Adult OA/TOF Management Handbook

WRITTEN BY DR CAROLINE LOVE

REVIEWED BY PROF NICK MAYNARD, PROF ALYN MORICE, DR VUOKKO WALLACE, MS JULIA FAULKNER

tofs.org.uk

Contents

Version Number	Purpose/Change	Date
1	Original document published	May22
1.1	Update to “The genetics of OA/TOF” section	Sep22

Introduction

Why is there a leaflet about adults with a childhood disease?

Many adults born with OA/TOF still have ongoing sequelae from their childhood anomalies. In the early days of repair, parents were told they were 'fixed' and should live an entirely normal life. However, as these babies have grown up into middle-aged adults, research consistently demonstrates that a repaired oesophagus and trachea do not function like an oesophagus and trachea that developed in normal continuity in utero. Oesophageal nerve and muscle do not function normally in almost all adults born with OA/TOF, and dysphagia, gastro-oesophageal reflux disease (GORD) and laryngopharyngeal reflux (LPR) are common as a result of this, though not universal, and many with these issues may not realise as they have never had a normal oesophagus. Similarly, alongside the TOF formation, the C shaped cartilage may not form properly, leaving tracheomalacia (TM) as a result, which can lead to ongoing respiratory problems.

However, whilst there is good awareness of health problems related to OA/TOF amongst paediatric surgeons who treat the condition, when these children transition to adult services, adults struggle to find doctors in primary and secondary care who are knowledgeable about the anomaly. Some adults are reluctant to seek medical opinions on their health issues due to negative experiences and lack of awareness in the past. Others have become their own expert patient but need the support of an advocate GP. With this leaflet, we hope that we can fill in the knowledge gap of a rare and complex condition to help GPs understand, treat and signpost treatment to the appropriate specialist when needed. It is impossible for GPs to be fully informed about the near-infinite number of rare diseases that exist, but since there are only a handful of tertiary care adult surgeons and physicians across the UK with experience in management of adults born with OA/TOF, and only one clinic in the UK specific for this group (and this is still being set up), this leaflet aims to be a management handbook for primary care developed from the most recent research in this area. Many adults born with OA/TOF seeking GP appointments have issues related to the condition that are commonly treatable in primary care, such as GORD, LPR, sinusitis; however the TOFS charity does have a list of experienced tertiary care doctors for when this is appropriate, and these doctors are usually happy to be written to/emailed with queries by GPs as well as referrals when needed.

Introduction to OA/TOF

Oesophageal atresia (OA) and tracheo-oesophageal fistula (TOF) are two congenital anomalies that occur in around 1/2,600 births. (1) Whilst the two can arise separately, they commonly arise together as the trachea and oesophagus develop from the separation of a common foregut early in foetal development. If this foregut fails to completely develop, and/or separate, then the anomalies arise. (2)

? diagram here of OA/TOF anomaly

The first successful surgical repair of the anomaly was performed in 1941, and survival is now consistently over 90% worldwide post repair. Survival is almost universal (98.9%) in infants born today with the condition at a birthweight over 1.5kg and no cardiac anomaly, 82% for those weighing either <1.5kg or with a cardiac anomaly, but only 50% for those infants with both low birth weight and cardiac anomaly, based on Great Ormond Street Hospital data. (3) Gross devised the most commonly used classification system in 1953, dividing the anomaly into five main types.

- Gross Type A, 7%. Isolated atresia without fistula, mainly these patients are long-gap and primary repair is not possible.
- Gross Type B, 2%. OA with proximal TOF.
- **Gross Type C, 86%. OA and distal TOF**.
- Gross Type D, <1%. OA and proximal and distal TOF.
- Gross Type E, 4%. TOF without atresia.

Short gap vs long gap

A further phenotypic separation, and the one that has the greatest ramifications for ongoing morbidity in childhood and adulthood, is the length of separation of the gap between distal and proximal oesophagus.

***Short gap* –** Atresia gap less than two vertebrae at birth. These can have primary repair (PR) of the oesophagus (anastomosis of the two ends together shortly after birth). Currently this is almost universally performed by thoracotomy or increasingly endoscopically, but in the past many current adults may have had other surgical approaches, including substernal.

***Long gap* –** When the gap is larger than two vertebrae, the closure may be delayed to allow baby and oesophagus to grow, at which point delayed primary closure is performed or, if it is larger still 'long gap' (six vertebrae plus), oesophageal replacement may be needed, such as gastric pull-up/transposition (as the name implies, the stomach is 'pulled up' to connect with the proximal end of the oesophagus), jejunal or colonic transposition (where a section of the jejunum or colon is used to bridge the gap between the two ends of the oesophagus). Long-gap OA patients spend much longer in Neonatal Intensive Care Unit (NICU)under anaesthetic, in hospital before discharge and may need several operative procedures before repair is complete. They also are more likely to need multiple admissions in childhood, need nutritional support and have ongoing OA/TOF morbidity in childhood and adulthood. Many adults born with long-gap OA spent their first year of life in hospital, with all the impact that thus follows on development, family life and attachment, and medical trauma. However, as the rest of the leaflet will demonstrate, short-gap OA/TOF also leaves a lifelong impact on the body.

Over 50% of those born with OA/TOF have additional anomalies, cardiovascular in 29%, anorectal in 14%, genitourinary in 14%, additional gastrointestinal in 13%, skeletal in 10%, respiratory in 6%, genetic in 4% and other anomalies outside the above in 11%. This is most frequently the case in those with pure OA, and least common in Type C OA/TOF. OA/TOF forms the T and E of the VACTERL association of anomalies, and is also associated with CHARGE syndrome. (3) As is the case with OA/TOF, sometimes these additional anomalies become more serious in adult life.

Respiratory Problems

Nearly half of adults with OA/TOF will have respiratory symptoms each year. In one study, 30% had physician-diagnosed asthma, 44% reported wheezing in the last year, 28% recurrent wheeze, 30% long-standing cough, 25% cough and sputum. (4) This is also reflected in pulmonary function test results, where 21% demonstrate a restrictive pattern, 21% obstructive and 36% both. (5)

Causes

1. **Dysphagia and aspiration**. This is multifactorial in cause, and varies between individuals. Factors include unsafe swallow, oesophageal dysmotility and reflux, and pooling of upper airway secretions due to dysmotility, airway reflux, strictures and tracheal pouches. (6) The Hull Airway Reflux Questionnaire is 95% sensitive in diagnosing airway reflux in chronic cough.
2. **Tracheomalacia (TM) and/or bronchomalacia (BM)**. In a prospective study, 87% had TM. (7) TM can significantly impair secretion clearance, impair cough and increase risk of infection, and in turn delays recovery from infections. Tracheobronchomaacia (TBM) can also aggravate GORD and airway reflux. (8)
3. **Abnormal airway anatomy**. Some patients have a tracheal posterior wall diverticulum from the repaired fistula site. These pouches can allow pooling of oral secretions and recurrent pneumonia. (9) These may not be discovered until bronchoscopy in adulthood.
4. **Restrictive lung disease**. This is again multifactorial, including congenital vertebral and chest wall anomalies, surgical trauma, aspiration and recurrent infection. (6)

TOF cough/chronic cough

The cough itself is typically a hoarse brassy 'seal-like' cough, due to TM. Some adults have persistent coughing; for others it arises post aspiration or infection and then subsides. Causes of persistent cough include airway reflux, excess or difficult-to-clear secretions, inflamed airways due to TM. The cough can cause embarrassment, staring and comments in public due to its unusual nature – the TOF charity has produced explanatory badges as this is such a universal experience amongst those with OA/TOF. It can also affect sleep, damage intercostal muscles, cause airway pain and fatigue, trigger vomiting and facial petechial bleeding due to raised pressure on the small vessels.

