority of patients born with EA. Although several studies have revealed signalling pathways and genes potentially involved in the development of EA, our understanding of the pathophysiology of EA lags behind the improvements in surgical and clinical care of patients born with this anomaly. EA is treated surgically to restore the oesophageal interruption and, if present, ligate and divide the TEF. Survival is now ~90% in those born with EA with severe associated anomalies and even higher in those born with EA alone. Despite these achievements, long-term gastrointestinal and respiratory complications and comorbidities in patients born with EA are common and lead to decreased quality of life. Oesophageal motility disorders are probably ubiquitous in patients after undergoing EA repair and often underlie these complications and comorbidities. The implementation of several new diagnostic and screening tools in clinical care, including high-resolution impedance manometry, pH-multichannel intraluminal impedance testing and disease-specific quality of life questionnaires now provide better insight into these problems and may contribute to better long-term outcomes in the future.

Oesophageal atresia (EA) is the most common congenital abnormality of the oesophagus. In ~70–90% of those born with EA, a tracheo-oesophageal fistula (TEF) co-occurs[1–4]. The condition is thought to arise as a result of deviations from the normal embryonic development of the foregut. The overall worldwide prevalence of EA as calculated from national and international databases for congenital anomalies is 2.4 per 100,000 births[1,2]. According to the Gross classification, five subtypes can be defined on the basis of the presence and/or proximity of the TEF (FIG. 1); an overlapping Vogt classification is also available[5]. Gross type C (EA with a distal TEF) is the most common variant[4,6].

In most patients born with EA, surgical repair of the atresia and closure of the fistula, if present, should be performed soon after stabilization of the patient and careful preoperative management and assessment of potential comorbidities. Respiratory distress syndrome is a rare indication to perform emergency surgery; transpleural ligation of the TEF is required to temporarily improve respiratory status[4]. By contrast, delayed surgery is the first option in cases of long-gap atresia (FIG. 1) or in those with high-risk severe comorbidities or multiple malformations. The prognosis for infants born with EA has greatly improved with advances in surgical techniques and preoperative and postoperative care. However, oesophageal dysfunction occurs in all patients born with EA and is related to primary motility disorders. These disorders can be part of the underlying abnormalities (for example, intrinsic abnormalities in myenteric plexus that provides motor innervation to the muscular layer of the gut) or related to operative and postoperative factors (for example, iatrogenic vagal nerve damage, postoperative stricture formation at the anastomosis, peptic oesophagitis and/or eosinophilic oesophagitis (EoE))[7]. EA is also associated with numerous comorbidities that affect the oesophagus, such as dysphagia, feeding difficulties, gastro-oesophageal reflux disease (GERD) and respiratory problems[8]. GERD can lead to further deterioration of oesophageal motility and cause chronic inflammation and development of gastric and intestinal metaplasia (Barrett oesophagus) and even adenocarcinoma in rare cases[9,10]. Delayed oesophageal clearance, resulting from the abnormal motility, may be one of the factors explaining a possible higher incidence of squamous cell carcinoma identified during screening in those born with EA[11].

The recent development and implementation of several diagnostic and screening tools in paediatric

*e-mail: m.a.benninga@amc.uva.nl

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Author addresses

[1]Emma Children's Hospital, Amsterdam UMC, University of Amsterdam, Pediatric Gastroenterology and Nutrition, Amsterdam, The Netherlands.
[2]Digestive Endoscopy and Surgery Unit, Bambino Gesu Children's Hospital-IRCCS, Rome, Italy.
[3]CHU Lille, University Lille, National Reference Center for Congenital Malformation of the Esophagus, Department of Pediatric Gastroenterology Hepatology and Nutrition, Lille, France.
[4]Department of Paediatric Gastroenterology, Sydney Children's Hospital, Sydney, New South Wales, Australia.
[5]Discipline of Paediatrics, School of Women's and Children's Health, University of New South Wales, Sydney, New South Wales, Australia.
[6]Emma Children's Hospital, Amsterdam UMC, University of Amsterdam, Pediatric Pulmonology, Amsterdam, The Netherlands.
[7]College of Medicine and Public Health, Flinders University, Adelaide, South Australia, Australia.
[8]Center for Neuroscience, Flinders University, Adelaide, South Australia, Australia.
[9]Emma Children's Hospital, Amsterdam UMC, Vrije Universiteit, Pediatric Gastroenterology, Amsterdam, The Netherlands.

care as well as standardized multidisciplinary follow-up programmes into adulthood have enabled better characterization of the clinical course of disease-related complications and given more insight into the pathophysiology underlying these problems. Such developments include high-resolution impedance manometry (HRIM) to assess oesophageal motility, bolus transit and intraluminal pressure-flow interactions and 24 h pH-multichannel intraluminal impedance (pH-MII) testing to assess the severity of gastro-oesophageal reflux (GER) and its association with symptoms. Additional developments include endoscopic screening programmes and a validated disease-specific quality of life (QOL) questionnaire[12].

In this Primer, we provide an overview of the latest research in the field of EA. Implications of these results for clinical practice will be summarized to provide recommendations on the management and long-term follow-up of patients born with EA.

Epidemiology

The overall worldwide prevalence of EA as calculated from national and international databases for congenital anomalies is 2.4 (range 1.3–4.6) per 100,000 births[1,2]. Although the wide range in prevalence could possibly be due to ethnic, environmental or geographical differences, this has not been shown in the available studies[1,2]. Among participating countries, only differences in surveillance and reporting procedures can explain the variation in prevalence. The majority of patients born with EA are live-born; spontaneous intrauterine death occurs in ~3% of cases and abortion is induced in 3–8%[1,2]. In one study, prenatally detected EA led to induced abortion in 95 out of 351 cases (27%)[1]. The majority (96.8%) of these fetuses had associated anomalies including vertebral, anorectal, cardiac, TEF, renal, radial and/or limb abnormalities (VACTERL association), trisomy 18 or multiple other malformations[1]. Although once considered a fatal anomaly, improved surgical techniques and paediatric care have increased survival to >90%[13–15], with reported 1-week survival up to 100% for babies born with EA and without other associated anomalies. Lower rates, up to 87%, are reported for patients born with long-gap EA (FIG. 1), associated cardiac anomalies and very low birthweight (<1,500 g)[1,16,17].

Approximately 55% of people born with EA have associated birth defects or other anomalies[1] (BOX 1). Approximately 10% of patients have a nonrandom VACTERL association[1,18,19], although no clear genetic abnormalities have yet been identified that may underlie this association. In addition, 1% of patients born with EA also have CHARGE syndrome, characterized by coloboma (a malformation of the eye affecting the lens, iris or retina), heart defects (such as tetralogy of Fallot, septal defects (atrial and ventral), aortic coarctation or aberrant subclavian artery, atresia choanae (failed recanalization of the nasal fossae during development leading to blockage), retarded growth and development, genital hypoplasia and/or ear anomalies and/or deafness[20]. CHARGE syndrome is caused by an autosomal dominant inherited mutation of the *CHD7* gene, encoding chromodomain helicase DNA binding protein 7, which is involved in the organization of chromatin during development[21]. In addition, of patients born with EA, 6% have a trisomy 18 (Edwards syndrome) and 1–3% of patients have a trisomy 21 (Down syndrome)[1,2,15].

Comorbidities

After surgical repair, patients born with EA are at risk of many EA-related problems. For example, dysphagia is reported in 21–84% of patients born with EA of varying ages, with the highest prevalence in adults[22,23]. Patients often develop strategies to cope with dysphagia including slow eating, dietary modifications and drinking water with meals, which may mask their symptoms[24]. Feeding difficulties and food aversion are reported in up to 80% of patients, which in severe cases may result in malnutrition and poor growth. In a study of 75 patients born with EA, malnourishment was common in children <1 year of age, in children with prior fundoplication (a surgical procedure to treat GERD and hiatal hernia), in those at risk of aspiration and in those who had additional surgery in the first year of life[25]. In addition, respiratory symptoms are frequently reported in patients born with EA, with coughing (in up to 75%), wheezing (in up to 40%) and dyspnoea (in up to 37%) being the most common symptoms[26–29]. These problems are often caused by the comorbidities described below.

GERD, oesophagitis and related complications. GERD is a common problem in patients born with EA, although only a few patients actually report symptoms, either because they cannot report symptoms or because they are asymptomatic. The prevalence of GERD, when objectively measured by endoscopy with biopsies and/or pH measurement, is in the range 30–70% and depends on the diagnostic test used and the EA types included in the studies[1,30–35]. Although only small studies objectively measuring GERD in patients born with long-gap EA are available, GERD is thought to be present in nearly all these patients[36]. If symptoms are present, infants show irritability, prolonged crying, feeding difficulties, failure to thrive, silent aspiration

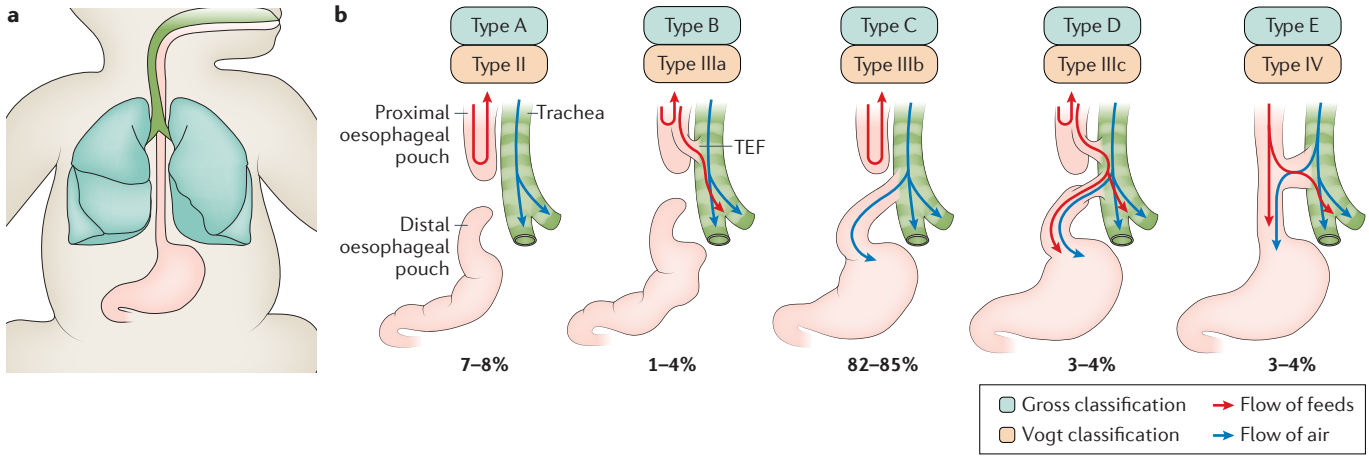

Fig. 1 | **Oesophageal atresia. a** | Normal oesophageal anatomy in which the oesophagus and trachea are anatomically distinct. **b** | The classification of oesophageal atresia (EA) is as follows: EA without tracheo-oesophageal fistula (TEF) (Gross type A, Vogt type II), EA with proximal TEF (Gross type B, Vogt type IIIa), EA with distal TEF (Gross type C, Vogt type IIIb), EA with distal and proximal TEF (Gross type D, Vogt type IIIc) and TEF without EA (Gross type E, Vogt type IV). Values in brackets indicate the frequency of each subtype. Double fistulas are possible but rare. EA can also be defined on the basis of the length of the gap between the proximal and distal oesophageal pouches. 'Long-gap EA' is generally considered the most difficult to repair, but its definition differs between studies and cut-offs are in the range 2–3 cm or 2–4 vertebral bodies[21–23]. In addition, long-gap EA may refer to EA without fistula (Gross type A) or, in the surgical literature, be defined as being difficult to repair by primary anastomosis. The International Network of Esophageal Atresia recommends that long-gap EA should be defined as any EA that has no intra-abdominal air, which, according to the Gross criteria, includes all type A and type B abnormalities, regardless of the exact length of the oesophageal gap[225].

and brief resolved unexpected events (BRUEs), which are events characterized by brief (<1 minute) and spontaneously resolving cyanosis, pallor, breathing interruptions, hypertonia or hypotonia and/or altered responsiveness[22,37]. Older patients (>6 years) often have typical GERD presentation with symptoms such as regurgitation, heartburn and chest pain[38].

