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Management of neonates with oesophageal atresia and tracheoesophageal fistula

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1. Introduction

Oesophageal atresia (OA) occurs in every 3000–4500 live births and is the result of incomplete separation of the trachea and oesophagus leading to an interruption in oesophageal continuity with or without a tracheoesophageal fistula (TOF) [1,2]. Associated congenital defects are reported in 55 % of patients with OA and are most commonly found in cardiac, genitourinary and gastrointestinal systems. Where three or more anomalies co-exist, the VACTERL association is diagnosed, found in approximately 10 % of OA patients [3,4]. Over the past 30 years, huge advances have been made in our understanding of the molecular and cellular processes involved in normal tracheo-oesophageal development and as such, how disruption of these can lead to OA/TOF. While causal genetic anomalies can be found in specific gene loci of approximately 12 % of patients, OA is predominantly a sporadic finding with a low familial recurrence rate suggesting epigenetic and environmental aetiological factors are at play [5].

Since the first successful surgical repair in the 1940s, survival has hugely improved, currently estimated at 90–95 % of all patients [6,7]. Aside from the introduction of minimally invasive surgery, the principles of surgical management remain vastly unchanged; emergent repair of the TOF is performed in the first days of life with primary or delayed repair of oesophageal continuity. Increased survival of neonates with OA/TOF can therefore be laid firmly at the door of improvements in pre- and post-operative neonatal care, particularly of low birth weight and premature babies. Many groups have identified independent predictors of mortality from longitudinal observational studies, including lower birth weight, congenital heart disease, congenital anomalies, and pre-operative mechanical ventilation [8,9]. To predict survival, Spitz classified OA/TOF patients according to birth weight and the presence of major cardiac defects [10]. The documented detrimental effect of birth weight < 1500 g alongside the presence of major cardiac disease has resulted in some centres advocating primary fistula ligation but delayed oesophageal repair in all cases of very low birth weight infants, irrespective or cardiac status [11,12]. More recent studies, however, indicate ongoing improvements in outcome in low-birth-weight infants, suggesting weight may not be as important for predicting outcome as originally thought. With improvements in neonatal care, we have seen increasing numbers of very low (VLBW) and more recently extremely low birth weight (ELBW) babies in our centre. We have shown that survival of 50 % is achievable in OA/TOF under 1 kg and that the Spitz classification is still applicable, with caution in extreme prematurity [13,14]. Primary repair of the oesophagus can be successful, but every case must be considered on an individual basis.

2. Anatomy and development of the oeophagus and trachea

Between the third to fourth gestational weeks, the common foregut undergoes a process of morphogenic separation into two tubes; the primitive oesophagus and trachea. This process is co-ordinated by a

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complex interplay of molecular signalling in key pathways including retinoic acid, sonic hedgehog (Shh), bone morphogenic protein (BMP) and Wnt [15]. These signalling cascades, co-ordinated by an interaction between the foregut endoderm and mesoderm, results in the regionalised expression of two 'master regulator' transcription factors, Nkx2.1 and Sox2. These pattern the common foregut tube into dorsal oesophageal (Sox2) and ventral tracheal (Nkx2.1) domains and reciprocally repress each other [16]. Disruption to this process or the signalling pathways involved has been shown to result in OA/TOF phenotypes in several mouse models [17]. A localised co-expression of both these transcription factors in the midline endoderm has recently been shown to be key to the development of a medial constriction at the dorsal-ventral boundary. This precipitates the fusion of the epithelium, forming a transient septum across the midline of the foregut tube with subsequent mesenchymal invasion remodelling the singular foregut into two separate organs [18]. The resulting oesophagus is composed of striated muscle in the upper third transitioning to smooth muscle in the lower two thirds, and is closely connected to the trachea anteriorly, comprised of C-shaped cartilage and an inferior wall of muscle. Despite their common origin, vascularisation of the two organs is distinct. The trachea is perfused by branches of the subclavian, internal mammary and brachiocephalic arteries. The blood supply to the oesophagus is also segmental, due to its protracted course through the neck, thorax and abdominal cavities; the upper third supplied by the inferior thyroid arteries, the middle third by oesophageal branches of the thoracic aorta, and the lower third by the left gastric artery. The trachea and oesophagus are both innervated by branches of the vagus and recurrent laryngeal nerve however the sympathetic supply differs between the two, with the posterior and anterior pulmonary plexus arising from the sympathetic trunk in the trachea and the thoracic spinal nerves in the oesophagus.