Management

Aimed at improving secretion clearance

- Carbocysteine can thin sputum viscosity, aiding clearance.
- Hypertonic saline nebuliser/device to thin sputum viscosity. (10)
- Chest physiotherapy can also help facilitate secretion drainage.

Aimed at treating chronic cough

This should address the underlying cause, usually airway reflux. This may mean investigations such as manometry, endoscopy, pH studies to assess this and look for any undiagnosed anatomical anomalies:

- Proton pump inhibitors once or twice a day can suppress acid reflux that triggers coughing.
- Pro-motility antibiotics such as azithromycin can improve oesophageal motility, improving all reflux and oesophageal content stasis. These have been very effective in adults born with OA/TOF treated by Professor Morice, an international (airway reflux) cough expert physician at Hull Teaching Hospitals, UK.
- Metoclopromide or domperidone can also improve oesophageal motility and reflux, and in turn cough in this specific patient subgroup with GORD cough.(6)
- Bronchodilator inhalers are often ineffective in TOF cough, and may aggravate TM. (6)
- Steroid inhalers may help TOF cough in the context of asthma, or improve tracheal inflammation, but may not be successful in many. (11)
- Rarely, severe cough may require more aggressive intervention if airway reflux is very severe, such as fundoplication, tube feeding, other surgical approaches due to risk to the lungs from aspiration.

Tracheomalacia, bronchomalacia and tracheobronchomalacia

These conditions are characterised by excessive collapse of the trachea and main bronchi (intrathoracic trachea collapsing during exhalation and extrathoracic trachea collapsing during inhalation) associated with increased compliance of the airway wall, cartilaginous rings or both. It is a common finding in those born with OA/TOF. A prospective study found that 87% TOFs had TM. (7) TM can significantly impair secretion clearance, impair cough and increase risk of infection, and in turn delays recovery from infections. TBM can also aggravate airway reflux. There is also associated upper airway inflammation, with over a third found to have inflammation on bronchoscopy visually and even higher histologically.(8)

Pathophysiology

Cartilage deficiency and cilia loss at fistula site →Airway collapse →Retention secretions→ Bacterial colonisation →Chronic bronchitis → Recurrent pneumonia → Bronchiectasis. (12)

Complicating factors

The unique nature of the OA/TOF anatomy post-surgery means that many factors can aggravate the TM, which can cause flares in symptoms. These include:

- Vocal cord paralysis
- Extrinsic tracheal compression
- Oesophageal stricture
- Food bolus (this can press on the floppy trachea through the oesophagus wall)
- Recurrent aspiration
- Cardiac/ vascular anomalies, eg VACTERL, aorta scarred onto trachea and oesophagus post surgery
- Allergic sensitisation of airways (12)

Symptoms

- Dyspnoea
- Chronic brassy/hoarse cough
- Wheeze due to collapse of the tracheal lumen and not responsive to bronchodilators
- Recurrent respiratory tract infections
- Delayed recovery from infections
- Aggravation of airway reflux
- Difficulty clearing secretions (13)
- Exercise intolerance
- Impaired lung function (12)

Investigations

- Flexible bronchoscopy – **This is the gold standard for investigation of TBM. It is recommended for anyone with OA/TOF with unexplained wheeze or exercise intolerance.**

(12) It may show upper airway inflammation – one prospective study found visible inflammation in a third of patients and higher levels histologically. (8,12)

- CT scan can also assess TBM.
- Spirometry can also assess severity of TBM.

Treatment

Aimed at improving secretion clearance

- Carbocysteine can thin sputum viscosity, aiding clearance.
- Hypertonic saline nebuliser/device to thin sputum viscosity. (10)
- Chest physiotherapy can also help facilitate secretion drainage.

Aimed at treating airway inflammation

- Bronchodilators should not be used as they may worsen airway collapse.
- Inhaled steroids should be used routinely in the presence of chronic airway inflammation and suspected pneumonia.
- Systemic steroids can also be helpful in suspected pneumonia.

Other treatments

- **Annual influenza vaccination is recommended in people born with OA/TOF.**
- Trial of anti-reflux treatment in those with persistent symptoms.
- Antibiotic threshold should be lower if there are worsening symptoms in a patient with TBM.
- Prophylactic azithromycin is recommended if there are persistent symptoms and a background of bronchiectasis. (12)

‘Chest infections’/bronchitis/aspiration pneumonitis

Aetiology

Multiple factors in adults with OA/TOF increase their prevalence of pulmonary morbidity. Sistonen et al. (2010) (14) found 56% of the adults aged between 22 and 56 had had pneumonia, 70% bronchitis and 52% reported recurrent respiratory infection. All below are strongly associated with recurrent pneumonia in repaired OA/TOF. (15)

- Oesophageal motility disorders/dysphagia
- Strictures
- GORD
- Anatomical anomalies (laryngeal cleft, vocal cord paralysis)

Symptoms

- Witnessed/known aspiration/choking event
- Fever
- Coughing
- Shortness of breath
- Raised heart and respiratory rate (16)

Diagnosis

This is easy when there is a witnessed episode of choking, but many result from ‘subclinical micro-aspiration and misidentification of chronic cough/wheeze and dyspnea’. (17) Diagnostic tools may include the following:

- Raised white cell count
- Chest X-ray – but changes aren’t necessarily visible
- Oesophageal manometry is useful to demonstrate the near universal disordered/absent peristalsis in those born with OA/TOF (18)
- CT, bronchoscopy and/or lung biopsy should be considered in patients with moderate-to-severe pulmonary morbidity due to airway reflux and aspiration episodes

Treatment

- Optimise management of airway reflux. (15)
- Antibiotics may not be needed if this is pneumonitis rather than aspiration pneumonia, but since one can’t differentiate clinically, empirical broad-spectrum antibiotics are usually advised. In addition, the difficulties clearing secretions from the airways can also allow bacterial infection to develop, so antibiotics are recommended in any episode lasting longer than two weeks. (6)
- Recurrent episodes or severe episodes of aspiration necessitate referral to a surgeon with knowledge of OA/TOF for consideration of fundoplication or tube feeding to protect the lungs.

Barium aspiration

Aspiration is the most common complication of barium swallow or follow-through investigations. It is still very rare, around 0.04%. However, most episodes of aspiration have no clinical sequaelae. (19)

The severity of barium aspiration usually depends on the volume of barium aspirated. The distribution of the barium into the lobes of the lungs is usually dependent on the position of the patient during the procedure, though it can be bilateral in large aspirations. (20–23) Barium aspiration causes respiratory problems by three main mechanisms. Firstly, the viscous barium sulphate may obstruct the airways, and the lungs can struggle to clear the liquid. Secondly, the presence in the airways interferes with gas exchange and ventilation-perfusion mismatch, and this can lead to hypoxia, pneumonia, adult respiratory distress syndrome, respiratory failure and death. Lastly, long term, the aspiration can cause pulmonary fibrosis (the barium is phagocytosed by alveolar macrophages, causing the fibrosis) and bronchial granulomas. (19,23)

Risk factors for aspiration in those born with OA/TOF

1. Barium swallow may be used to diagnose feeding issues in infancy before diagnosis is known, allowing aspiration via the unrepaired TOF. (24)
2. Infancy is also a risk factor. (21)
3. Those born with OA/TOF are much more likely to have this investigation, both as children and in adulthood, though some previous rationales for the investigation are now superseded by newer investigations, and due to concerns about lifelong radiation exposure. (19)
4. The presence of undiagnosed recurrent TOF, albeit rare, will also lead to barium aspiration, and some adults will have endured barium aspiration as infants when these investigations were carried out before the diagnosis of OA/TOF was known. (20)
5. Dysphagia is a major risk factor for barium aspiration.
6. GORD, another common OA/TOF issue, also increases the risk of aspiration. (21)