Oesophageal motility is often disordered in patients born with EA, leading to delayed oesophageal clearance. In combination with chronic GER, this may damage the oesophageal wall and lead to gastric metaplasia, Barrett oesophagus (the histological pre-malignant precursor of oesophageal adenocarcinoma) and oesophageal adenocarcinoma in rare cases[32,34,39–41]. In a prospective study of 151 adults born with EA (mean age 25 years, range 16.8–68.6 years), histologically confirmed oesophagitis was present in 23%, gastric metaplasia in 17% and Barrett oesophagus was reported in 7% of patients, which is four times higher than the prevalence in the general population[40]. An even higher proportion of confirmed oesophagitis (67%) was found in a study in 120 adolescents (aged 15–19 years) born with EA; gastric metaplasia (41%) and intestinal metaplasia (1%) were also identified[39]. Interestingly, only 41% of patients in this study reported GERD symptoms and only 28% received anti-reflux medication before endoscopy. Even in young children (median age 10.9 years, range 2.0–17.2 years), intestinal and gastric metaplasia was reported, with 7 out of 542 patients (1.3%) in one study being diagnosed with intestinal metaplasia, of which the youngest was 2 years of age[42]. In addition, oesophageal squamous cell carcinoma in patients born with EA is likely to be caused by delayed oesophageal clearance as a result of abnormal motility[11].

Eosinophilic oesophagitis. EoE, an oesophageal inflammatory disease in which non-immunoglobulin E (IgE)-mediated antigen-related reactions cause eosinophilic inflammation of the oesophagus, can lead to oesophageal dysfunction via loss of oesophageal wall compliance[43]. Symptoms of EoE are nonspecific and include dysphagia, food bolus impaction (food getting 'stuck' in the oesophagus) and regurgitation; these symptoms can also be attributed to other EA-related conditions including GERD, oesophageal strictures and oesophageal dysmotility, which often leads to a delayed diagnosis of EoE. Although the worldwide prevalence of EoE is 0.03%, prevalence rates of up to 17% are reported in children born with EA[44].

Oesophageal strictures. Anastomotic strictures after surgical repair of the anomaly occur in up to two-thirds of patients[45]. Strictures can give rise to symptoms of dysphagia and feeding difficulties but also less typical symptoms such as regurgitation, weight loss or poor weight gain, respiratory problems, chest pain, BRUEs and hoarseness[46–48].

Refractory strictures (in which the stricture persists despite dilation attempts to expand it) are reported in 7% of patients after an end-to-end anastomosis, with a median number of 10 (range 5–34) dilations needed[45]. Patients with refractory strictures have a considerable burden of care. They require frequent hospital admissions for dilations or other therapeutic interventions that involve anaesthesia[49,50], may require post-intervention tube feeding and carry the risk of adverse events. Risk factors for refractory strictures are long-gap EA, anastomotic leaks and the occurrence of early postoperative strictures[45].

Congenital oesophageal stenosis. Congenital oesophageal stenosis (CES) is a congenital narrowing of the oesophageal lumen; it occurs in ~1 in 25,000–50,000 live births (0.002–0.004%)[8]. However, patients born with EA are diagnosed with CES in 3–14% of cases[51–53]. CES can be subdivided into three types: tracheobronchial remnants (the presence of tracheobronchial tissue in the oesophageal wall), segmental fibromuscular stenosis (the presence of fibromuscular hypertrophy in the oesophageal wall) and membranous stenosis (the presence of a thin membrane or membranous web in the oesophagus). Although histological examination is not routinely performed in patients born with EA, only one small retrospective study ($n = 6$) has reported the prevalence of CES subtypes[51], with five patients undergoing histological examination revealing tracheobronchial remnants in three patients and segmental fibromuscular stenosis in two patients. Symptoms of CES are similar to symptoms caused by oesophageal strictures.

Box 1 | **Anomalies associated with EA**

Cardiovascular anomalies
- Occur in 29% of patients born with EA
- Tetralogy of Fallot, atrial and ventral septal defects and transposition of the great arteries are screened for using echocardiography and/or electrocardiography
- Vascular malformations are screened for using MRI or CT when dysphagia, dyspnoea and/or cyanosis are present

Gastrointestinal anomalies
- Occur in 16% of patients born with EA
- Anorectal malformations[220] are screened for by physical examination and ultrasonography
- Duodenal atresia is screened for using radiography ('double bubble' sign is suggestive)
- Intestinal malrotation (using small intestine follow-through (if needed))
- Heterotopic pancreas and hypertrophic pyloric stenosis are screened for using ultrasonography (if needed)
- Heterotopic gastric mucosa is screened for using gastroscopy (if needed)
- Dumping syndrome is screened for using the oral glucose tolerance test (if needed)

Genitourinary anomalies
- Occur in 16% of patients born with EA
- Renal agenesis, cystic kidneys and ureteral anomalies are screened for using ultrasonography

Musculoskeletal anomalies
- Occur in 13% of patients born with EA
- Vertebral and/or rib anomalies and limb reduction deficiencies are screened for by physical examination and radiography
- Tethered cords are screened for using sacral ultrasonography

Respiratory anomalies
- Laryngotracheomalacia occurs in >17%, laryngeal cleft in <5%, vocal cord paresis in 24% (in which 7% have bilateral paresis) and subglottic stenosis in 16% of patients born with EA
- These anomalies are screened for using laryngotracheobronchoscopy

Dermatological anomalies
- Skin anomalies and clinodactyly occur in 21% of patients born with Gross type A (FIG. 1) EA and are screened for by physical examination
- Malformations of the ear are screened for by physical examination

EA, oesophageal atresia. Data from REFS[1,3,22,221].

Respiratory comorbidities. Bronchitis is diagnosed in up to 74% of patients born with EA, bronchial hyperresponsiveness and atopic predisposition in up to 65%, restrictive pulmonary disease in up to 58%, respiratory infections in up to 53% and obstructive pulmonary disease in up to 50%[26–29]. Hospital admissions for respiratory problems are reported in almost half of all patients in all age groups[28]. Of those hospitalized, 58% were readmitted to the hospital more than once and 11% were admitted to the hospital more than five times owing to respiratory problems[28].

Mechanisms/pathophysiology

The oesophagus and trachea originate from the embryonic foregut[54], between week 4 and week 6 of gestation when the separation of these two systems takes place[55]. Although the exact mechanism of separation of the embryonic foregut into the oesophagus and trachea has not yet been verified, experimental animal studies have led to the development of several morphological models to explain the development of EA and TEF (FIG. 2). These models are the outgrowth, watershed and septation models. The septation model describes the formation of a septum that divides the foregut into the oesophagus and trachea[56]; investigators have hypothesized that lateral ridges along the dorsoventral midline merge together to form such a septum[57], but a 'real' septum has not been identified[58]. By contrast, the watershed model postulates that foregut tissue grows at both sides and new tissue becomes either oesophagus or trachea[58], and the outgrowth model suggests that the trachea is created by an outgrowth process and the remaining foregut becomes oesophageal tissue[59]. Little evidence supports any of these models, but a single study in mouse embryos showed decreased length of the undivided foregut during compartmentalization, which can only be explained by the septation model[60].

Genes and signalling pathways

To better understand the pathophysiology of EA, it is necessary to reveal the mechanisms by which abnormal embryonic development of the oesophagus and trachea in these individuals occurs. However, little is known about this process in human embryos because only few are available for research purposes. Accordingly, owing to similarities in early embryonic development between rodents and humans, mouse and rat models are often used. Indeed, several mouse models have been studied to assess the involvement of certain genes in the development of EA.

These studies in mice have identified several markers that are crucial for the precise dorsoventral formation of the foregut (FIG. 3). Precise bilateral activation and inhibition of transcription factor Nkx2.1 (a respiratory marker expressed in the ventral foregut) and transcription factor SOX2 (a gastrointestinal marker expressed in the dorsal foregut) result in separation of the oesophagus and trachea[61–63]. Signalling pathways regulate the activity of Nkx2.1 and SOX2. In the dorsal foregut, the bone morphogenetic protein 4 (BMP4) antagonist NOGGIN directly activates SOX2 and indirectly activates SOX2 by suppressing its suppressor, BMP4.

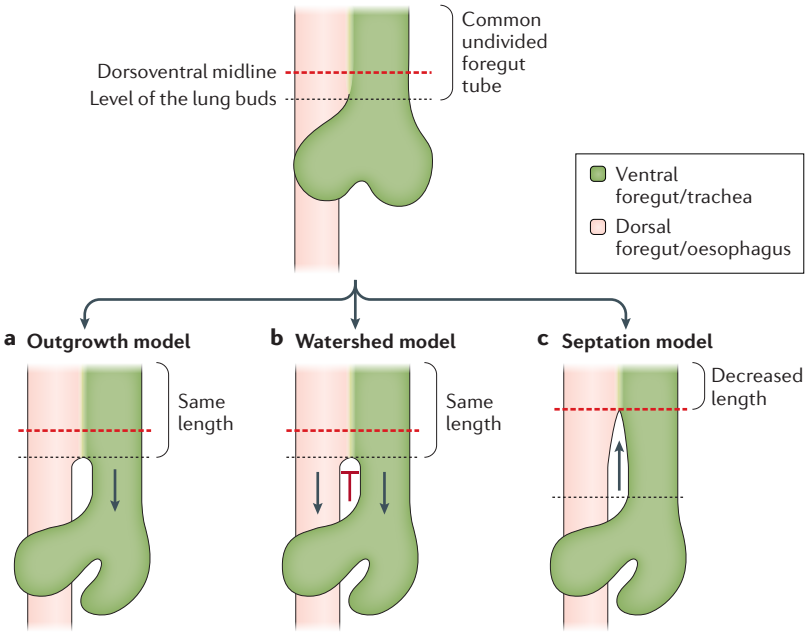

Fig. 2 | **Foregut separation.** Three hypotheses have been put forth to explain the separation of the dorsal (oesophageal) and ventral (tracheal) foregut in embryos. These models are the outgrowth model (panel **a**), in which the trachea is created by an outgrowth process and the remaining foregut becomes oesophageal tissue; the watershed model (panel **b**), in which foregut tissue grows at both sides and new tissue becomes either the trachea or the oesophagus; and the septation model (panel **c**), in which the formation of a septum (located at the dorsoventral midline) divides the foregut into the oesophagus and the trachea. The watershed model is the most widely accepted model. Compartmentalization starts at the level of the lung buds, which is indicated in each panel as a reference point. The dorsoventral midline is also indicated; in the septation model (panel **c**), this point also indicates the place where a septum would be localized. Arrows indicate the direction in which the compartmentalization process takes place. Figure adapted with permission from REF.[226], Wiley VCS.

The protein WNT blocks Nkx2.1 in the dorsal foregut; however, in the ventral foregut, WNT activates Nkx2.1 and suppresses SOX2. When this precise dorsoventral pattern is disturbed, failure of tracheo-oesophageal separation occurs.

Another important signalling pathway for the differentiation of the foregut is sonic hedgehog (SHH), which is expressed in the endoderm[64]. SHH regulates the *FOX* genes; *FOXF1* is associated with abnormal foregut compartmentalization in animal models, and its human counterpart has recently been shown to be associated with human EA and VACTERL association[65]. Retinoic acid has also been described as an important factor for differentiation of foregut areas in animal models. Although not confirmed in humans, retinoic acid signalling deficiency in mice leads to defects in foregut compartmentalization[66].