The separation of the developing trachea and oesophagus is tightly regulated in the developing embryo, and failure in this process leads to OA/TOF. The classification system championed by Gross in 1953 remains the predominant system in place today and has been used to describe the incidence of varying types. By far the most common is type C, where the proximal oesophagus is blind-ending, with a TOF between the trachea and the stomach in approximately 85 %. Less commonly seen but more surgically challenging include type A (OA with no TOF, 7–8 %) and type B (OA with TOF between the trachea and upper portion of the oesophagus, 1–4 %), commonly called 'long-gap' because of a large tissue deficit between the proximal and distal ends. Rarer still are type D (OA with proximal and distal TOF, 3–4 % and type E, also known as an 'H-type' (TOF with no atresia of the oesophagus, 3–4 % [19] (Fig. 1).

3. Diagnosis

3.1. Prenatal

The presence of a combination of polyhydramnios and a small or absent stomach bubble on antenatal ultrasound may indicate a diagnosis of OA. A recent systematic review of antenatal ultrasounds in 70,000 foetuses, of which 1760 were affected by OA, identified polyhydramnios in 56 % of OA patients and small stomach bubble in 50 %. The false positive rates were 66 % and 72 % respectively, however, limiting the usefulness of these findings in isolation [20]. While neither of these signs are particularly sensitive or specific, they become increasingly reliable when seen in conjunction with each other or to persist over serial ultrasounds throughout the pregnancy [21]. In addition, particularly at later stages, it is occasionally possible to comment on the presence of a proximal oesophageal pouch or oesophageal continuity although identification of these signs require experience and are time consuming. The presence of other anomalies associated with VACTERL antenatally such as cardiac or genitourinary abnormalities may also serve to raise the index of suspicion for OA.

The likelihood of prenatal diagnosis appears to be dependent on the phenotype of OA; where no fistula exists, patients are more likely to present with the triad of ultrasonographic findings. The same systematic review identified that the overall sensitivity of prenatal USS was considerably higher in the type A subgroup; 77.9 % of cases were correctly identified compared to 21.9 % in those with an associated TOF. Going forwards, it is likely that the increased use of prenatal MRI will help increase the rate of prenatally diagnosed OA, reported to have a sensitivity and specificity of over 90 % [20]. The importance of improving opportunities for pre-natal detection should not be underestimated; some studies have suggested a significantly increased time to surgical repair, length of hospital stay and incidence of oesophageal replacement surgery in patients detected pre-natally, likely associated with higher underlying numbers of 'long-gap' OA [22]. The opportunity to offer prenatal counselling to the family of these particularly complex cases is therefore of huge value.

3.2. Postnatal

Babies born without antenatal detection usually present within the first hours or days of life with excess saliva, coughing and gagging during feeds, occasionally with apnoeic episodes due to aspiration of milk. Diagnosis is confirmed or ruled out by the passage of a nasogastric tube; if this coils in a dilated, proximal pouch on chest X-ray, the diagnosis is confirmed. For routine OA diagnosis, contrast visualization of

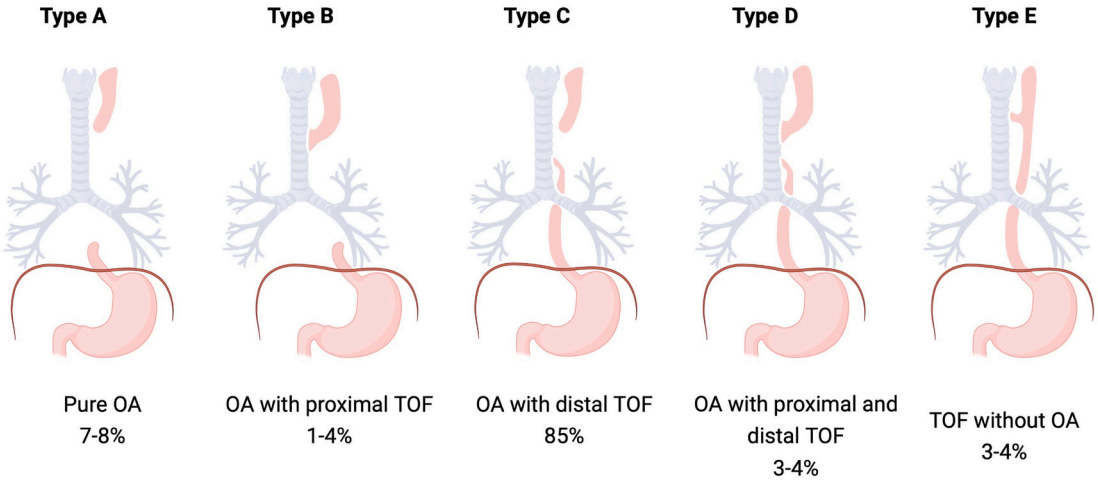

Fig. 1. Gross classification and incidence of oesophageal atresia.