Treatment

There is no standard management protocol for management of acute aspiration of barium. Treatment of symptoms and stabilising the patient is the priority:

- Oxygen
- Antibiotics if infection is present
- Stabilise the patient
- Bronchio-alveolar lavage isn't routinely recommended as it may disperse the barium through the lungs
- Chest physiotherapy may promote clearance of the barium (21)

Long term

Management of symptomatic pulmonary fibrosis and bronchial granuloma is beyond the scope of this booklet. However, if respiratory symptoms develop/persist after a known episode of barium aspiration, chest x-ray and CT chest can delineate the extent of the problem, and/or endoscopy for

bronchial granuloma, and referral to respiratory physicians is recommended. Voloudaki et al. (2002) reported such CT changes as 'thickened interlobular septa, subpleural lines, subpleural cysts, and centrilobular micronodules along with barium particles in a subpleural distribution'. (25)

Bronchiectasis

Between 4% and 27% of children born with OA/TOF across various research had radiological evidence of bronchiectasis, and whilst data is lacking in older patients, one can extrapolate that this is likely to increase with age. (17)

As in other patients, signs of bronchiectasis include:

- Cough
- Daily sputum production, lasting months to years
- Haemoptysis (blood-streaked sputum) during acute exacerbations
- Dyspnoea, chest pain, wheezing, fever, fatigue and weight loss (26)

Flares of bronchiectasis may result in:

- Increased sputum
- Increased thickness of sputum
- A foul-smelling sputum occasionally
- Low-grade fever (rare)
- Increased fatigue, malaise
- Increased dyspnoea, shortness of breath, wheezing or pleuritic pain

There should be a high index of suspicion for bronchiectasis in adults with repaired OA/TOF with recurrent episodes of chest infections, and/or cough with daily purulent or mucopurulent sputum and consideration of CT scan or respiratory referral. The British Thoracic Society (BTS) recommends investigating patients with chronic purulent or mucopurulent cough and risk factors such as GORD and chronic obstructive pulmonary disease (COPD). (27)

Investigations

The BTS guideline recommends the following investigations:

1. Full blood count, urea and electrolytes, serum total IgE, specific IgE to Aspergillus fumigatus.
2. Serum immunoglobulins
3. Sputum cultures for routine and mycobacterial culture
4. CT scan (27)

- **Normal CXR does not rule out bronchiectasis** but may show increased pulmonary markings, honeycombing, atelectasis, tram tracking.
- **Chest CT without contrast is the best way to diagnose bronchiectasis** and may show parallel tram track lines, signet ring appearance, dilated bronchus lumen, cystic spaces and honeycomb appearance. There may also be bronchial wall thickening, mucous impaction and air trapping on expiratory CT. (26,27)
- **Chest CT is recommended in any adult born with OA/TOF with irreversible changes on CXR.** (12)
- **Pulmonary function tests** may show obstructive changes and a yearly decline in FEV1.

Treatment

- Supportive – smoking cessation and avoidance of second-hand smoke, immunisations for pneumonia, influenza, measles, rubeola, pertussis (whooping cough).
- Chest physiotherapy. Active cycle of breathing techniques or oscillating positive expiratory pressure should be taught to all patients with bronchiectasis, and sitting airway clearance techniques rather than postural drainage due to adults born with OA/TOF's GORD. (27)
- Mucolytics – see TM section.
- Broad spectrum antibiotics for acute exacerbations/flares for seven to ten days, eg amoxicillin, clarithromycin.
- Regular antibiotics to control the infectious process are needed in some patients, eg macrolides. The BTS advise this for those with three or more exacerbations per year when physiotherapy or mucolytics have not improved this. (26,27)

Late onset asthma/eosinophilic bronchitis

Whilst it is common for those born with OA/TOF to be diagnosed with asthma incorrectly, in some the exposure of the airway to frequent micro-aspiration can trigger airway eosinophilia, leading to late-onset asthma and eosinophilic bronchitis. It is thought that those with an atopic diathesis (history of eczema/asthma/urticarial/hay fever) are predisposed to develop inflammation through the T helper 2 pathway when exposed to chronic inflammation through reflux. Airway reflux is also a known exacerbatory factor in existing asthma. (28–30)

Investigations and treatment

- Diagnosis and treatment of asthma and eosinophilic airway disease follows standard National Institute for Clinical Excellence (NICE) and local protocols.
- If the development of eosinophilic airway disease in patients with OA/TOF is suspected, an eosinophil count of 0.3 or higher is highly suggestive in the presence of other symptoms. (11)
- Management of airway reflux and asthma/eosinophilic airway disease is important to optimise airway symptoms. (11,28)

Restrictive airway disease in OA/TOF

Numerous research studies have consistently shown a restrictive pattern of pulmonary function impairment. Prevalence varies from 21% to 51.5%. (5,14,31,32) Lung volume is also reduced compared to matched non-TOF peers, as is exercise capacity. This is attributed to a number of factors, but mainly the impact of surgery on the developing lungs, with previous thoracotomy, scoliosis and vertebral anomalies reducing lung growth and thoracic movement. (14,15)

Even with these abnormalities evident on lung function testing, these often produce no symptoms in younger people, but those over 35 may develop shortness of breath, reduced exercise tolerance and increased respiratory infections as a result of this. (33)

Treatment is limited but it is important to keep the chest free of secretions to minimise risk of infection, eg by chest physiotherapy and secretion thinning agents.

Recurrent tracheo-oesophageal fistula in adulthood

Recurrent TOF is a known complication of surgical repair of OA in infancy, but can also occur, very rarely, in adulthood. There are a small number of case reports of this occurring, including multiple in the same adult patient. Symptoms include severe coughing symptoms and recurrent aspiration pneumonia. The case reports identified the fistulae using bronchoscopy and were repaired surgically. (34,35)

Recommended long-term management of patients with repaired OA/TOF and respiratory morbidity (15)

Mild

Defined as SpO2 at rest from 90% to 93% and/or normal-to-slightly abnormal chest radiography and/or FEV1 ≥ 70% predicted and/or FVC ≥ 70% predicted:

- Primary care follow-up
- Prompt aggressive treatment of infection
- Functional assessment once a year
- Consider referral to respiratory physician (preferably one experienced with OA/TOF) if clinical deterioration
- **Annual influenza vaccination is recommended in people born with OA/TOF**
- **Pneumococcal vaccination is recommended**
- **Covid booster is recommended as those with OA/TOF are a vulnerable group**

Moderate/severe

Defined as SpO2 at rest < 90% and/or relevant abnormalities at chest radiography and/or FEV1 < 70% predicted and/or FVC < 70% predicted

- Regular respiratory physician follow-up (preferably one experienced with OA/TOF)
- Advanced lung imaging at least at baseline
- Endoscopy
- **Annual influenza vaccination is recommended in people born with OA/TOF**
- **Pneumococcal vaccination is recommended**
- **Covid booster is recommended as those with OA/TOF are a vulnerable group**

Gastrointestinal Problems

The main symptoms that patients experience in adult life are swallowing difficulties (dysphagia) and reflux symptoms (heartburn and regurgitation of food). These symptoms are very common, occurring in up to 80% of adults who have had surgery for OA.