Alongside studying normal embryonic development, the adriamycin mouse model is frequently used to investigate the development of EA[67]. Adriamycin is a cytostatic drug that induces EA and associated anomalies (including VACTERL association) in mice and rats. The model is imperfect; adriamycin-treated mice display a lower level of apoptosis in the foregut than in untreated animal embryos[48,68], but this loss of cell death is unlikely to be essential for tracheo-oesophageal morphogenesis as the foregut of untreated mice with lower apoptosis levels still divides into the oesophageal and tracheal tubes[60]. In adriamycin-treated mice embryos, notochord (the cartilaginous rod of mesodermal cells at the dorsal midline of all chordate embryos) abnormalities frequently occur[68]. Very early in gestation, progenitors of the notochord and foregut are created by anterior midline cells, forming a notochord that is embedded within the foregut. Although this process remains unclear, it is known that the notochord dislocates from the foregut normally in animal models. However, hampered notochord resolution may result in faulty foregut compartmentalization[68,69].

EA-related problems and comorbidities

Oesophageal dysmotility. Oesophageal dysmotility is present in all children born with EA and is a key factor in the pathophysiology of numerous EA-associated comorbidities; it leads to dysphagia, feeding difficulties and GERD and its associated complications (FIG. 4) and can contribute to a higher aspiration risk with pulmonary complications as a result. To provide a better understanding of the pathophysiology underlying dysmotility, several studies have examined the oesophageal tissue of patients born with EA (obtained during either autopsy or surgical repair) or in animal models[70–72]. These studies have identified abnormalities in the myenteric plexus of the proximal oesophageal segment (such as hypoplasia and abnormal interganglionic connections)[70,71] and reduced density and immaturity of interstitial cells of Cajal (intestinal cells that are important for gastrointestinal motility) in the proximal and distal segment[72]. Rat models also revealed abnormalities in the branching pattern of the vagus nerve and abnormal intrinsic innervation of the oesophagus[73–75].

In vivo recordings of oesophageal motility to better understand the underlying dysmotility before surgery are difficult to perform. Accordingly, such measurements are available only for a small number of representative individuals, who required different surgical procedures and were studied with different techniques[76,77]. One study in two patients with TEF who underwent high-resolution manometry (HRM) before surgery showed defects in oesophageal peristalsis, providing direct evidence that neural innervation may be aberrant before surgery[76]. By contrast, another study in two patients born with long-gap EA (FIG. 1) who underwent manometry recordings of the proximal and distal oesophageal segments, demonstrated seemingly normal contractile patterns[77]. That is, the motor patterns in these patients became aberrant only after surgical repair. Indeed, surgical repair may worsen dysmotility by potentially causing denervation of extrinsic inputs to the proximal oesophageal muscle and the enteric nervous system of the distal oesophagus[78]. However, owing to the extremely small numbers, no firm conclusions regarding differences in surgical techniques and their influence on oesophageal motility can be drawn at this stage.

Oesophageal dysmotility may lead to impaired bolus transit, increased bolus perception, reduced clearance of GER episodes and, consequently, GERD, all of which can lead to dysphagia symptoms. In addition, numerous

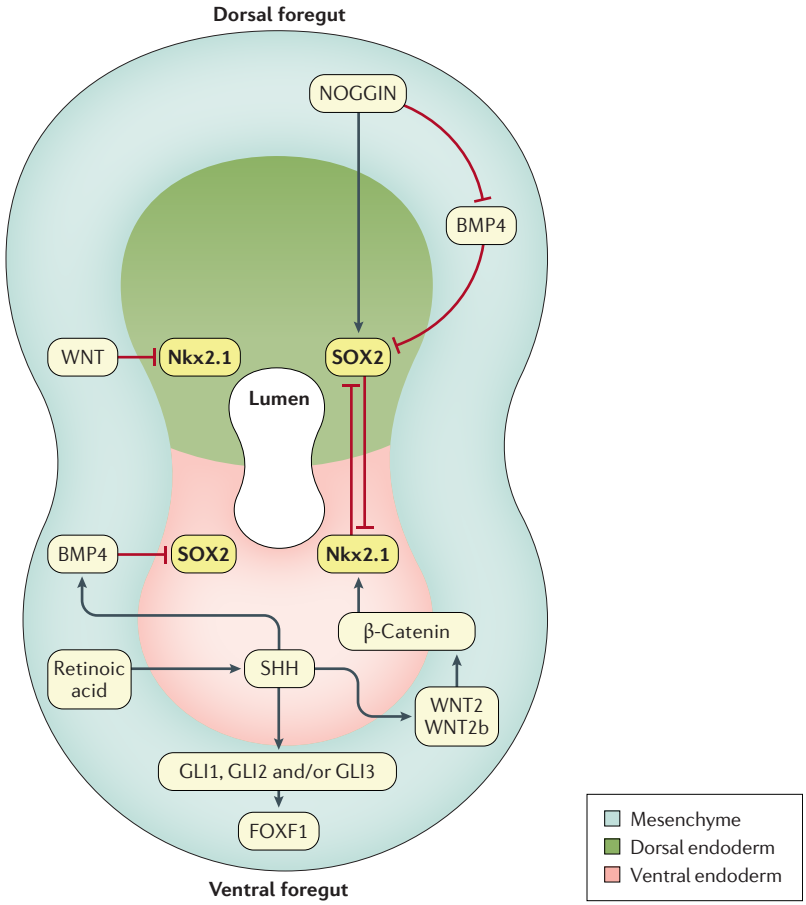

Fig. 3 | **Genes and transcription factors involved in foregut separation.** Foregut separation is under the control of signalling pathways and factors that act on different regions of the developing embryo. Although several genes and pathways seem to be essential for foregut compartmentalization, their specific roles in this process are still poorly understood. From studies in mice, we understand that the dorsal foregut (green) expresses SOX2 (REF.[63]), a gastrointestinal transcription factor, whereas the ventral foregut (pink) expresses Nkx2.1 (REF.[227]), a respiratory transcription factor. The precise dorsoventral activation is regulated by the inhibition of genes in the developing embryo and results in separation of the foregut into the oesophagus and the trachea. Bone morphogenetic protein 4 (BMP4), expressed by the mesenchyme (blue), suppresses SOX2. The mesenchyme also expresses NOGGIN[62,228], a BMP4 antagonist and SOX2 agonist in the dorsal foregut that is primarily involved in removing notochord cells from the foregut in *Noggin*-mutant mice. At the same time, BMP4 (REF.[62]) regulates the notochord and foregut endoderm by suppressing the activity of SOX2 in the ventral endoderm. WNT activates Nkx2.1 in the ventral foregut through β-catenin, but suppresses it in the dorsal foregut, enabling separation of the foregut. Sonic hedgehog (SHH)[64,229], activated by retinoic acid, activates BMP4, WNT and FOXF1, the latter activated via transcriptional activator GLI1, GLI2 and/or GLI3 in the ventral foregut endoderm. Adapted from REF.[230], CC-BY-4.0 https://creativecommons.org/licenses/by/4.0/.

other factors can be involved in the pathophysiology of dysphagia, including GERD, anastomotic strictures, EoE, peptic stricture, reflux oesophagitis, anatomical malformations (such as vascular slings or rings (congenital conditions in which vascular anomalies of the aortic arch or its associated vessels partly or completely surround the trachea and/or oesophagus) and an aberrant subclavian artery or diverticulum) and fundoplication[22]. In addition, severe peptic oesophagitis requires appropriate treatment as it is known to worsen oesophageal peristaltic function in children and adults[79–81].

Oesophageal dysmotility and dysphagia may play a part in the aetiology of feeding difficulties. Other possible aetiologies for feeding problems include GERD, oesophageal strictures, tracheomalacia (due to softening and malformation of the cartilage, and most commonly to posterior membrane intrusion), aspiration, associated CES, EoE and dumping syndrome[7,25,82]. As clinical signs of dumping syndrome in children can be nonspecific, the condition needs to be considered in patients born with EA who demonstrate feeding difficulties. In those born with EA, dumping syndrome can occur without a history of prior fundoplication and could be related to accidental vagal trauma inherent to surgical repair or to intrinsic dysmotility (oesophageal and/or gastric) associated with the underlying digestive malformation[83]. Finally, feeding skills can be delayed in patients born with EA who are in need of prolonged tube feeding or a gastrostomy catheter[84]. Over time, ongoing feeding difficulties may be maintained by behavioural factors as ongoing aversive events can delay feeding skills and reduce interest in feeding[85,86].

GERD. The mechanisms underlying individual GER episodes in infants and adults born with EA are similar to those with GER but without EA, with transient lower oesophageal sphincter (LES) relaxation being the most common factor[87]. This shared mechanism suggests that GER episodes do not occur more frequently, but the delayed bolus clearance in response to a GER episode might be responsible for the symptoms and complications observed. One study comparing pH-MII data between infants born with EA and controls with GERD showed significantly prolonged acid clearance and bolus clearance times in the EA group (281 s and 39 s in the EA group versus 110 s and 15 s in controls; $P<0.0005$)[30]. On the other hand, a retrospective study in 35 children born with EA and 35 age-matched controls with suspicion of GERD showed an equal number of GER episodes and similar bolus clearance times[88]. In addition, reflux episodes in patients born with EA were significantly less acidic than in controls because most patients were taking acid-suppressing proton pump inhibitors (PPIs). Mean distal baseline impedance was also significantly lower in those born with EA[88], which might be due to reduced mucosal integrity as can occur in oesophagitis. Further research is needed to evaluate the clinical relevance of this finding in patients born with EA.

As infants feed, the milk serves as a strong buffer to acidic gastric contents. As a result, GER in the early postprandial period is usually non-acidic. However, infants spend long periods in the supine position, and this can delay chemical clearance of acidity, leading to longer periods of oesophageal acid exposure when the refluxate is acidic[89]. Other factors that may influence the presence and characteristics of GER in patients born with EA include gastric motility and emptying, which are delayed in a substantial number of infants (57%) and adults (22%) born with EA[82,87,90]. It can be argued that abnormal enteric nervous system development and postnatal surgery are factors that contribute to these gastric function abnormalities[82].

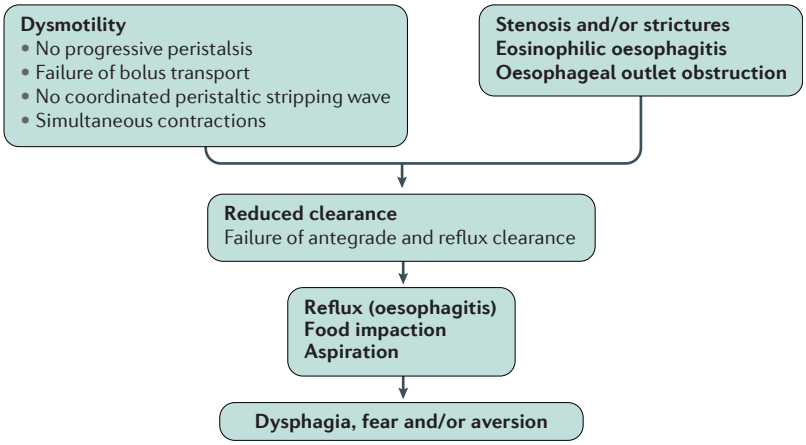

Fig. 4 | **Factors contributing to feeding difficulties in EA.** Dysmotility is nearly universal in patients born with oesophageal atresia (EA). Dysmotility causes delayed clearance and, therefore, increases the chances of developing gastro-oesophageal reflux disease, which is thought to induce peptic stenosis and worsen anastomotic strictures. Any stricture or stenosis leads to further delay in clearance, which in turn causes dysphagia. In many patients born with EA, dysphagia is present and causes fear of choking and increased symptoms, which may lead to food aversion, especially in the young. Another complicating factor is the higher prevalence of eosinophilic oesophagitis in children born with EA, which causes dysphagia and dysmotility and can, therefore, worsen symptoms and consequently fear and aversion to food in this patient population.