the upper pouch is not usually necessary and should be avoided due to the risk of aspiration. However, its use may be required if a diagnosis of an 'H-type' (Type E) TOF is in question. In this scenario, the passage of an NG is usually normal as oesophageal continuity is not interrupted. Patients often present outside the neonatal period with recurrent respiratory symptoms, including coughing, choking or cyanosis during feeding, aspiration pneumonia and abdominal distension. In this scenario, a specialised tube oesophagogram is requested which should rule out any underlying communication between the trachea and oesophagus. If diagnostic uncertainty remains, bronchoscopy and oesophageal endoscopy can definitively exclude this rare variant.

4. Management

In recent years, the wide variation in practise and outcomes reported amongst centres dealing with rare diseases has resulted in an increased emphasis on unifying management protocols. In 2020, the European Reference Network on Rare Inherited and Congenital Anomalies (ERN-ICA) published the first international consensus guidelines on the diagnosis and pre-, peri- and post-operative management of patients presenting with OA [23]. They state the minimum acceptable in-house expertise available in centres dedicated to treating children with OA including neonatologists, neonatal surgeons, ENT specialists, gastroenterologists, cardiologists, respiratory physicians, speech and language therapists and nutritionists. Additionally, and somewhat controversially, they recommend a minimum caseload of five new EA a year to meet the requirement of a specialist centre [24]. These recommendations both guide clinicians as to the key peri-operative priorities shown to improve outcomes but also help standardise reporting of these outcomes by ensuring similar definitions and protocols are used, and their introduction has been welcomed and encouraged by patient support groups.

4.1. Pre-operative considerations

Agreed upon pre-operative priorities include the use of a replogle tube in the proximal pouch to allow continuous suction at a low pressure and prevent build-up of saliva. Pre-operative echocardiography is essential to exclude the presence of a right aortic arch and more importantly, underlying cardiac anomalies which may influence the requirement for surgery in a cardiac specialist centre due to anesthetic expertise. Spontaneous breathing should be encouraged, and if ventilation is required, this should be via intubation rather than non-invasive ventilation. Timing of operation is also important with a recent shift in attitude. Most centres now agree that a stable neonate with OA should be operated on a semi-elective basis during working hours in the working week. Previously, those presenting intubated and ventilated were performed urgently because of the theoretical risk of stomach perforation due to bypass of air through the fistula. With continued improvement in neonatal ventilation, however, this is no longer a major concern and repair in these scenarios can also be performed in an expedited, but not urgent, manner.

4.2. Operative details

The incidence of both tracheomalacia and laryngeo-tracheal-oesophageal clefts are significantly higher in OA patients than the background population at 11–33 % and 19.6 % respectively in differing patient series [25,26]. Ideally, therefore, tracheoscopy should be performed immediately prior to OA repair with the advantage of both excluding concomitant tracheal pathologies and helping to identify the location and number of TOFs. Thoracoscopic repair of OA+/−TOF was introduced over twenty years ago however unfortunately this approach is still only preferred by a limited number of surgeons and the majority of babies undergoing OA+/−TOF repair undergo thoracotomy. The repair of the most common type (C) is performed using the steps described below:

i) The patient is placed under general anesthetic and positioned on their left side with their right arm extended over their head
ii) A thoracotomy incision is made 1 cm below the right scapula extending from the mid axillary line posteriorly. The muscle layers are split using a muscle-sparing approach and entry to the thoracic cavity is at the fourth intercostal space with an extra-pleural approach
iii) After gently retracting the right lung, the azygos vein running across the trachea should be identified and ligated
iv) The lower pouch TOF is identified following the vagus nerve and carefully dissected. A sloop should be placed to temporarily occlude the fistula and the lungs insufflated prior to ligation to exclude iatrogenic isolation of a major airway rather than the TOF
v) A transfixion suture is placed across the TOF close to the trachea which is then divided distally
vi) The replogle tube is advanced from the mouth and an incision is made over its tip in the blind ending upper pouch. The distal oesophagus (previously the fistula) is mobilised superiorly to meet the proximal oesophagus.
vii) An end-to-end anastomosis is performed with interrupted absorbable sutures taking care to include both mucosal and muscle layers
viii) A small NG tube, also known as a trans-anastomotic tube (TAT), is placed to enable early NG feeding post-operatively. A chest drain is only necessary in cases of a difficult dissection
ix) The chest wall is closed in layers.