Such issues occur as a result of a loss of normal anatomy and nerve supply to the lower oesophagus:

- Surgery to repair OA involves bridging the gap between the upper and lower oesophagus. This almost invariably leads to some shortening of the oesophagus, which tends to pull the junction between the oesophagus and the stomach up above the diaphragm. This is known as a sliding hiatus hernia. Normally the oesophago-gastric junction (the point at which the oesophagus meets the stomach) lies below the diaphragm, in the abdomen.
- The nerve supply to the oesophagus consists of two parts. The left and right vagus nerves travel down along the oesophagus from the brain to supply organs in the chest and abdomen, including the oesophagus, and an intrinsic network of nerves in the wall of the oesophagus, which makes the oesophagus contract to create peristaltic waves pushing the food to the stomach. Although the vagus nerves usually remain intact after repair of OA, there is always an interruption of the network of nerves within the wall. The nerve supply to the lower segment of oesophagus is therefore invariably impaired. This leads to poor functioning of the muscles in the wall of the lower oesophagus.

The likelihood that an adult who underwent surgery for OA in infancy will suffer from continuing oesophageal symptoms depends on:

- The amount of scar tissue from surgery
- The length of the gap that had to be covered by the surgery
- The presence or absence of a hiatus hernia
- Whether or not an oesophageal replacement had to be used (36)

Whilst most people with repaired OA/TOF will have dysphagia, GORD or other gastrointestinal symptoms; one difficulty for the patient and doctor is that they may not be aware what is pathological. Adults born with OA/TOF have had a lifetime of adaptation to these symptoms, and no experience of a normal oesophagus, so it is often useful to use a reflux or dysphagia questionnaire in this instance to help determine symptoms fully.

Dysphagia

Up to 90% of adults born with OA/TOF have occasional symptoms of dysphagia, and 25% have daily symptoms. (37) Cartabuke et al. (37) found this was predominantly to solids with 72% reporting this, but a significant minority also report dysphagia to liquids (44%).

Causes

1. **Dysmotility**. Manometry studies on adults with repaired OA/TOF show universally disordered peristalsis. Deurloo et al. (18) found 75% had low or moderate contraction and 35% had retrograde contraction. All had ineffective swallowing. In addition, 25% were found to have undiagnosed strictures. This follows on from another study in children where 66.7% had absent peristalsis and 33.3% weak peristalsis. (37) Poor motility is a result of poor nerve supply to the oesophagus below the repair site, and thus peristalsis is usually absent in the lower oesophagus below the repair. If a colon interposition graft was used (long-gap OA) to join the gap in the oesophagus, peristalsis is also impaired or absent in this segment. (36) There is growing anecdotal evidence that the oesophagus post OA repair deteriorates more rapidly than the normal oesophagus, and dysmotility can increase with age.
2. **Strictures**. A stricture is a narrowing in the oesophagus from scar tissue. The most common place for a stricture to occur is at the anastomosis (join) from the original surgery where the oesophagus was repaired. When tissues heal, they contract – and this can result in narrowing. Many children will have had dilatations of the oesophagus to improve their swallowing; residual narrowing may persist into adulthood. (38) The normal oesophagus in an adult is about 18mm to 20mm wide (similar in diameter to your thumb) and if this is reduced by even 3mm or 4mm it can lead to problems with swallowing. The inevitable dysmotility compounds the effect of a stricture, so even a very mild stricture can cause significant dysphagia. Severe strictures reduce the oesophagus to only 2mm or 3mm in diameter and this will restrict swallowing to liquids only. Strictures can also occur as a result of reflux, with damage to the oesophageal lining by acid. Acid reflux will cause inflammation of the wall of the oesophagus; if this is severe, it can heal by forming scar tissue. This scarring tends to contract and cause narrowing of the oesophagus in the same way as above. Sometimes the join from the original surgery can behave like a stricture even if it is not particularly narrowed because there is disproportion between the diameter of the tube above and below the anastomosis. The typical example of this is when the colon has been used to bridge the gap in long-gap atresia of the oesophagus. The colon is wider than the oesophagus and therefore there is always some disproportion. Over years the colon graft often dilates further and this disproportion becomes more pronounced. The difference in size between the colon and the oesophagus will often cause food to stick above the join even if the join itself is not narrowed. (36)
3. **Diverticulum**. Rarely, a diverticulum (pouch) can form in the oesophagus, usually at an area of weakness just above an area of high pressure. The most common place for a diverticulum is just above the site of the original anastomosis, but a diverticulum may also form above an area of persistent spasm in the lower oesophagus. This can cause dysphagia in two ways:
a) As a result of food going into the diverticulum rather than down the oesophagus
b) As a result of the stricture or area of spasm which led to the diverticulum in the first place.

4. **Hiatus hernia**. In sliding hiatus hernias, the diaphragm may press on the top of the stomach and this pressure can cause dysphagia. The presence of the hiatus hernia can also worsen any reflux, which may exacerbate the dysphagia (36); 28% of adults born with OA/TOF were found to have hiatus hernia on endoscopy. (5)

Symptoms

1. Sensation of food or fluid getting 'stuck'
2. Choking – reported in 33% post repair whilst eating (8)
3. Regurgitation
4. Worsening heartburn/reflux symptoms

Investigations

These are suggested when symptoms change, food is repeatedly getting stuck for prolonged periods (or needing hospital visits), weight loss or recurrent aspiration occurs. The aim is to look for new or worsening strictures or malignant changes and assess degree of dysphagia and whether oral feeding remains safe.

- Gastroscopy
- Oesophageal manometry and 24-hour pH studies (see below)
- Barium swallow will not aid in diagnosis of dysphagia and will provide additional unnecessary radiation

Treatment

Whilst there is no way to cure underlying issues with peristalsis, there are some measures that can ameliorate symptoms:

- Feeding adaptations – dietician/speech and language therapist input may be helpful, though many adults born with OA/TOF have spent their lifetime modulating their food intake to help their dysphagia, such as avoiding meats and difficult textures, hyperalimentation (drinking excess water), use of carbonated beverages.
- Treatment of GORD and oesophagitis (see below).
- Prokinetics (metoclopramide/domperidone (both 10mg up to three times a day), macrolide antibiotics such as azithromycin 250mg, dosage varies between clinicians between three times a week to daily).
- Treatment of any structural obstruction, such as strictures, stenosis or diverticula. This needs the involvement of gastroenterology or GI surgeons for consideration of endoscopic oesophageal dilatation (most commonly), stenting (temporary to hold open resistant strictures) or, rarely, surgery is required for a resistant stricture – either an operation to open up the stricture permanently (oesophagoplasty) or to remove the stricture. If the stricture is related to reflux, it is essential to treat the underlying reflux properly, otherwise the stricture will recur rapidly. (36)
- In severe cases, rarely, tube feeding (gastrostomy, nasogastric (NG), percutaneous endoscopic gastrostomy (PEG)) may be needed. (39)

Food bolus obstruction

Most born with OA will experience episodes of food bolus obstruction, whether this is with every solid food item ingested or infrequently. However, the vast majority have developed a wide range of techniques to mitigate this problem. This ranges from drinking copious fluids with each meal, avoiding certain foods and textures, and using particular postures to encourage difficult items to move in the oesophagus. Even when prolonged obstruction occurs, many will use tried and trusted methods such as carbonated drinks and fruit juices to dissolve the obstruction. Nonetheless, on occasion, this obstruction will need medical attention.

Aetiology

Patients presenting with food bolus obstruction usually have oesophageal pathology causing the impaction. (40) Those born with OA/TOF are at high risk of food bolus obstruction compared to the general population due to a number of factors. These include oesophageal dysmotility, prior oesophageal surgery scarring, eosinophilic oesophagitis and new stricture formations.