In patients born with long-gap EA (FIG. 1), surgical repair may cause separation of the LES from the crural diaphragm, leading to an impaired reflux barrier function of the oesophago-gastric junction. As a result, patients born with long-gap EA are even more susceptible to GERD and, accordingly, many of them undergo fundoplication during the first year of life[91,92]. Although fundoplication likely effectively reduces the number of reflux episodes and oesophageal acid exposure, it can also contribute to (or exacerbate) dysphagia secondary to the combination of the pre-existing reduced clearance capacity of a dysfunctional oesophageal body, increased oesophageal outflow resistance and decreased distensibility of the oesophago-gastric junction, the latter two caused by the surgical wrap[91,93]. Furthermore, gastric motility dysfunction, including dumping syndrome, has been reported after fundoplication[94]. Overall, the indications for fundoplication should be carefully evaluated in each patient, preferably in a multidisciplinary team with a surgeon, gastroenterologist and pulmonologist to evaluate the potential advantages as well as the drawbacks of the surgical procedure. Historically, physicians strongly focused on effective GERD treatment, leading to a high number of patients born with EA undergoing fundoplication but increasing insights into the role of oesophageal dysmotility and the potential for post-fundoplication dysphagia, have now made multidisciplinary teams more reserved in performing fundoplications. The joint European Society for Paediatric Gastroenterology Hepatology and Nutrition (ESPGHAN) and North American Society for Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN) EA guidelines suggest that a fundoplication may be beneficial in cases of recurrent anastomotic stricture (especially in those with long-gap EA), poorly controlled GERD despite optimal PPI therapy, cyanotic spells or long-term transpyloric feeding[22]. Despite being tailored to the general GERD population and based only on expert opinion, the ESPGHAN–NASPGHAN guidelines for paediatric GERD suggest attempting transpyloric feeding before or as an alternative to fundoplication to reduce symptoms[95]. A recent study in nine patients born with long-gap EA suggested that fundoplication may not be necessary in all because some could be managed with an optimal dose of PPI therapy[96]. Thus, further studies are needed to find the optimal GERD treatment for patients born with long-gap EA and, more specifically, to identify those patients in need of fundoplication.

EoE. EoE is a result of a type 2 helper T cell immune response and is associated with atopic predisposition[97]. Several gene array and genome-wide association studies have revealed CC-chemokine ligand 26 (CCL26) and several interleukins to play an important part in the development of EoE[97–99]. Furthermore, because of the high prevalence of EoE in those born with EA, a genetic association between EA and EoE has been postulated[100]. For example, microdeletions in the *Fox* gene cluster are associated with EA and other anomalies[65]. As the binding site for FOXF1 in mice is in the promoter region of several inflammatory genes (including *Ccl28*)[101], mutations in *FOX* genes in humans may contribute to EA and other congenital malformations and predispose to EoE[100].

Other hypotheses for the high prevalence of EoE in patients born with EA include a decreased mucosal barrier as result of severe GERD, which enables food allergens to enter the submucosal layer and cause eosinophilic inflammation[102], oesophageal dysmotility, food stasis and/or food impaction, which causes a prolonged exposure of the damaged mucosa to food allergens[100,103]. Chronic GERD requires patients born with EA to take long-term PPI therapy from early infancy. Early and prolonged acid suppression could prevent the breakdown of food antigens, thereby increasing the potential for sensitization and the development of EoE[104]. Recently, the transcriptomes of patients born with EA with EoE, patients born with EA without EoE, patients with EoE but without EA and healthy controls were compared, showing dysregulated epithelial barrier and type 2 immune-associated gene expression in those born with EA without EoE[105]; these genes were also found to be even more dysregulated in those with EoE but without EA and patients born with EA with EoE. The presence of this genetic dysregulation in patients born with EA at baseline before the development of EoE might be the reason why there is a higher prevalence of EoE in this population. Interestingly, patients born with EA with EoE and with EoE but without EA had similar molecular transcriptomes at baseline at time of diagnosis of EoE and in remission after treatment, which is likely to be due to a similar pathogenesis induced by food allergy. However, EoE in patients born with EA was associated with a more-severe clinical phenotype, with substantially higher rates of dysphagia, episodes of food bolus impaction and strictures requiring dilation than in those with EoE but without EA[105].

Oesophageal strictures. Risk factors for the development of anastomotic strictures include anastomotic leaks, anastomotic tension, GER and EoE. Long-gap EA is also considered a risk factor for strictures given that anastomotic tension is usually higher in these patients[106,107]. Although some studies advocate the use of PPIs to prevent anastomotic stricture formation in patients born with EA[47,107], others conclude that the incidence of strictures does not decrease after prescription of PPIs[108,109]. Whether low birthweight, prematurity, tracheomalacia, VACTERL association and EA subtype (FIG. 1) are risk factors for the development of strictures also remains a matter of debate[106,107,110].

CES. Oesophageal biopsy specimens from patients with CES can contain cartilage or respiratory tissue[111]. Thus, CES might be the result of abnormal development of the foregut[112]. Further research is needed to investigate the underlying embryonic developmental mechanisms resulting in CES.

Respiratory comorbidities. The aetiology of respiratory problems is multifactorial. Experimental and animal models (such as adriamycin mice and rat models) suggest that disrupted molecular signalling involving fibroblast growth factor, vascular endothelial growth factor and HOX signalling pathways have roles in the development of pulmonary problems in EA[113–115]. Abnormal development of the lung buds can result in compromised airway branching and, consequently, bronchomalacia and hypoplastic lungs[116]. In addition, abnormal development of tracheal cartilage and increased width of the transverse muscle in the posterior tracheal membrane (pars membranacea) result in tracheomalacia[117]. Tracheomalacia may lead to impaired mucociliary clearance of the airways with subsequent cough, bronchitis and pneumonia[118,119].

Other factors contributing to respiratory problems include nerve damage during surgical repair as well as anastomotic leak, which can cause pleural effusion, although small leaks may go undetected as they can be contained. Strictures can cause aspiration or choking[78]. The majority of patients born with EA who experience recurrent laryngeal nerve injury perioperatively have a true left vocal cord flaccidity[120]; the lack of motor activity causes the flaccidity and the lack of sensory fibres causes an alteration in sensation in the posterior pharynx, which induces an increased aspiration risk. Furthermore, aspiration in patients born with EA can be initiated during swallowing owing to a laryngeal cleft but may also be caused by recurrent TEF, GERD and disordered oesophageal motility. The latter may hamper adequate coordination between the digestive tract and airway protective mechanisms[121–123].

Diagnosis, screening and prevention

Although EA can be diagnosed antenatally, most patients (>90%) are diagnosed after birth[124]. A newborn baby with EA usually presents with blowing bubbles (saliva combined with air through a TEF leads to bubbly saliva) and respiratory distress caused by a TEF or associated malformations. The diagnosis can be confirmed when it is impossible to position a nasogastric catheter in the stomach. Although this diagnosis is straightforward in well-resourced regions (BOX 2), many diagnostic issues remain regarding the type of EA and the presence of associated anomalies.

Antenatal diagnosis

EA is prenatally diagnosed in a minority of cases and is usually only suspected[125] on the basis of the presence of indirect or direct signs on ultrasonography. MRI with dynamic sequence and biochemical evaluation of the amniotic fluid have been developed to help in the diagnosis of EA[126]. The combination of ultrasonography and of second-line tests could improve antenatal diagnosis of EA[125,127,128].

Ultrasonography. EA without TEF can be detected prenatally on ultrasonography by a small or absent stomach 'bubble' (that is, no fluid in the stomach) and the presence of polyhydramnios (excess of amniotic fluid in the amniotic sac) from the 14th and 24th week of gestation onwards, respectively[129]. However, these findings are indirect (nonspecific) and are reported in association with many other anomalies such as other intestinal atresias, lung hypoplasia, chromosomal abnormalities and twin-to-twin transfusion syndrome[124]. From the third trimester onwards, a dilated blind-ending oesophageal pouch may be visualized as an echoic area in the midline of the fetal neck, when the fetus swallows[130]. Although this so-called upper neck pouch sign has shown excellent predictive values in some small series, its diagnostic value is debated[131,132]. As a result, EA without TEF is suspected by standard ultrasonography in 10–70% of cases[124,133,134]. In EA with a distal TEF, detection rates are even lower as amniotic fluid may pass through the TEF into the stomach, resulting in the absence of polyhydramnios and the presence of fluid in the fetal stomach (small or normal volumes)[127,135]. In cases of EA with a proximal TEF, amniotic fluid may pass though the fistula, which prevents visualization of the pouch sign.

Box 2 | **Global variation in diagnosis and management**

Whereas survival in well-developed countries is up to 100%, mortality due to oesophageal atresia (EA) in developing countries is still very high (>50%)[222,223]. Mortality in these countries is associated with lower birthweight (<2,500 g), prematurity, delayed diagnosis taking >48 h, aspiration pneumonia, respiratory distress, long-gap EA (FIG. 1) and associated abnormalities. In the case of coexisting congenital heart disease, survival is poorer. Indeed, in peripheral hospitals without paediatricians and lacking in expertise on congenital anomalies such as EA, the diagnosis is often missed. Age at presentation in developing countries is approximately 4–5 days, with reported cases up to 21 days after birth[222,223]. As a consequence, infants present malnourished, in shock and/or hypothermic. Owing to ongoing feeding attempts, up to 60% of patients present with aspiration pneumonia, leading to further deteriorating health. Available diagnostic facilities may only — or in worst cases not even — include radiography (with contrast), ultrasonography and/or echocardiography. Associated anomalies may, therefore, be missed, with poorer health outcomes as a consequence. In addition, neonatal transport facilities in these countries are poor (for example, lacking in supplemental oxygen and temperature maintenance). Lack of adequate health care, including neonatal intensive care units, continuous Replogle suction, ventilatory support, total parenteral nutrition, medication and surgical equipment, also contributes to high mortality and high morbidity.

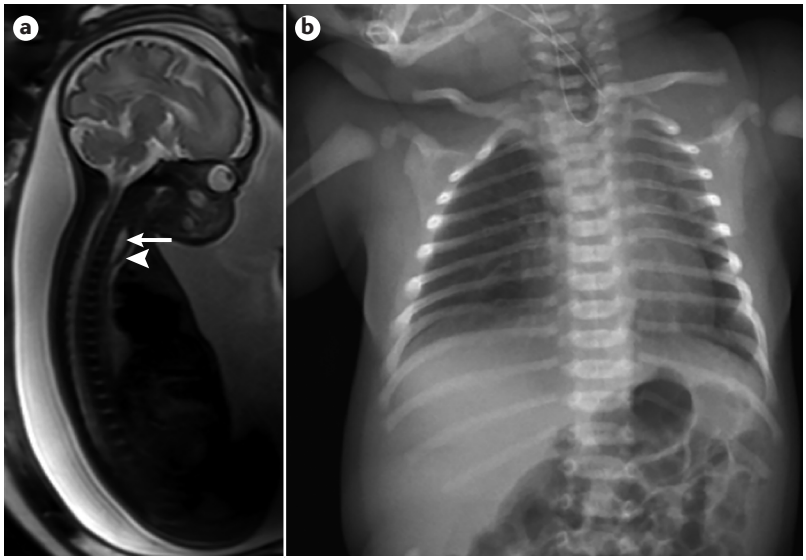

Fig. 5 | **Diagnosis of EA. a** | The upper pouch sign (arrow) on MRI is used to confirm a diagnosis prenatally. Arrowhead points to the trachea. **b** | Radiograph showing a curled catheter in the upper oesophageal pouch and gas in the stomach, confirming the postnatal diagnosis of oesophageal atresia (EA) with a distal tracheo-oesophageal fistula. Panel **a** courtesy of T. Fourquet, de Broucker Radiology CHU Lille, France.