The steps for thoracoscopic repair are similar to those described above however the baby is positioned prone with three ports introduced to triangulate instruments in the thoracic cavity. The excellent visualization of the thoracic inlet allows for extensive mobilisation creating sufficient length for long gaps and safe management of high fistulas. While long term studies using this approach are still limited, a thoracoscopic approach may limit injury to adjacent structures, avoid a neck incision, reduce chest wall deformity, and improve cosmesis. A recent systematic review of 447 subjects indicated length of hospital stay and time to first feed is shorter in the thoracoscopically repaired group. No difference in anastomotic leak, stricture or GORD rate were observed however operative time was significantly longer [27]. In our recently published series of 95 patients, the stricture rate was higher using the thoracoscopic approach, however the median number of dilatations was the same between groups indicating this finding may not be clinically significant [28].

In the case of a long-gap OA, gastrostomy formation and a gap assessment is performed at birth to establish feeds and assess the degree of tissue deficit. Occasionally, the gap also cannot be bridged in type C or D, where it is greater than three vertebral bodies under tension [24]. In these scenarios, oesophageal continuity may be achieved after a period of growth, re-assessment and delayed primary anastomosis after several weeks. Where this is not successful, continuity can be obtained only by using alternative surgical techniques. These include oesophageal-lengthening procedures using tissue flaps, spiral myotomy, gastric division or more recently internal or external traction; all of these have varied results, likely related to experience and heterogenous underlying cohorts [29–32]. More recently, magnamosis, closure of the defect by placement of magnets in upper and lower pouches, has also had delivered some promising results [33]. Finally, and more conventionally, where no other approach to closure of the deficit is possible, oesophageal substitution is undertaken by one of four main techniques: colonic interposition, gastric tube oesophagoplasty, jejunal interposition and gastric interposition. Although it is controversial which of these techniques represents the best option, all techniques results in loss of function of the autologous organ used to replace the oesophagus and are

plagued by significant postoperative complications including dysmotility and dysphagia, stricture, and gastroesophageal reflux disease resulting in impaired quality of life [34,35]. Tissue engineering, discussed later, may play a significant role in future treatment of long gap patients (Fig. 2).

4.3. Post-operative management

Management of patients post primary anastomosis has become increasingly less conservative in recent years, with consensus guidelines empowering earlier feeding and extubation of neonates post-operatively. Ventilation and relaxation post-operatively should not be routine and reserved for those whom have an anastomosis under significant tension. Feeding via the TAT tube should be commenced 24 h post-operatively with early introduction of oral feeding where possible to avoid oral aversion [23].

4.4. Complications

Mortality has decreased dramatically and is predominantly only seen in those with birthweights below 1Kg or with significant associated co-morbidities. Immediate and late post-operative morbidity includes anastomotic leak (15–20 %), anastomotic stricture (30–40 %) and recurrent tracheoesophageal fistula (5–14 %) [7]. Interestingly, the treatment of these complications has evolved towards a more conservative approach. Anastomotic leak should be treated conservatively with antibiotics, chest drain insertion and a period of nil-by-mouth (NBM) [23]. Chylothorax, due to damage to the thoracic duct, is also primarily treated conservatively with chest drain and NBM and usually resolve spontaneously. Strictures respond well to endoscopic dilatation and rarely require more significant surgery.