Symptoms

There is usually a history of acute dysphagia after consumption of a food bolus, which may be severe enough to prevent swallowing saliva, resulting in drooling. Chest pain, neck pain, odynophagia may also be present. Aspiration may occur, as may perforation of the oesophagus if obstruction is prolonged.

Diagnosis

Patients can usually identify the bolus ingestion and onset of symptoms and may be able to localise discomfort. However, even in a normally innervated oesophagus this correlates poorly with the site of obstruction, and this is even more true in adults born with OA, as the repaired oesophagus or interposition may be insensate in some areas. (40,41)

Investigation and treatment

In uncomplicated food bolus obstruction, endoscopy and biopsies is the investigation/treatment of choice without need for radiology. These patients need to be managed in a hospital setting, usually Accident and Emergency, or on-call gastroenterology admission.

- Watch and wait. In a stable patient able to manage secretions, urgent endoscopy may not be necessary; however, an obstruction lasting more than 24 hours makes retrieval more difficult.
- Adult guidelines recommend rapid endoscopy for the removal of oesophageal obstruction within two or, at the latest, six hours when there is complete obstruction (unable to swallow saliva), and urgent within 24 hours when there is partial oesophageal obstruction. (210,211)
- Endoscopic intervention is urgent in those who can't swallow their own secretions due to risk of aspiration and respiratory compromise due to pressure of the bolus on floppy airways. This is usually retrieval using nets, baskets or forceps, though pushing is used in some instances but can increase the risk of perforation. (40,41) Endoscopic dilatation may sometimes be appropriate at the same time as retrieval of the food bolus.

Gastro-oesophageal reflux disease (GORD)

Symptomatic GORD is extremely common in adults born with OA/TOF. Amongst adults who underwent primary repair, 75% had occasional symptoms, 17% daily, 40% weekly and 65% monthly. (31) Those with gastric transpositions have considerably higher frequency of symptoms.

Causes

Most reflux symptoms are due to gastro-oesophageal reflux – reflux of stomach contents (acid, bile, food) up into the oesophagus, and sometimes higher into the throat and mouth. Normally the lower oesophageal sphincter keeps the lower oesophagus closed and prevents gastric contents refluxing up the oesophagus. The diaphragm also helps prevent reflux by exerting pressure on the lower oesophagus. The presence of a hiatus hernia prevents the diaphragm exerting pressure on the oesophagus and this also causes reflux. In patients who have had OA repair, reflux is caused by the combination of impaired nerve supply in the lower oesophagus, leading to poor motility and poor functioning of the lower oesophageal sphincter, and the anatomical changes in the position of the oesophagus and stomach effected during repair of the OA. The pulling up of the stomach to the blind end of the oesophageal pouch to create a functional oesophagus means that the lower oesophageal sphincter has been elevated, creating a hiatus hernia, and is no longer aligned with the diaphragm, creating an additional reason for poor lower oesophageal sphincter function.

Identical symptoms can also be caused by intra-oesophageal reflux – reflux of contents within the oesophagus. This is due to oesophageal contents stagnating in the lower oesophagus because they are very slow to pass into the stomach. The main causes of this are either a stricture in the lower oesophagus or severely impaired motility with spasm. Rarer causes are a diverticulum, a dilated colon or small bowel graft if this was necessary to bridge a long-gap atresia. Intra-oesophageal reflux may cause exactly the same symptoms as gastro-oesophageal reflux, but it is very important to distinguish between the two as the treatments are completely different.

Rarely, the impaired nerve supply of the lower oesophagus can affect the stomach, leading to delayed emptying of the stomach or gastroparesis. This may cause a sensation of being very full and bloated after eating. Delayed gastric emptying worsens reflux symptoms. Although this is rarely a major problem, mild forms probably occur in up to 30% of patients. (36)

Symptoms

The symptoms for GORD are the same as in those born with a normal oesophagus and stomach. These include heartburn, regurgitation of food, acid brash. There are often associated respiratory, sinus and dental issues. Most severely, it can rarely cause respiratory distress, which may be a life-threatening event, and is a medical emergency.

However, it is often difficult for adults born with OA/TOF to recognise symptoms as GORD as they have been present since birth. It is common for adults born with OA/TOF *to find they have severe reflux when filling in a GORD questionnaire, and not have realised these symptoms were abnormal or part of reflux.*

Investigations

All patients with persistent oesophageal symptoms should be investigated, firstly to rule out Barratt's oesophagus and oesophageal cancer, and then to inform treatment. (36,39)

1. Oesophagogastroduodenoscopy – to look for oesophagitis, Barratt's oesophagus and oesophageal carcinoma. It is a poor tool to assess motility, but oesophageal dilatation and the presence of food in the oesophagus will be very suggestive of underlying dysmotility. Oesophagitis is commonly found in those born with OA/TOF on surveillance – 23% by age 10. (38) and 8–26.4% in surveillance of adults. (5,33) A recent systematic review found a prevalence of histological esophagitis of 56.5% in OA patients. (42)
2. Barium swallow – to provide information about motility, as well as identify hiatus hernias, strictures and diverticula.
3. CT scan – if the oesophagus or colon graft is very dilated to delineate anatomy.
4. Oesophageal manometry and 24-hr pH testing and impedance testing – to provide details about the differences in peristalsis above and below the anastomosis site of the repair.
5. Radionucleotide studies – occasionally needed to assess the length of time for passage of food through the oesophagus and stomach. (36)

Treatment

1. **Lifestyle advice**. Advice on healthy eating, weight loss and smoking cessation if appropriate may alleviate symptoms somewhat, though this is unlikely to be curative in this population.
2. **Diet modifications**. Alcohol, fatty foods, acidic drinks such as fruit juices, coffee and chocolate may all aggravate GORD.
3. **Behaviour modification**. Raising the head of the bed, or a bed wedge pillow may help, and some adults born with OA/TOF need to use a hospital-style bed to reduce risk of aspiration. Avoiding eating and drinking well before bed time, avoiding bending to the floor after a meal or drink will also reduce risk of reflux and aspiration. (43)
4. **Proton pump inhibitors (PPIs)**. As with other patient groups, these are the mainstay of treatment. It may be necessary to prescribe these twice a day. (39) Those with past history of dilatations may be advised to stay on full dose PPIs long term. (43)
5. **H2 receptor antagonists.** When available, in resistant GORD, this can be added to the PPI regimen, usually in the regimen PPI breakfast and lunch and H2 receptor in the evening.
6. **Prokinetics**. Metoclopramide, domperidone and macrolide antibiotics can increase the rate of oesophageal and gastric emptying and reduce the volume of oesophageal and gastric contents available to reflux and be regurgitated. (11)
7. **Fundoplication**. If medication does not control the symptoms, particularly if reflux is causing recurrent aspiration and chest infections, anti-reflux surgery may be necessary.
    - This usually involves keyhole (laparoscopic) surgery to repair the hiatus hernia (if present) and some form of fundoplication (wrapping the top of the stomach, or fundus, around the bottom of the oesophagus) to reinforce the oesophagogastric junction 'valve'.
    - The motility in the lower oesophagus is usually very poor and a full fundoplication (Nissen fundoplication) involving a 360° wrap could make swallowing worse, so most surgeons carry out a partial fundoplication whereby only the back (Toupet fundoplication) or front (Dor fundoplication) is covered by the fundus of the stomach. (36)

However, fundoplication is not a universal solution as it may aggravate dysphagia in those with the poorest oesophageal motility. In those with an existing fundoplication, this should still be assessed as an option since up to 25% of fundoplications in OA/TOF need to be redone. (42)

8. **Poorly functioning colon interposition graft**. Some patients with long-gap OA have a segment of colon or small intestine taken up to bridge the gap. These grafts can become progressively dilated and tortuous (baggy), leading to progressive difficulties in swallowing and intra-oesophageal reflux symptoms.
    - If there is significant disproportion between the colon and the oesophagus beyond it, endoscopic dilatation of the join up to 20mm may help.
    - When symptoms cannot be managed by dilatation and dietary changes, surgery may be necessary, either by oesophagoplasty (opening up the join to a wider diameter) or removing the colon graft and replacing with stomach or small intestine. (36)

It is advised that adults born with OA/TOF needing reflux surgery are referred to an upper GI surgeon at a tertiary centre with a specialist interest in the condition.