MRI. MRI may be used to further support the ultrasonographic suspicion of EA and to detect possible associated anomalies. Fetal MRI has an overall sensitivity of 95%, a specificity of 89%, a positive likelihood ratio of 8.8, a negative likelihood ratio of 0.06 and an OR of 154 (REF.[134]). The pouch sign on MRI (FIG. 5) has a sensitivity of 82% and a specificity of 100%[126,127,136]. Recently, the distended fetal hypopharynx sign (that is, distension of the hypopharynx as a result of the obstruction) was proposed as an additional indicative prenatal sign for EA. This sign is caused by retrograde flow of amniotic fluid owing to obstruction and has, although investigated only in a small retrospective study, a higher sensitivity but a lower specificity than the pouch sign[137]. Overall, the true clinical value of MRI for the prenatal detection of EA needs further investigation as it is not available in all centres, is highly dependent on the amount of amniotic fluid, and the available data are from small, often retrospective, studies[127,136].

Postnatal diagnosis

In newborn babies with EA, saliva and oral feeds cannot pass through the oesophagus, and if there is a proximal TEF, saliva can reach the lungs. Thus, symptoms include excessive oral bubbly salivation, respiratory problems and distress during the first feeding attempt[4,138]. When an oral catheter cannot be passed into the oesophagus beyond 10–12 cm (FIG. 5), the diagnosis should be considered.

Assessment of EA-related comorbidities (BOX 1) should be considered before surgery to assess preoperative risks and the possibility of combining other surgical procedures. Echocardiography should, if available, be performed before the operation to detect cardiac or vascular anomalies such as tetralogy of Fallot or a right-sided aortic arch, which may change the surgical or anaesthetic approach. In the same procedure, but before surgery, a laryngotracheobronchoscopy (see below) should ideally be performed to localize the TEF and assess tracheomalacia.

Given that VACTERL association are common in those with EA, routine VACTERL screening is recommended, comprising physical examination; radiography of the thorax and the entire spine; ultrasonography of the abdomen, kidneys and sacrum; echocardiography; and electrocardiography[139]. These investigations can also be of diagnostic value for CHARGE syndrome. Although VACTERL screening is usually completed after surgical repair, at minimum echocardiography and electrocardiography are recommended before surgery to identify potential cardiac anomalies as these might change the surgical and/or anaesthetic approach. The diagnostic evaluation after surgical repair depends on the patient's symptoms, the availability of diagnostic tests and local follow-up protocols and can further involve swallow assessment (for example, with videofluoroscopic imaging), oesophageal motility assessment (for example, with HRM or HRIM) and respiratory function assessment.

Oesophagogastroscopy. Oesophagogastroscopy in infants and children can be performed only when well-trained (paediatric) gastroenterologists, anaesthetists and equipment are available. Upper endoscopy with biopsy is the gold standard to evaluate the oesophageal mucosa for complications of GERD (such as oesophagitis, Barrett oesophagus and oesophageal strictures) and signs of EoE[8,140]. Furthermore, evaluation for the presence of stenosis and its treatment is possible, and (recurrent) TEF can be identified[8,141,142]. Patients with EoE or GERD can be asymptomatic despite severe oesophageal mucosal damage; the ESPGHAN–NASPGHAN EA guidelines recommend performing routine endoscopy with multilevel biopsies (four biopsies in each quadrant at multiple levels) at least three times in all patients born with EA during childhood (after stopping PPI therapy, before the age of 10 years and at transition to adulthood)[22,31,143]. In adults, screening programmes for this specific patient population are under evaluation, but until long-term follow-up data become available, endoscopy every 5–10 years is considered the standard of care.

Videofluoroscopic swallowing study. A videofluoroscopic swallowing study (VFSS) can be used to assess dysphagia and its underlying causes, including aspiration and oesophageal strictures, and is available in the majority of large hospitals in well-developed countries[144]. Especially in infants and children, a multidisciplinary approach with a specialized speech therapist and radiologist is required. VFSS is a dynamic assessment of the oral, pharyngeal and oesophageal phase of the swallow function[145]. In a study with 32 patients born with EA (median age 48 months, range 2–120 months), the oral and pharyngeal phases of swallowing were normal in almost all cases, but the oesophageal phase was abnormal in 30 patients and showed dysmotility, oesophageal stasis, oesophageal backflow and aspiration, again showing the key importance of oesophageal motility problems in these children[146].

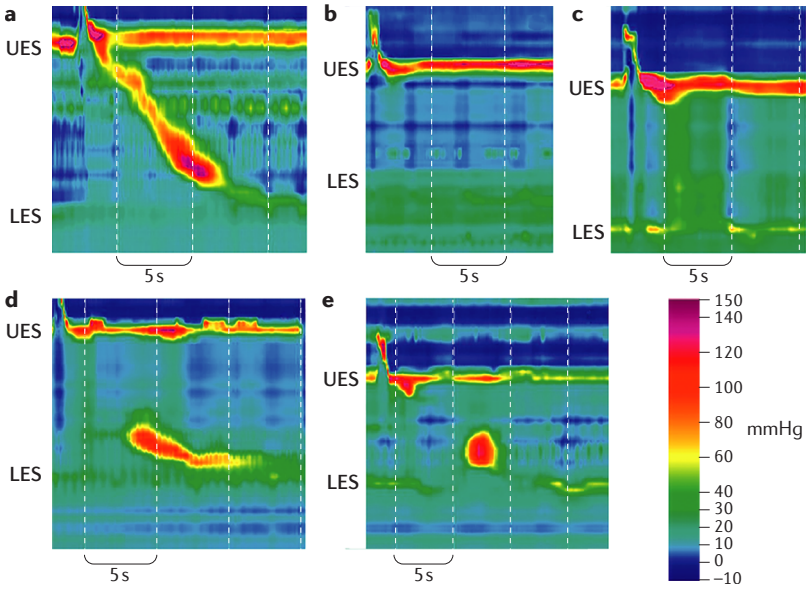

Fig. 6 | **Contraction patterns on HRM in patients born with EA.** High-resolution manometry (HRM) measures oesophageal pressure using a transnasally placed catheter with pressure sensors. Pressure patterns can be visualized as a topography colour plot with time on the *x*-axis and the position of the catheter on the *y*-axis; red indicates high pressure and blue indicates low pressure. **a** | A normal swallow in a healthy control individual. The red-yellow bar at the top indicates the high-pressure zone at the upper oesophageal sphincter (UES). A peristaltic contraction wave is seen throughout the oesophagus. At the bottom of the contraction wave, a subtle green band is visible indicating the high-pressure zone at the lower oesophageal sphincter (LES). Note the clear relaxation of the UES and LES as part of the coordinated swallow mechanism. **b**–**e** | HRM tracings of patients born with oesophageal atresia (EA) are depicted. Three different types of dysmotility have been described in EA: aperistalsis with a complete lack of oesophageal pressure change during swallowing (panel **b**); pan-oesophageal pressurization, a simultaneous pressure rise in the entire oesophagus due to oesophageal shortening rather than peristaltic contractions (panel **c**); and several types of distal contraction in the most distal oesophagus (panel **d**) and more proximally (panel **e**). Adapted with permission from Lemoine, C. et al. Characterization of esophageal motility following esophageal atresia repair using high-resolution esophageal manometry. *J. Pediatr. Gastroenterol. Nutr.* **56**, 609–614 (2013), ESPGHAN–NASPGHAN, https://journals.lww.com/jpgn/.

HRM. Although HRM (FIG. 6) is crucial to differentiate motility problems from other causes of dysphagia, it is available only in a few centres. HRM optimally combined with impedance recording (that is, HRIM) provides information on oesophageal body contractility, bolus flow and flow resistance[147]. The high spatial resolution of recordings enables derivation of several biomechanical measures (such as flow, distension caused by the swallow of a bolus, distension pressure and oesophageal body clearance as the bolus travels to the stomach) that discriminate between increased bolus flow resistance, ineffective oesophageal bolus propulsion or both[148]. Oesophageal motor function or peristalsis can be characterized on the basis of contractile vigour, timing and/or fragmentation, and these features can be associated with bolus transit using intraluminal impedance to detect bolus flow and presence[149].

Of relevance to GER is the ability of HRIM to characterize oesophago-gastric junction basal tone, morphology (that is, the crural diaphgram–LES separation) and contractility as measures of oesophago-gastric junction barrier function[150,151]. Bolus flow resistance proximal to the anastomosis or at the oesophago-gastric junction can be assessed qualitatively, through recognition of pressure patterns consistent with compartmentalization, and quantitatively by measuring intrabolus distension pressures that may indicate reduced luminal calibre and/or increased wall stiffness due to stricture, external pressure by a vascular malformation or a more globalized inflammatory process (such as EoE)[148].

At this time, the precise role for HRIM in the management algorithm for patients born with EA is a matter for discussion and further research[7]. However, clear evidence supports that patients born with EA display one of a number of typical patterns ranging from (essentially) normal motility to absent peristalsis[24,87] (FIG. 6). HRIM may provide valuable information on postsurgical outcome in patients when a fundoplication is considered, as susceptibility to post-fundoplication dysphagia is related to a pre-existing subclinical variation in combined pressure-flow analysis[152,153].

Automated pressure-impedance analysis, an integrated method for the analysis of HRIM, has also been developed[154,155]. Pressure-impedance analysis objectively derives swallow function variables, which, in numerous experimental and clinical investigations, have now been shown to offer the potential to evaluate aspiration risk and quantify ineffective pharyngeal and oesophageal peristaltic propagation and dysphagia risk[155]. This information may be important when assessing a child born with EA who may, as a consequence of congenital and operative factors, demonstrate disordered oesophageal motility and/or resistance to bolus flow at the anastomotic site or oesophago-gastric junction[148].

Twenty-four-hour pH-MII testing. Similar to HRM and HRIM, 24-h GER monitoring can be performed only in a few centres. A 24-h pH study measures acid exposure of the distal oesophagus as an indirect marker for GER but has several drawbacks as it does not detect all GER. When combined with multichannel intraluminal impedance monitoring, alterations in impedance can measure the direction of movement of fluid, solids and air in the oesophagus; that is, pH-MII monitoring can detect both acidic and non-acidic GER and discern between liquid and gas GER[16]. The ability of pH-MII to detect all GER events enhances the potential of finding an association between GER episodes and symptoms. These advantages are important in infants and children, in whom weakly acidic GER is prevalent as a result of frequent feeding and consequent buffering of stomach contents. In infants and children born with EA, acid-suppressive medication is commonly prescribed that further increases stomach pH, leading to non-acidic GER[156,157]. Furthermore, patients born with EA have a higher exposure to non-acidic GER than controls with GERD, which has also been shown to be responsible for substantial symptom burden in these patients[88,158]. These findings imply that, specifically in children born with EA, pH-MII monitoring has a much higher diagnostic yield than pH monitoring alone.

Using pH-MII tests, the proportion of proximal GER events can be quantified and correlated to the occurrence of extra-oesophageal symptoms such as coughing

or BRUEs. However, the timing of the symptom in relation to the GER episode may be different for various symptoms, and the ideal period to assess whether a single symptom is associated with a GER episode is not clear. In addition, symptoms that occur less frequently or symptoms caused by chronic GER, including wheezing and bronchial hyperreactivity, may not benefit from symptom association[159]. Apart from GER detection, pH-MII may also be useful to calculate volume clearance from the oesophagus and chemical clearance (acid neutralization)[160]. However, the clinical applicability of pH-MII monitoring in children is limited by a lack of true normative data in the paediatric age range as a result of ethical considerations given the invasive nature of the test[161]. In addition, in patients born with EA, the software often fails to pick up GER events owing to the low baseline impedance values in this population[158]. As a result, automated analysis has to be complemented by manual analysis, which is challenging and time-consuming[22].