Where recurrent TOF is suspected, contrast study, tracheoscopy and endoscopy should be performed for diagnosis. Success of endoscopic treatment is variable and a surgical approach is often required. In rare cases, more extreme intervention using a combined approach with cardiothoracic surgeons and cardiac bypass is required with complete separation of the oesophagus from the posterior trachea wall. As such, these cases should be discussed and managed by a multi-disciplinary team [36]. Tracheomalacia should be routinely assessed for in OA patients and may require surgical intervention by anterior aortopexy or a combined aortopexy and posterior tracheopexy [37,38]. Interestingly, some centres now propose assessment of trachobronchomalacia at birth with concomitant tracheopexy at the time of OA+/−TOF repair. Finally, OA children are significantly more likely to develop severe gastro-oesophageal reflux disease (GORD) than the background population. ERNICA and ESPGHAN guidelines clearly advise the use of routine prophylactic proton pump inhibitors for the first year of life to prevent peptic complications and anastomotic stricture. Prior to discontinuation of therapy, the presence of GORD should be assessed for using an impedance or pH study +/− endoscopy [39,40]. Nissen's fundoplication was previously used in a number of OA patients, but has now been shown to be associated with high recurrence rates and may contribute to oesophageal dysmotility. As such, its use should be reserved for treatment of those with recurrent anastomotic stricture, failure of maximal pharmacological treatment, long-term dependency on trans-pyloric feeding or acute life-threatening events.

5. Follow up

In a similar vein to that seen for standardisation of diagnosis and

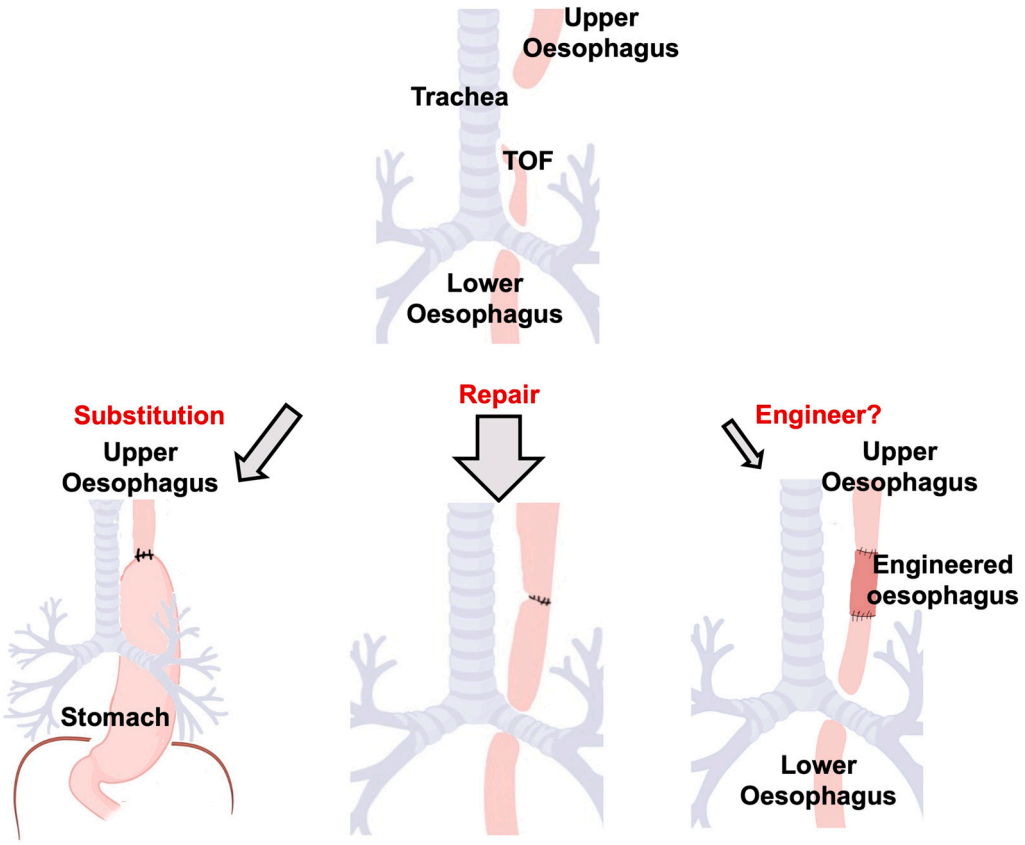

Fig. 2. Correction of long gap oesophageal atresia
While in the vast majority of cases OA can be corrected by primary or delayed repair, occasionally oesophageal substitution is required. Tissue engineered oesophagus may become the solution in the near future for long gap oesophageal atresia.

peri-operative management, frameworks for long-term follow-up have recently been published based on concerns that there was a high variability in delivery of follow-up, age of discharge and a lack of a structured approach to transition for adult patients. A recent systematic review identified the prevalence of chronic health problems in teenage and adult patients with OA is astonishingly high; dysphagia was seen in 50 %, GORD in 40 % and recurrent respiratory tract infections, asthma and wheeze in 24 %, 22 % and 35 % respectively. The prevalence of Barrett's oesophagus was also found to be four times higher than the general population at 6 % [41]. This highlights the key importance of life-long follow up for OA patients.