Chest symptoms due to GORD/oesophageal spasm

Non-cardiac chest pain is defined as recurring angina like substernal chest pain of non-cardiac origin. This can be a squeezing, burning substernal chest pain which can radiate to the back, neck, arms and jaws. The symptoms are intermittent and can last from minutes to days. It may also be accompanied by symptoms of GORD. Pain may be triggered by eating quickly or consuming hot, cold or carbonated drinks Whilst this needs evaluation for cardiac causes, adult patients born with OA/TOF are usually younger than typical of cardiac causes of chest pain and may lack personal and family history of cardiac disease. (123,124,125)

Diagnosis

- Normal ECG/troponin blood test/ECHO (if appropriate)
- pH monitoring/oesophageal manometry/24-hour manometry
- Gastroscopy

Treatment

1. PPIs and GORD treatment are first line treatments.
2. Smooth muscle relaxants have been used but show limited efficacy, eg diltiazem 60–90mg four times per day, nifedipine 10–30mg three times per day.
3. Nitrates have also been used, such as isosorbide mononitrate.
4. Pain modulators such as tricyclic antidepressants (eg low-dose amitryptiline) or trazadone improve symptoms due to neuromodulatory and analgesic properties. (124)
5. Medical interventions by gastroenterologists are sometimes used, such as botulinum toxin or balloon dilatation of the affected area. However, there is no research in the management of oesophageal spasm on the background of OA/TOF at present so it is hard to say how botulinum toxin might affect the already precarious oesophageal motility here. (125)

Barrett's oesophagus and oesophageal carcinoma

In Barrett's oesophagus, healthy oesophageal epithelium is replaced with metaplastic columnar cells – the result, it is believed, of damage from prolonged exposure of the oesophagus to the refluxate of GORD. The inherent risk of progression from Barrett's oesophagus to adenocarcinoma of the oesophagus has been established. (44)

Barrett's oesophagus occurs more frequently and at an earlier age than in the general population, and this is believed to be due to exposure of the oesophagus to GORD from birth. Prevalence of Barrett's in children born with OA/TOF is between 6.4% and 15% with a lag time from initial surgical correction of around ten years. (37,42,45) Prospective surveillance endoscopy of adults born with OA/TOF found prevalence of Barrett's oesophagus between 6.6% and 31%, meaning the prevalence is at least four times that of the general population. (46,47) This data is even more striking when one considers that the vast majority of the repaired OA/TOF population is <50. TOF recurrence, long-gap OA, oesophageal stricture resection in childhood, oesophageal stricture present in adulthood, severe reflux symptoms, and age above 30 years are at increased risk for developing Barrett's oesophagus. (46,48)

Most recently, Ten Kate et al. (in press) (49) have been routinely performing endoscopy in all adults born with OA/TOF enrolled as children in their Rotterdam OA/TOF cohort since 2013. They report endoscopic oesophagitis in 9%, columnar lined epithelium in 27% and hiatus hernia in 68%. Barratt's oesophagus was found in 9% of this cohort. Progression to Barratt's occurred in 4% of patients over the duration of the programme, a rate of around 0.8% per year. These patients were older, with an increased rate of hiatus hernia and GORD symptoms. They recommend endoscopic surveillance of all adults born with OA/TOF, starting at 20 years old, and recommend extending the interval to ten years (contrasting with the ESPGHAN guidelines). This recommendation is based on their youngest diagnosis of Barratt's at 20.9 years old, and no dysplasia or malignancy diagnosed before 40 years old.

Barrett's oesophagus should also be considered in those long-gap patients repaired by gastric pull-up and colonic interposition, as these changes have been found in the oesophageal remnant. (31,50)

Management of Barratt's is with acid suppression medication with the aim of preventing high-grade dysplasia and malignant transformation, and occasionally anti-reflux surgery is required to control the reflux. However, neither acid suppression medicine nor anti-reflux surgery will necessarily prevent the development of Barratt's – 40% of those who had surgery still went on to develop the changes. (46)

There is also growing evidence that there is an increased risk of oesophageal cancer in adults born with OA/TOF, although this is an ongoing area of research. There are case reports of both adenocarcinoma and squamous carcinoma in adults aged between 20 and 46. (47,51–55) A retrospective review of the OA database from the Royal Children's Hospital in Melbourne (798 patients [309 patients older than 40 years]) was performed to identify cases of oesophageal cancer developing in this cohort. At the time of the publication, four of 309 patients had developed oesophageal squamous cell carcinoma before the age of 40 years. The cumulative incidence of oesophageal squamous cell carcinoma in this age group was 50 times that expected in the general

population. (56) A fuller picture of the increased risk of oesophageal carcinoma should emerge as the population ages.

Those who have colonic interpositions are also at risk of malignancy developing. There are a number of case reports of adenocarcinoma and squamous cell carcinoma developing within colonic interpositions, including two in adults born with OA/TOF. (55,57,58)

ESPGHAN recommendations are regular clinical follow-up in every adult patient with OA, with special reference to presence of dysphagia, GORD, respiratory symptoms and anaemia with:

1. Routine endoscopy (with biopsies in four quadrants at gastroesophageal junction and anastomotic site) at time of transition into adulthood and every five to ten years

2. Additional endoscopy if new or worsening symptoms develop

3. In the presence of Barrett's oesophagus, as per standard guidelines (39)

Dumping syndrome

Dumping syndrome, or rapid gastric emptying, occurs when food moves too quickly from the stomach to the bowel. Whilst it is very rare in those born with short-gap OA, it occurs relatively frequently in long-gap OA. There is good research on the condition in those with long-gap OA repaired by gastric pull-up. Hannon et al. (2020) (31) found 12% of their cohort were formally diagnosed with the condition, whilst 25% were symptomatic but had yet to be formally diagnosed. The research is scanty in those with jejunal or colonic interpositions, but there are a number of adults with these oesophageal replacements who have this diagnosis. However, even some with short-gap OA have dumping syndrome, secondary to anti-reflux surgery, and in fact anti-reflux surgery is the main cause of the condition in childhood. It has also been found in short-gap OA in the absence of anti-reflux surgery, and this is thought to be due to vagal nerve damage during repair triggering abnormal gastric emptying, alongside the congenital neuromuscular anomalies in oesophageal and gastric emptying. (59)

Symptoms

Early dumping systemic symptoms

Within the first hour after the meal, due to rapid transit of nutrients to the small intestine:

- Desire to lie down
- Palpitations
- Fatigue
- Faintness
- Syncope (sudden loss of consciousness)
- Diaphoresis (sudden onset of sweating)
- Headache
- Flushing

Early dumping gastrointestinal symptoms

Within the first hour after the meal:

- Epigastric fullness
- Diarrhoea
- Nausea
- Abdominal cramps
- Borborygmi (loud bowel noises)

Late dumping symptoms

Occurs one to three hours post meals:

- Perspiration
- Shakiness
- Difficulty concentrating
- Decreased consciousness
- Hunger

Weight loss and lower body mass index (BMI)