Assessment of respiratory problems. Several diagnostic tests can be performed to assess the severity of respiratory problems and their underlying causes. Upper airway abnormalities (including laryngeal cleft, vocal cord paralysis and subglottic stenosis), tracheomalacia and the presence of a TEF can be assessed using laryngotracheobronchoscopy. To improve standardization and quantification of tracheomalacia, a scoring system based on dynamic airway evaluation can be used[162].

If aspiration is suspected, a VFSS can be used to evaluate the patient's swallow function[163]. Biopsy samples taken during laryngotracheobronchoscopy may reveal foreign body granulomas when aspiration is present, which can be resected during laryngotracheobronchoscopy. In addition, sputum and bronchoalveolar lavage (BAL) samples can be used to culture opportunistic pathogens. pH-MII can potentially be of value in diagnosing the aetiology of aerodigestive symptoms, but studies in EA are lacking. In patients without EA but with GER, studies have shown associations between non-acidic refluxate and respiratory symptoms[164–166]. No data are available from patients born with EA or those born without EA to support the role of laryngotracheobronchoscopy as a diagnostic tool for GER aspiration[167,168].

Several biomarkers including pepsin in BAL fluids, saliva and tracheal aspirates, have been suggested as predictors for GER aspirations. Although these biomarkers have shown some potential in those without EA[169], studies evaluating biomarkers as predictors of clinical outcome are critical to determine the true value of these new tests in the diagnosis of aspiration in patients born with EA. In those patients with respiratory infections, radiographs can document the extent and localization of respiratory infection. An additional chest CT can be performed to detect sequelae such as atelectasis (incomplete or complete collapse of the lung), air trapping (abnormal retention of air in the lungs), bronchiectasis (dilatation of the bronchi), tracheal diverticula, vascular compression of the trachea, bronchial stenosis or cysts. Spirometry can be performed to diagnose obstructive pulmonary problems[170], and body plethysmography can be used to evaluate restrictive pulmonary problems[171].

Management

EA is treated surgically to create an anastomosis of the proximal and distal oesophageal pouches and, if present, ligate and divide the TEF. Recent guideline development regarding the primary treatment of EA, diagnosis and treatment of comorbidities shows that there is increased interest in the long-term care of these patients. However, inherent to the rarity of the disease, most of the recommendations in these guidelines are based on expert opinion or on very little evidence that mainly came from small retrospective studies; great variation in the management of EA exists between different countries[172,173]. Large prospective studies with control arms will prove difficult to perform, but international cooperation is ongoing and attempts will be made to perform such trials that question the recommendations of the guidelines and lead to evidence-based revisions.

Preoperative management

When the diagnosis EA has been confirmed, the neonate should be transported to a paediatric surgical centre as soon as possible. Unfortunately, patients who cannot undergo surgery (for example, who do not have access to a surgical centre) will die soon after birth owing to dehydration, respiratory problems (respiratory distress due to TEF and/or aspiration and infection) or major cardiac anomalies. Although prolonged total parenteral feeding can be an option to prevent dehydration and malnourishment, this is not normally available when surgical facilities are not.

Patients in whom an anastomosis is difficult to perform (for example, those with long-gap EA or patients born severely premature or with cardiac malformations) should be referred to a centre that is equipped and experienced in the treatment of such conditions. To correctly assess the gap length between the two pouches, combined tracheoscopy and fluoroscopy should be performed. If these tests are not available, patients born with type A EA (FIG. 1) could be suspected as having a long gap. To prevent aspiration, a Replogle tube (a double-lumen tube that is inserted through the nostril into the oesophageal pouch to drain saliva) on continuous suction is maintained and the patient is placed in reverse-Trendelenburg position (supine with the head tilted upwards) to avoid aspiration of refluxed gastric contents through a distal TEF[4]. To avoid damage to the upper pouch (which may lead to problematic surgical repair of the atresia), oesophagostomy should be discouraged. However, if a Replogle tube is not available for oesophageal suction, oesophagostomy may be the only way to avoid aspiration. Gastric puncture may provide additional time for proper preparation and stabilization of the patient before surgery. In addition, if major surgery is impossible, an indwelling balloon catheter through a gastrostomy may provide additional time for preparation for surgery. When mechanical ventilation is needed, air can escape through a distal TEF into the stomach, resulting in diaphragm elevation or gastric perforation. Accordingly, low-pressure ventilation is recommended and, if possible, the tip of the endotracheal tube is placed distal to the fistula, preferentially using laryngotracheobronchoscopy, as the endotracheal tube

Table 1 | **Surgical techniques for primary oesophageal repair in EA**

Technique	Procedure	Advantages	Disadvantages	Refs
General approaches				
Extrapleural approach[a]	• Right posterolateral thoracotomy • Identification and ligation of TEF • Detection and dissection of oesophageal pouches • Anastomotic repair	Keeping potential anastomotic leak within the extrapleural space; easier access for future procedures	More time-consuming than transpleural approach; higher morbidity than with thoracoscopic surgery	177,198
Pleural approach[a]		Less time-consuming than the extrapleural approach	Risk of developing empyema in the case of anastomotic leaks	177,198
Thoracoscopic surgery	• Insertion of 3–4 trocars • Identification and ligation of TEF • Detection and dissection of oesophageal pouches • Anastomotic repair	Improved visualization of thoracic anatomy, reduced pain and lower degree of skeletal deformities than with open surgery; minimal scarring and higher patient satisfaction with cosmetic results	More difficult technique to perform	175,176,231
Emergency surgery[b]				
Emergency TEF ligation	• Thoracotomy • Ligation of TEF	Immediate improvement of respiratory function	Risk of recurrent fistula when surgical repair is delayed	48

EA, oesophageal atresia; TEF, trachea-oesophageal fistula. [a]Open approach. [b]In patients born with EA, patients with TEF and respiratory distress.

may go into the TEF[135,174]. Tracheoscopic insertion of a Fogarty catheter into the fistula, with a balloon inflated in the oesophagus, enables better ventilation and reduces the risk of aspiration.

Surgery

Although EA surgery is ideally scheduled after careful preoperative management and assessment of potential comorbidities, this may not be possible in patients with respiratory distress syndrome in whom emergency transpleural ligation of TEF is required to temporarily improve respiratory status[4].

Different surgical techniques are available (TABLES 1,2). The optimal approach is dependent on the type of EA (FIG. 1) and the expertise of the surgeon and operative team. For example, thoracoscopic oesophageal repair (TABLE 1) has the benefits of being minimally invasive and is as effective as open surgery in terms of operating time, postoperative ventilation time and postoperative leaks and strictures; several studies have reported reduced pain, a lower degree of skeletal deformities and minimal scarring after thoracoscopic surgery[175,176]. However, the procedure has not (yet) replaced thoracotomy because the transpleural approach requires well-trained surgeons and a special thoracoscopic operating room[177]. Accordingly, an open thoracotomy using an extrapleural approach (TABLE 1) to protect the pleura in the case of an anastomotic leak is, at the moment, still favoured by the majority of surgeons[172].

In long-gap EA (FIG. 1), primary repair is often impossible. Several surgical techniques can preserve the natural oesophagus, including delayed primary (thoracoscopic or open) repair, circular myotomy and oesophageal elongation techniques (TABLE 2). Delayed primary repair (to wait until the oesophageal pouches spontaneously grow such that they are close enough to perform oesophageal repair) is currently the most preferred technique. Circular myotomy or oesophageal elongation with maximum traction may lead to damage of the oesophageal wall and could result in severe stricture, pseudo-diverticulum or severe dysmotility. Thus, the use of these techniques should be discouraged and they should be used only when (delayed) primary repair is impossible. When an anastomosis between the proximal and distal pouch of the oesophagus remains impossible, replacement therapy with gastric conduits or small bowel or colonic interposition is performed in centres with expertise in oesophageal replacement[178].

Postoperative complications

Early postoperative complications include anastomotic leakage, stricture and recurrent TEF. To minimize the risk of complications, several strategies have been developed that are used by many surgeons, but some strategies remain controversial[172,179]. For example, historically, a postoperative chest drain would be left in situ next to the anastomosis for timely detection and treatment of anastomotic leaks. However, recently published studies reported that postoperative chest drainage does not decrease complication risk and length of hospital stay[180,181]. Another strategy to avoid stress and tension on the anastomotic site is elective paralysis and ventilation, but the literature on this strategy is scarce and shows conflicting results[182,183]. Although small retrospective studies conclude that transanastomotic nasogastric tubes do not decrease anastomotic complication rates, they are nearly always left in situ[172,179,184].

Anastomotic leak. Risk factors for anastomotic leaks are anastomotic tension, long-gap EA, use of prosthetic materials (for example, glue or mesh) and surgery outside of normal hospital hours[46,177,185,186]. Minor anastomotic leakage with an involvement <25% of the anastomotic circumference (in our experience) occurs in up to 20% of patients born with EA and can almost always be treated non-operatively. Non-operative therapies include continuous nasal–pharyngeal saliva suction through a Replogle tube, fasting or post-pyloric nutrition, total parenteral nutrition, external drainage (in patients with pleural effusion) and antibiotics.

In a retrospective study of 41 patients born with EA, oesophageal stenting was compared with a customized oesophageal vacuum-assisted closure (EVAC) device for the treatment of iatrogenic endoscopic and surgical

Table 2 | **Surgical techniques for long-gap EA**

Technique	Procedure	Advantages	Disadvantages	Refs
Techniques without traction or elongation				
Delayed primary repair	• Gastrostomy feeding • Replogle tube for upper oesophageal pouch decompression • Waiting for the oesophageal pouches to grow • Repair when gap is less than two vertebral bodies	Preservation of natural oesophagus	Oral food aversion due to prolonged gastrostomy feeds; prolonged hospital stay	178
Traction or elongation techniques				
Foker process: intrathoracic elongation	• Positioning of traction sutures on proximal and distal oesophageal pouch • Externalization of sutures to chest wall • Serial tension	Preservation of natural oesophagus; as successful as delayed anastomotic repair; fewer anastomotic leaks and strictures and less GERD than delayed repair	Risk of suture dislocation and need for re-thoracotomy; oral food aversion due to prolonged gastrostomy feeds	178,232
Kimura technique: extrathoracic elongation	• Creation of cutaneous oesophagostomy of upper oesophageal pouch • Staged oesophageal tension-induced elongation	Preservation of natural oesophagus	Difficult technique; need for externalization of oesophagus; oral food aversion due to prolonged gastrostomy feeds	178
Thoracoscopic traction (internal)	• Insertion of three trocars • Mobilization of upper and lower oesophageal pouch • Identification and closure of TEF • Approximation of pouches with nonabsorbable sutures under moderate tension • Total parenteral nutrition	Preservation of natural oesophagus; no gastrostomy; minimal thoracic wall damage	Described only in a few cases ($n=4$, with 3 successful); long-term results lacking; loss of oesophageal length if elongation fails (owing closure of oesophageal ends); risk of developing oesophageal stricture; oral food aversion due to prolonged gastrostomy feeds; transpleural access; highly difficult procedure	233
Thoracoscopic traction (external)	• Insertion of three trocars • Mobilization of upper and lower oesophageal pouch • Identification and closure of TEF • Approximation of pouches with traction sutures • Placement of clips on sutures, close to oesophageal ends • Externalization of sutures outside the thorax • Gastropexy to prevent migration of the stomach into the thorax • Daily radiograph to assess gap length	Preservation of natural oesophagus; minimal thoracic wall damage	Described only in a few cases ($n=10$, with 8 successful); transpleural access; highly difficult procedure	234
Oesophageal myotomy[a]	Circular or spiral myotomy to gain ~0.5 cm of oesophageal length	Preservation of natural oesophagus	Risk of ischaemia and food impaction in myotomy; pseudo-diverticulum in 20% of cases; increased risk of anastomotic leak and stricture; oesophageal dysmotility	178
Transposition techniques				
Gastric transposition	• Cervical or laparotomy incision • Use of well-vascularized gastric conduit • Single anastomosis	Relatively easy technique	Increased risk of anastomotic leak and stricture; increased risk of GERD and Barrett oesophagus due to displaced EGJ; loss of gastric reservoir function; delayed gastric emptying	178
Gastric tube	Creation of gastric tube along greater curvature	Calibre-equalizing oesophagus	Long suture line with increased risk of leak and stricture; delayed gastric emptying; more complications than with delayed anastomosis; more respiratory complications than with colon interposition	178
Colon interposition	• Aquisition of colon graft • Colonic anastomosis • Colon transposition	Can be performed with minimally invasive surgery	Difficult technique; risk of elongation and dilation of colonic conduit over time	178,232
Jejunal interposition	• Acquisition of jejunal graft • Jejunal anastomosis • Jejunal transposition	More resistant to GERD owing to preservation of intrinsic jejunal peristalsis; less dilation of conduit than with other replacement therapies	Most challenging replacement therapy with a need for a multidisciplinary surgical team; more short-term complications than with gastric transposition	178,235