Centres dedicated to the ongoing care of patients with OA should have a specific interdisciplinary follow-up programmes with a multifacetted team of surgeons, gastroenterologists, respiratory physicians, ENT specialists, dieticians, speech and language therapists and psychologists. Because of the high incidence of Barrett's oesophagus, eosinophilic oesophagitis and GORD, routine endoscopy should be performed at 1 year old and at two other timepoints prior to transition. Ph/impedance studies +/− manometry should be considered at similar time points, with the use of contrast studies reserved for investigation of anastomotic stricture in symptomatic patients. As the incidence of respiratory complications is high, lung function tests should also be routinely performed during follow-up. An established transition clinic with an adult physician or surgeon is highly recommended for formal handover of care of adult patients. Some retrospective reports have estimated the rate of oesophageal squamous cell carcinoma to be 50 times higher in OA patients than in the normal population [42]. As such, routine endoscopy should occur at transition and every 5–10 years after this in adult patients [39,40].

6. Innovative care

When OA cannot be repaired by simple primary anastomosis, current alternatives are technically challenging and associated with a high incidence of acute and chronic complications. In addition, the treatment of OA is associated with a high economical cost due to the complexity of existing procedures, frequent complications and long hospitalisations. As such, The British Association of Paediatric Surgeons (BAPS) have identified long-gap OA as one of the most challenging congenital defects to treat and stress the urgency with which alternative therapeutic approaches should be sought as research priority.

To this end, partnerships of clinicians, scientists and patient support organisations have dedicated extensive research resources to ameliorating current surgical outcomes in long gap OA. While traction of the oesophagus through external or intrathoracic suturing has resulted in some promising primary outcomes, more extensive use of these techniques in less experienced hands has led to reports of controversial results such as a high incidence of anastomotic leak and damage to the oesophagus. Internal traction using magnets has the advantage of minimising surgical trauma and is significantly less invasive than current alternatives however the advent of this technology is in its infancy and much more extensive use is required to determine long-term safety and efficacy.

Thanks to discoveries in the fields of stem cells and material sciences over the last ten years, tissue engineering has emerged as a possible solution to replace the physiologic functions of tissues lost due to disease or injury, and has already been adopted clinically to substitute trachea, urethra and bladder [43,44]. The development of a tissue engineered oesophageal substitution to utilise for transplantation into large tissue defects could circumnavigate many issues seen in current oesophageal replacement techniques. Having previously successfully decellularised lung and kidneys derived from large animal models and human donors, we are now able to show that an acellular oesophageal matrix can be successfully obtained by decellularisation of pig oesophagus using a gentle detergent enzymatic treatment (DET) via the lumen. This decellularisation method preserves the ultrastructure of the native tissue and could represent the basis for a tissue-engineered oesophagus [45–47]. In 2018, we published a proof of principle approach whereby decellularised rat oesophagus was seeded with mesenchymal and neural stem cells which were differentiated into smooth muscle cells in vitro using a bioreactor. Implantation of this graft into the omentum demonstrated successful vascularisation of the scaffold [48]. The feasibility and safety of this approach are currently under investigation in a large animal model; how the graft functions in vivo is currently unknown, and coordinated peristalsis post-transplantation remains one of the biggest challenges. If successful, this approach may be applied to children and adults that need substitution of the entire oesophagus in the near future. We aim to deliver a validated, GMP-compliant manufacturing process, freely available for transfer to other licensed EU facilities for manufacture as an unlicensed medicine under the Hospital Exemption Clause of Regulation 1394/2007. This will ensure the high-quality provision of these novel therapies for an unmet clinical need across the EU and may in the future be applied to other congenital and acquired diseases of the oesophagus.

7. Final considerations

OA+/− TOF remains a complex condition to treat. While mortality is now limited to very premature and low birth weight babies, long-term morbidities still affect outcome and quality of life of children with OA. Finding solutions which reduce surgical trauma, preserve the native oesophagus and aid its regeneration will improve OA care and, ultimately, long-term outcomes for these children.

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