There is good research to show that many patients lose weight post anti-reflux surgery or oesophageal surgery in adulthood, due to the symptoms of dumping syndrome and avoiding eating or modifying the diet to avoid symptoms. (60)

Investigations

Whilst there are a number of investigations that can be used to aid in diagnosis, a symptom-based questionnaire can also be used whilst waiting for these to be done. All of the investigations below necessitate referral to secondary care:

1. Oral glucose tolerance test is the gold standard for diagnosis.
2. Hydrogen breath test post ingestion of glucose.
3. Gastric emptying study – can be done to determine likely neuromuscular causes but not diagnostic for dumping syndrome.
4. Barium swallow and gastroscopy can help assess the anatomy but don't help in diagnosis. (60)

Treatment

- Dietary modification is first line of treatment, and dietitian referral. The recommended changes include daily nutritional intake being divided into six small meals. For most with dumping syndrome, fluid intake with meals is restricted, but this isn't possible in OA/TOF. Rapidly absorbable carbohydrates, eg sugary foods such as sweets, sugary breakfast cereals, honey, syrups and sugary drinks, should be avoided. Nutrient-rich supplement drinks (milkshake/juice style) commonly advised by healthcare professionals may make symptoms worse due to their high sugar content. Eat more complex carbohydrates like whole grains, pasta, potato, rice, wholemeal breads and unsweetened cereal.

  Include a protein source at each meal, eg eggs, meat, poultry, fish, milk, yogurt, cheese, pulses and nuts. Foods high in soluble fibre slow gastric emptying and prevent sugars from being absorbed too rapidly. Foods high in soluble fibre include: broccoli, Brussels sprouts, carrots, nuts, oats, okra, peas, pears, prunes, pulses and soya beans.

  Eat slowly and chew food thoroughly. Avoid alcohol. (59)

- Acarbose can slow carbohydrate absorption and in turn hypoglycaemia in late dumping, but are less useful in early dumping, which represents most patients with OA/TOF.
- Somatostatin analogues, such as octreotide, are able to slow the rate of gastric emptying, slow small bowel transit, inhibit the release of gastrointestinal hormones, inhibit insulin secretion and inhibit postprandial vasodilation (60)

Recommendations

A multinational Delphi consensus process produced the following recommendations for diagnosis and management of dumping syndrome. (61)

The presence of symptoms suggestive of early or late dumping syndrome in a patient who has undergone oesophageal or gastric surgery should raise clinical suspicion. Patients often mention the need to lie down after meals due to profound weakness.

The modified oral glucose tolerance test is the preferred diagnostic method to confirm the diagnosis of dumping syndrome.

Dietary measures, focusing on low-volume meals with elimination of rapidly absorbable carbohydrates and delay of fluid intake, are the preferred initial approach.

In patients who do not respond to diet modification, the use of acarbose is recommended, especially for late dumping syndrome, but with an unclear effect on early dumping syndrome.

In patients who do not respond to diet and/or acarbose, somatostatin analogues can control symptoms of both early and late dumping syndrome. It is unclear whether short-acting analogues are superior to long-acting formulations.

Gastroparesis

Rarely, the impaired nerve supply of the lower oesophagus can affect the stomach, leading to delayed emptying of the stomach or gastroparesis. This may cause a sensation of being very full and bloated after eating. Delayed gastric emptying worsens reflux symptoms. Although this is rarely a major problem, mild forms probably occur in up to 30% of patients. If suspected, this is a secondary care/tertiary care diagnosis and management issue.

Symptoms

- Early satiety
- Postprandial fullness
- Nausea
- Vomiting
- Abdominal pain

Diagnosis

- Gastroscopy to rule out obstructive causes of symptoms
- Gastric emptying studies

Severity

Grade 1 (most TOFs). Mild symptoms only, weight and nutrition unaffected.

Grade 2 – Moderate. Manageable by medication.

Grade 3 – Severe. Not managed by medication. Weight and nutrition not managed by oral intake. Frequent hospitalisations.

Treatment

1. **Nutrition**. A symptom and diet history are needed to determine if intervention is needed. Most may need to change meal size and frequency only. Frequent, small, low-fibre, low-fat meals are advised, and alcohol and carbonated drinks discouraged. Liquid nutrients are also encouraged. If they are not eating enough calories to maintain weight, they are at risk of nutritional deficiencies including A, B_1, B_2, B_3, B_6, B_{12}, C, D, folate and minerals. Weight should be monitored. It is essential to have a dietician experienced in gastroparesis involved from first diagnosis.
2. **Prokinetic agents**. These improve gastric motility and gastric emptying times. These include metaclopramide, domperidone, erythromycin and azithromycin. Metaclopramide can also act as an anti-emetic.
3. **Anti-emetics**. Prochlorperazine is the most commonly prescribed in gastroparesis. Ondansetron is also used, both orally and intravenously during hospital admissions.
4. **Endoscopic treatment with Botox injection to pylorus of stomach or dilation of the pylorus with a balloon to 20–30mm**.
5. **Surgery to remove part or all of the stomach or widen the pylorus**. This is only rarely necessary in severe cases.

6. **Gastric pacemakers**. These have been used in some centres to strengthen contractions and improve emptying but they remain experimental and any benefit remains unclear. (62,63)

Achalasia-like symptoms

Achalasia is defined as a 'primary oesophageal motility disorder characterised by the absence of oesophageal motility and failure to relax of the lower oesophageal sphincter'. (64) There are a number of case reports of achalasia-like symptoms developing in those born with OA/TOF. (65–67) The condition is also much more prevalent in those born with Down's syndrome (1/1000 compared with 1/100 000 general population), which is relevant given OA/TOF may present as part of the syndrome. (68) However, one difficulty with the diagnosis of achalasia-like symptoms in those born with OA/TOF is that the symptoms are very similar to all the other oesophageal conditions found in these patients which are much more common. This means it is likely only to be diagnosed and/or suspected when barium swallow or oesophageal manometry show the characteristic appearance of the condition. This is particularly important as gastroscopy may show no obvious obstruction or inflammation. (64)

Symptoms

- Dysphagia
- Regurgitation
- Weight loss
- Chest pain
- Heartburn

Investigations

This is investigated and diagnosed in secondary care. The American College of Gastroenterologists guidelines (2020) recommend the following investigations. (69)

- Barium swallow, which shows the oesophagus is dilated, and the lower oesophagus narrowed, with a 'bird's beak' appearance. Contrast empties slowly as the sphincter only opens occasionally.
- Oesophageal manometry is the gold standard for diagnosis of achalasia but is more difficult to interpret in those born with OA/TOF due to congenital peristalsis abnormality. In those with a previously typical oesophagus, incomplete relaxation of the lower oesophageal sphincter (LOS), high resting LOS pressure and absence of peristalsis are all essential to confirm a diagnosis of achalasia.
- Oesophagogastroscopy is also recommended to rule out other causes of these symptoms.

Treatment

- Drug treatment is rarely effective and effects are usually only of short-term benefit. Nitrates such as isosorbide mononitrate and calcium channel blockers like nifedipine are most commonly used to relax the LOS, but are usually reserved for those not suitable for more definitive interventions.
- Pneumatic (balloon) dilatation is successful in alleviating symptoms in up to 90% of patients but may need to be repeated several times.
- Myotomy – surgical division of the LOS (usually laparoscopically, but can be thoracotomy) is very successful in alleviating symptoms, and provides relief in 83% of patients.