Long-gap EA can be defined as the length of the gap between the proximal and distal oesophageal pouches as being 2–3 cm or 2–4 vertebral bodies, or it can refer to EA without fistula (Gross type A), without intra-abdominal air[225], or can be defined as being difficult to repair by primary anastomosis. EA, oesophageal atresia; EGJ, oesophago-gastric junction; GERD, gastro-oesophageal reflux disease; TEF, tracheo-oesophageal fistula. [a]This technique should be used only in patients born with long-gap EA with a relatively short gap between the upper and lower oesophageal pouch.

oesophageal perforations and anastomotic leaks. The success rate of EVAC to seal all perforations was 88% (15 out of 17 patients), whereas the success rate of stents to seal all perforations was 63% (15 out of 24 patients), a difference that did not reach statistical significance ($P = 0.360$). However, for the treatment of surgical anastomotic leaks, EVAC had favourable results compared with oesophageal stents ($P = 0.032$)[187]. Major leaks, which may require temporal placement of a chest tube or in severe cases even for surgery to be redone, occur in 3–5% of patients[177]. Glycopyrrolate has been proposed to accelerate oesophageal healing, decrease mechanical ventilation time and enable early oral feeds[188], but efficacy has not been studied.

Oesophageal strictures. Oesophageal dilation is the non-operative therapy of choice for congenital and anastomotic strictures[22]. Two types of dilation can be performed: balloon dilation (under fluoroscopic or endoscopic guidance) and bougienage dilation[189]. During bougienage, several bougie dilators (thin cylinders of plastic, metal or another material that are inserted into the oesophagus) with increasing diameters are successively passed through the stricture until dilation is achieved[189]. During endoscopic balloon dilation, a balloon is inflated within the stenotic site under endoscopic or fluoroscopic guidance. An endoscopic working channel <2.8 mm in paediatric endoscopes is not compatible with endoscopically guided balloons. Thus, balloon dilation under fluoroscopy using a guidewire can be used in smaller children[189]. Another option is the use of a guidewire that is passed next to the endoscope and then advanced through the stricture under direct sight. Both bougienage and balloon dilation can be performed this way, but literature is lacking on its safety and efficacy.

Prospective studies comparing the safety and efficacy of bougienage and balloon dilators in general are not available either. Retrospectively, the safety of balloon dilation and bougienage was compared in two studies: perforations occurred less frequently after balloon dilation (1.6% versus 5.7% in one study and 0% versus 3.8% in the other)[190,191]. In addition, more dilations were needed after bougienage (median 9 dilations, range 1–60) than after balloon dilation (median 2 dilations, range 1–7)[190]. Two other retrospective studies in children with benign strictures of varying aetiology (including EA) have reported perforation rates of 0.9% (6 out of 114 dilations) after bougienage dilation and 1.5% after endoscopic balloon dilation (4 out of 260 dilations); in both studies, most perforations could be treated non-operatively[192,193].

In the case of recurrent or refractory strictures, several other non-operative therapies have been reported in the literature, including local or systemic steroid therapy, topical mitomycin C, endoscopic electrocautery incisional therapy[194], indwelling balloon catheter placement or placement of oesophageal stents. Most of these therapeutic options have been reported only in a limited number of EA case series[189,195].

If none of the abovementioned therapies is successful, surgical resection of the stenotic site or, ultimately, oesophageal replacement can be considered. Until larger, prospective studies are available to compare these therapeutic strategies, therapeutic choice should depend on the skills of the attending physician and the preferences of the patient's family[189].

CES. Patients born with EA with CES are usually treated with (multiple) oesophageal dilations, with reported success rates of 22–89%[51,53,196]. Reported dilation success rates are lowest in patients with tracheobronchial remnants, although some undergo multiple dilations with adequate symptom relief[197]. When symptoms recur after (multiple) dilations, surgical therapy is indicated. Both resection of the stenosis[51,53,183,196] and oesophageal myotomy[53] have been described in the literature. In the case of an oesophageal web, endoscopic membranectomy represents the treatment of choice because of its efficacy and safety.

Recurrent TEF. Reported incidences of recurrent TEF range between 3% and 10%[198]. Risk factors for the development of recurrent TEF include anastomotic tension, anastomotic leak and TEF ligation instead of division[198]. Symptoms of recurrent TEF are nonspecific and include respiratory problems and feeding difficulties[199]. Although mediastinal air can be seen on a chest radiograph, it can be challenging to diagnose recurrent TEF; instead, an oesophagram with contrast through a nasogastric tube can (in some cases) reveal a TEF, but this should always be followed by a laryngotracheobronchoscopy combined with isotonic contrast or methylene blue test[4]. Intra-oesophageal insufflation of air during laryngotracheobronchoscopy may also be able to detect a (recurrent) TEF. Therapies for recurrent TEF include endoscopic injection of glue, trichloroacetic acid and corrective surgery[198,200].

EA-related comorbidities

The management of EA-related problems includes evaluation of possible underlying causes of dysphagia and feeding difficulties. According to the ESPGHAN–NASPGHAN guidelines, patients born with EA should ideally be evaluated in a multidisciplinary team consisting of a paediatric surgeon, gastroenterologist, pulmonologist and otolaryngologist[22]. In addition, a clinical geneticist, speech pathologist, physiotherapist and/or dietician should be consulted if needed.

Although feeding difficulties are frequent in patients born with EA, the majority have normal growth parameters. Undernourishment (weight for height z-scores less than −2 s.d.) is reported in <10% of cases[25,26]. The accurate evaluation of pathophysiology underlying feeding problems in infants born with EA is critical to improve and allow safe oral intake and prevent aspiration. Detecting functional abnormalities at an early stage in life may also allow for timely intervention, targeted at achieving a normal age-appropriate feeding pattern and preventing the occurrence of serious complications. This target can be achieved by treating the underlying problems, such as optimizing GERD therapy, managing underlying respiratory problems and treating dumping syndrome. Indeed, treatment of dumping syndrome in patients born with EA does not differ from the treatment

of patients without EA. It generally involves dietary modification by avoiding simple carbohydrates, supplementation with complex carbohydrates (corn starch and pectin), continuous gastric or transpyloric feeds or use of acarbose. Dietary modifications may include thickening of feeds and use of tube feeding, which is reported to be required in ~30% of patients born with EA. Cyproheptadine has been reported to increase appetite, improve gastric volume and decrease saliva volume[201].

GERD. Owing to the high risk of GERD and its potential complications, ESPGHAN–NASPGHAN guidelines recommend routinely treating patients with PPIs in the first year of life[22]. To date, prospective studies on the efficacy and safety of prophylactic anti-reflux medication in patients born with EA are lacking. Endoscopy with biopsy, pH monitoring and/or pH-MII is, therefore, recommended to evaluate whether cessation of PPIs is possible or not[22]. Fundoplication is performed in up to 45% of patients born with EA[22]; this relatively high number of fundoplications performed in patients born with EA when compared with the general GERD population can be explained by the severity of GERD and the high prevalence of GERD-induced comorbidities such as aspiration, respiratory tract infections and anastomotic stenosis in these patients. However, increasing insights into the role of oesophageal dysmotility and the potential for post-fundoplication dysphagia have made physicians more reserved in performing a fundoplication. A recently performed retrospective study reported recurrent anastomotic stricture, respiratory problems, BRUEs and oesophagitis as the main reasons for performing a fundoplication in patients born with EA[92]. However, no prospective studies are available regarding the indications for fundoplication or the relationship between GER and extra-oesophageal symptoms.

Indeed, fundoplication can also worsen dysphagia owing to the increased outflow resistance of the oesophagus and consequently cause or worsen swallowing problems, aspiration and respiratory complications. In one study, one-quarter of patients who underwent fundoplication because of recurrent stricture were in need of further therapies for recurrent stricture, including resection of anastomosis or replacement therapies[92]. Moderate to severe oesophagitis and intestinal metaplasia was present in 7% and 3% of patients, respectively, after a median of 115 months after fundoplication. In the absence of prospective studies, results from these retrospective studies do stress the need for thorough multidisciplinary evaluation before fundoplication.

EoE. Therapy for EoE in patients born with EA is similar to treatment of EoE in non-EA patients and consists of PPI therapy, elemental or elimination diets and/or topical corticosteroids or systemic corticosteroids. The only study to report EoE treatment outcomes in patients born with EA ($n = 20$; median age 26 months, range 8–103 months) assessed an elimination diet, budesonide suspension, swallowed fluticasone and a combination of these therapies. A significant reduction in intraepithelial eosinophil count, symptoms of dysphagia and GER, and incidence of strictures needing dilation after each of the therapies was observed. Six patients had a gastrostomy catheter at baseline. Feeding improved on EoE treatment, and the gastrostomy was no longer needed in four out of six patients. There was also a nonsignificant trend towards improvement in weight and height *z*-scores[202].

Respiratory comorbidities. In the case of moderate to severe symptomatic tracheomalacia (as evaluated by laryngotracheobronchoscopy), surgical intervention may be indicated. Aortopexy (in which the aortic arch is fixed to the sternum) indirectly treats tracheomalacia by pulling the overlying arteries towards the sternum to open the trachea; it is performed in up to 6% of patients born with EA. Aortopexy has a higher success rate when tracheomalacia is caused by a cartilaginous malformation or anterior vascular impression. As mentioned previously, children with EA mainly have tracheomalacia caused by posterior membranous intrusion. Several groups have successfully performed posterior tracheopexy to address the posterior membranous intrusion[162,203]. Aortopexy can be performed by thoracotomy or thoracoscopy and can also be combined with initial EA repair. However, whether this technique should be combined with primary repair of EA in all children with moderate to severe tracheomalacia in order to prevent the respiratory sequelae still requires further investigation.

Aspiration-related respiratory problems should be managed by treatment of postsurgical complications, thickened feeds in the case of swallowing dysfunction and/or adequate therapy for GERD. However, several studies have reported that fundoplication does not prevent and might even worsen respiratory problems by increasing resistance to flow in the distal oesophagus, thereby promoting oesophageal stasis[22]. Patients with respiratory infection may benefit from antibiotic prophylaxis, ideally after confirmatory sputum culture[204]. In the case of obstructive and reversible lung function tests (measured by spirometry), patients may benefit from treatment with inhaled corticosteroids and β_2-agonists. Obstructive flow patterns on spirometric measurements might also be caused by tracheomalacia and/or bronchomalacia or bronchiectasis, but these patterns do not improve with the use of β_2-agonists.

Follow-up into adulthood

Although standardized multidisciplinary follow-up programmes into adulthood are considered very important given the high risk of lifelong comorbidities that patients born with EA carry, they are not available everywhere. These programmes should focus on the higher risk of developing oesophagitis, intestinal metaplasia or oesophageal cancer due to excessive GERD. Gastroduodenoscopy with biopsies are recommended every 5–10 years and when symptoms deteriorate or change over time[22].

Quality of life

Patients born with EA are exposed to many lifelong comorbidities and complications. Unfortunately, the literature on the impact of EA and its morbidities on QOL is scarce. Only a few single-centre uncontrolled

studies using different generic questionnaires have been reported, with contradicting results. In a study using Child Health Score questionnaires (50–87 items depending on the patient's age, assessing physical functioning, emotional and behavioural functioning, physical and bodily pain, general behaviour, mental health, self-esteem, general health perceptions, family activities and family cohesion), overall QOL was normal, whereas another study measured lower QOL scores in those born with EA than in healthy controls using the PedsQL questionnaire (23 items assessing physical, emotional, social and school functioning)[26,205]. In another study, the Kidscreen questionnaire (63 items assessing physical well-being, psychological well-being, autonomy and parent relation, social support and peers and school environment) showed overall QOL of patients born with EA with complications and comorbidities to be similar to the QOL of healthy controls[206]. Although the overall QOL of children born with EA was normal, lower well-being scores were reported by children who underwent oesophageal replacement surgery, multiple oesophageal dilations or revision surgery. In this study, 30% of parents (19 out of 63) reported depressive symptoms[206]. Few studies on QOL in adult patients born with EA measured with different generic questionnaires are available[205–207]. In the majority of patients, QOL was comparable to that of healthy controls, although lower well-being scores (indicative of depression) were reported by 23% of patients[206] and one study reported that EA symptoms, mainly gastrointestinal, negatively affected QOL in one-third of patients[207].

Owing to the use of different generic questionnaires, results are difficult to compare. To improve the insight of QOL outcomes of children born with EA, Dellenmark and colleagues recently developed and validated an EA-specific QOL questionnaire[12]. Using focus groups of children with EA and their families, two related questionnaires were developed on the basis of age — one for those aged 2–7 years (58 questions) and one for those aged 8–17 years (118 questions) — with questions regarding eating and drinking, relationships with other people, general life issues, communicative and interactive processes of one's health condition, body issues, bothersome symptoms, impact of health-care use, medical treatment, self-confidence and additional problems due to EA-related abnormalities. Preliminary results of the disease-specific QOL questionnaires indicate that feeding difficulties, dysphagia, vomiting, heartburn and respiratory problems as well as a previous gastrostomy catheter decrease QOL in patients born with EA aged 2–7 years. In children aged 8–17 years of age, oesophageal dilation and surgical procedures other than primary repair, such as delayed anastomotic repair or oesophageal replacement techniques, were factors associated with decreased QOL[12].

A recently published study among 49 German families of patients born with EA reported decreased QOL in parents (assessed with the Short Form-8 questionnaire, assessing mental health, global health, social functioning, physical functioning, role physical, role emotional, bodily pain and vitality)[208]. QOL was most impaired in parents of young patients (<7 years of age), parents of children with high school absences and families with low income. Mothers had a lower QOL than fathers. Several other studies assessed QOL in caregivers of patients born with EA, the majority of whom also report decreased QOL[205,206,208,209].

Outlook

Although our understanding of the pathophysiology of EA has increased over past decades, many issues have yet to be unravelled. For example, a better insight into foregut compartmentalization is needed. In addition, revealing the underlying mechanisms that cause EA and identifying (more) genes and pathways involved in the development of EA will help us to better understand EA and its underlying causes. With promising new techniques such as next-generation sequencing, genetic alterations in patients born with EA may soon be unravelled[210]. A next step may be the discovery of preventive targets for the development of EA, similar to the prevention of some neural crest deformities by folic acid supplementation[54].

Improvements to surgical techniques and supportive care in the immediate postnatal period have changed EA from a lethal disease (in the early 1900s) to a chronic disease. As a consequence, comorbidities and long-term sequelae have become increasingly important. Furthermore, given the scarce evidence base to support current management paradigms, many questions remain that require answering, directing the research agenda in EA (BOX 3). The rarity of the disease has been and will be one of the major hindrances to performing well-designed and adequately powered clinical trials. National and international consortia should, therefore, start to build prospective databases and biobanks to optimize the amount of data that we can obtain from patients[211]. Although classic double-blind placebo or sham-controlled trials in EA would take years to complete and, in many cases, be considered unethical (owing to withholding treatment), alternative trial designs could be used in EA[212]. For example, crossover trials (with smaller sample sizes and lower chance of confounding factors) may be helpful in conditions that are not likely to be completely cured but may improve by a novel treatment (such as dysphagia and GERD), and a randomized enriched enrolment withdrawal design could be used for medication trials for any of the EA-related comorbidities. Furthermore, Bayesian analysis methods (or equivalents) should be used in future studies to incorporate data that are already available[213]. In surgical interventional trials or conditions for which multiple treatment options are available, a ranking and selection design may be appropriate[214].

In addition to trial design, consensus on outcome measures (including QOL, need for hospital readmission and need for dietary adaptation) for patients born with EA needs to be decided and — ideally — used globally. To determine such measures, input from patient associations will be needed to understand what is truly important from the patient's perspective. In this light, it is promising that efforts are now ongoing to translate the aforementioned disease-specific QOL questionnaire into different languages[12]. Depending on the core outcome measures, it may be necessary, for example, to shift focus towards trials of nutritional support by a dietician,

guidance by a speech pathologist or psychosocial parental support rather than medical interventions alone.

From a more technical point of view, a proof-of-concept study demonstrated the transplantation of a bioengineered oesophagus (containing both muscular and epithelial tissue) into the omentum of a mouse, forming a functional blood supply[215]. Such surgical and bioengineering techniques hold promise[216,217]. Indeed, enteric nervous system stem cells of the gastrointestinal human tract have already shown the ability to integrate into gastrointestinal mouse tissue after transplantation[218], a promising step forward in overcoming surgical difficulties in patients born with EA. However, in the near future, head-to-head intervention studies comparing different surgical techniques are perhaps most important — closing the ongoing discussions as to which technique is best for which child. Indeed, several techniques exist for the repair of long-gap EA (TABLE 2), some of which are highly complex and available only in selected centres around the world. Whether the conceived advantages of such techniques prevail when formally assessed against conventional techniques remains unclear. Another topic of debate is the best treatment of the strictures that occur in many of these children. Treatments to prevent further recurrence of strictures (such as steroid injection during dilation) have been proposed but require further investigation in controlled trials. For the prevention of strictures, more data are needed regarding risk factors and how treatment changes the course of recurrence. Even the role of one of the most commonly proposed risk factors, GERD, is debated, and prospective studies that study GERD with long-term follow-up are needed.

Box 3 | **Future research priorities in EA**

General

- Develop large international databases and biobanks regarding all aspects of incidence, associated comorbidities, malformation, treatment and follow-up of patients
- Develop core outcome sets for interventions and develop instruments to measure outcomes accordingly
- Translate disease-specific QOL questionnaires into multiple languages and validate them
- Set up a national register for patients born with EA (currently ongoing; NCT02883725)
- Perform exome sequencing on samples from patients with tracheal and oesophageal birth defects and their biologically related family members (currently ongoing; NCT03455881)
- Use advanced non-invasive MRI techniques to assess tracheal, oesophageal, lung and cardiac morphology and function in patients born with EA in neonatal intensive care units (currently ongoing; NCT03455881)

Prenatal diagnosis

- Develop and validate a prenatal diagnostic approach in mothers at risk using analysis of prenatal MRI and amniotic fluid

Surgical management

- Compare and evaluate the efficacy, safety, cost-effectiveness, parent satisfaction, QOL and development of complications between different oesophageal elongation techniques
- Assess staged oesophageal elongation of the proximal and distal segments in long-gap EA by bougienage through mouth and gastrostomy catheter (currently ongoing; NCT03023865)
- Assess the Flourish Pediatric Esophageal Atresia Device[224] (based on magnetic oesophageal and gastric catheters; currently ongoing; NCT03615495)
- Conduct an RCT to compare and evaluate open versus thoracoscopic surgery with long-term follow-up for different types of EA
- Introduce robot-assisted surgery and machine learning to select and perform the best surgical strategy (and follow-up), beginning with animal model trials
- Further develop bioengineered oesophagus, beginning with animal model trials
- Compare and evaluate anaesthetic risks during thoracotomy versus thoracoscopy using near-infrared spectrometry assessment of cerebral perfusion
- Evaluate blood ropivacaine levels following nerve block in infants and toddlers undergoing EA repair (currently ongoing; NCT02860091)
- Assess risk of anastomotic stricture formation with transanastomotic tube (currently ongoing; NCT03730454)

Complications

- Evaluate dumping syndrome in infants born with EA using an oral glucose tolerance test and assessment of glycaemia and insulinaemia (currently ongoing; NCT02525705)
- Compare and evaluate treatment strategies for recurrent and/or refractory oesophageal stenosis
- Assess oesophageal motility in teenagers born with EA with dysphagia using HRM (currently ongoing; NCT03415893)
- Investigate whether HRM can have a more direct role in detecting dysmotility and oesophageal flow resistance
- Conduct an RCT comparing the presence of GERD and related complications in patients on different regimens of prophylactic PPI
- Evaluate the effects of antacid therapy on oesophagitis in children born with EA (currently ongoing; NCT03619408)
- Assess the safety, efficacy and complications of fundoplications performed in patients born with EA; identify selection criteria of patients to avoid postoperative dysphagia
- Establish the incidence of EoE in a larger cohort of patients born with EA
- Investigate cardiopulmonary performance capacity using spirometry and pulmonary microbiomes of adolescent and adult patients born with EA compared with a control group; characterize the composition of the pulmonary microbiome in EA (currently ongoing; NCT03767673)
- Evaluate the efficacy, safety, cost-effectiveness, parent satisfaction, QOL and development of respiratory problems

Quality of life

- Assess disease-specific QOL in patients born with EA in a large cohort

Other

- Compare intravenous Omegaven (Fresenius Kabi, Bad Homburg, Germany) treatment (rich in omega-3 fatty acids) with standard Intralipid (Baxter, Deerfield, IL, USA) treatment (soybean-based lipid formulation) on bone health outcomes in infants born with EA (currently ongoing; NCT03127345)
- Assess lung function parameters, QOL, cognitive development and assessment of parental stress longitudinally (currently ongoing; NCT02466451)

EA, oesophageal atresia; EoE, eosinophilic oesophagitis; GERD, gastro-oesophageal reflux disease; HRM, high-resolution manometry; PPI, proton pump inhibitor; QOL, quality of life; RCT, randomized controlled trial.

In contrast to other malformations (such as diaphragmatic hernia or hydronephrosis) in which surgery in utero can be effective to improve the patient's outcome, problems in those with EA generally occur only after birth. In combination with the fact that antenatal diagnosis of EA is difficult, this reality means that there is no place for surgery in utero for EA at this moment. Indeed, novel diagnostic techniques are being developed, such as evaluation of the biochemistry of amniotic fluid. Levels of microvillar enzyme activity in the amniotic fluid are reduced in fetuses with intestinal obstruction compared with healthy fetuses[138]. In addition, levels of total protein, α-fetoprotein (protein produced by the fetal liver and yolk sac) and γ-glutamyl transpeptidase (fetal digestive enzyme) appeared to be elevated in the amniotic fluid of EA pregnancies[219]. A recently published systematic review on antenatal diagnosis of EA reported an overall specificity of 89.9% and a specificity of 99.6% for the assessment of amniotic fluid with an EA index of ≥3. However, more work is needed to determine whether this and other emerging techniques can be optimized and used to confidently diagnose EA during pregnancy, predict comorbidity at the time of symptoms, predict long-term outcome and tailor management.

Finally, multidisciplinary programmes for long-term follow-up are ongoing but are still in their infancy and should be considered as only a first step in optimizing the care for patients born with EA. In particular, follow-up programmes as patients transition into adulthood and programmes for adult patients are not yet standardized and should become available in the coming years.

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