- Oesophagectomy is rarely needed for those in whom other therapies have failed, and aspiration and malnutrition means action is essential.
- Botox injection of the LOS is very effective in treating achalasia, but effects last only a matter of months, so is reserved for those unfit for dilatation or myotomy. (69)

Complications

- Aspiration pneumonia due to retained contents of the oesophagus from the poorly emptying LOS.
- Aggravation of GORD.
- Oesophageal cancer – risk is increased in patients with achalasia by five times the risk of the general population. (70)

Malrotation

Malrotation of the bowel is the commonest non-syndromic anomaly associated with OA/TOF. During normal foetal development (week 6 gestation), the bowel herniates into the umbilical cord then returns back into the body, rotating as it does so. In malrotation, this goes wrong in a number of possible ways, resulting in the bowel being wrongly positioned and/or fixed incorrectly. This can cause severe twisting, causing disruption to blood flow to the bowel, volvulus and death of a large part of bowel. (52, 64–66)

Prevalence of malrotation in the presence of OA/TOF varies in different studies between 3% and 5% (71–73). This compares to a population prevalence of 1 in 500. Most present at less than 1 month old with vomiting, but can present later, including adulthood. In this instance, it can be with non-specific symptoms like diarrhoea, abdominal colic, recurrent vomiting, but also volvulus and intestinal herniation is possible. (74)

Symptoms

This can vary from vague symptoms post eating to an acute abdomen. These milder symptoms may have persisted for many years undiagnosed: (75)

- Vague abdominal pain, especially post meals
- Diarrhoea
- Abdominal colic
- Recurrent vomiting (74)

Risks

This can present as an acute surgical emergency such as:

- Intestinal ischaemia (non-localised pain disproportionate to examination findings, vomiting, anorexia and diarrhoea progressing to constipation, abdominal distension and GI bleedings, progressing to sepsis and shock) (76)
- Intestinal herniation
- Acute bowel obstruction (nausea and vomiting [including bilious vomiting], constipation and absence of flatus, distended abdomen, fever and tachycardia in later stages) (77)
- Volvulus (abdominal distension, vomiting green bile, constipation, abdominal pain, shock) (78)

Diagnosis

- Upper GI contrast series (Gold standard)
- CT scan with IV and oral contrast (unless volvulus suspected)
- Abdominal X-ray not helpful
- Full blood count may be normal unless extended period of volvulus (79)

Treatment

This is surgical – Ladd's procedure which reduces volvulus, removal of Ladd's bands, and widening of the mesenteric base to prevent the bowel twisting again.

Assessment of nutritional status and treatment of any deficiencies.

Long-term complications

- Short bowel syndrome, if volvulus etc have necessitated bowel resection (see section in Long-gap oestophageal atresia section).
- Volvulus following Ladd procedure – there is still a risk of volvulus even post Ladd procedure, so this should be considered even in those with malrotation repaired in childhood.
- Small bowel obstruction following Ladd procedure secondary to adhesions. Similarly, this may occur in those with malrotation diagnosed and repaired at any age.
- Malabsorption – this can be part of short bowel syndrome when bowel has been removed due to ischaemia or volvulus. This can result in iron, B12 and folate deficiency. It can also result from chronic volvulus and ischaemia in undiagnosed malrotation. (79)

Eosinophilic oesophagitis (EOE)

'Eosinophilic esophagitis represents a chronic immune/antigen mediated oesophageal disease characterized clinically by symptoms related to oesophageal dysfunction and histologically by eosinophil-predominant inflammation' (80), as defined by a multidisciplinary panel in 2011.
The American College of Gastroenterology define EOE as: 'The presence of symptoms related to oesophageal dysfunction such as dysphagia, food impaction, chest pain, etc.'

- Oesophageal mucosa with eosinophil-predominant inflammation, up to 15 eosinophils per high power field.
- Mucosal eosinophils limited to the oesophagus and persist after a trial of PPIs.
- Exclusion of secondary causes of oesophageal eosinophilia. (39)

There is a higher prevalence of EOE in adolescents and adults born with OA/TOF. The prevalence in the general population is <4/10000, compared with 9.5% prospectively biopsied adolescents born with OA/TOF. (75,48)

The causes of this are thought to be multifactorial. One cause is the high prevalence of GORD in the TOF population, exposing the oesophagus to injury and damaging the mucosa. This damage to the mucosal barrier allows easier penetration of allergens. Secondly, the near universal dysmotility of the oesophagus increases contact time between food/allergens and the oesophageal mucosa, leading to chronic irritation which triggers increased mucosal permeability to allergens and the influx of eosinophils and mast cells.

It is difficult to differentiate EOE and severe GORD from symptoms alone. In one study, patients with EOE had higher levels of dysphagia, retrosternal pain and food impaction, but some in patient groups with repaired OA/TOF and those without EOE reported these symptoms. (81)

Investigations

- Referral for oesophagogastroduodenoscopy (OGD) and oesophageal biopsy
- Full blood count may show peripheral eosinophilia

Treatment

This is known as the 3Ds: diet, drugs and dilatation. Either drugs or diet can be used as first-line treatment. In OA/TOF patients there may be a greater proportion of patients that respond to PPI treatment as a first-line therapy. (212)

1. Drugs. Oral steroids are the mainstay here, either budesonide oral dispersible tablet, which dissolves in the mouth over two minutes, swallowed by saliva, or swallowing post use of multi-dose inhalers (eg fluticasone, mometasone, beclomethasone) so that the steroid reaches the oesophagus rather than the traditional aim of the airways. Patients should then avoid eating and drinking for 30 to 60 mins post steroid to keep the steroid in place. This is initiated for eight weeks, then success judged by repeat OGD and biopsy.
2. Diet. This is an elimination diet, again followed strictly for six to eight weeks, then reinvestigated by OGD and biopsy. An elimination diet should only be undertaken with input from a dietitian as part of a tertiary centre multidisciplinary team (MDT) looking after EOE patients. The diet may be a six-food elimination diet (dairy, wheat, egg, soya, nuts and seafood) or an elemental diet.
3. Dilatation. This is needed in those patients with signs of strictures and stenosis, but does not treat the underlying EOE leading to the formation of strictures. (82)

The European Society for Paediatric Gastroenterology, Hepatology and Nutrition guidelines state that EOE needs to be excluded in OA patients of all ages with dysphagia, reflux symptoms, coughing,

choking or recurrent strictures that are refractory to PPI, before proceeding to anti-reflux surgery. (39)

Pyloric stenosis/muscle hypertrophy

Pyloric stenosis (PS) usually occurs and is diagnosed in the first few weeks of life, where the muscle at the outlet of the stomach hypertrophies in the newborn, and presents as projectile postprandial vomiting. The condition is much more frequent in those born with OA/TOF, at around 7.5% compared to 0.25% of the general population, a 30-fold increase. It is unclear if this is a result of the surgical repair of the OA or due to shared genetic aetiology. In infants with both conditions, this is often diagnosed late, due to the overlap in symptoms of PS and oesophageal strictures, severe reflux etc. (83)

Rarely, this may not be diagnosed until adulthood. While there are a number of causes of PS in adulthood, such as malignancy and gastric and duodenal ulceration, most authors on the subject regard idiopathic adult PS (which we are discussing here) to be a milder form and continuation of infantile PS. However, it can be made evident by inflammation or oedema in the area, eg due to GORD. (84–86)

Symptoms

- Pain in the epigastrium.
- Early fullness after meals and feeling full all the time.
- Vomiting and nausea after eating.

Diagnosis

- Palpation of the abdomen does not usually show a mass, unlike in infantile PS.
- Barium swallow and follow through shows markedly delayed gastric emptying.
- Endoscopy shows a fixed narrowed pylorus with smooth border.

Treatment

- Surgery, including pyloromyotomy, partial gastrectomy and pyloroplasty, is usually the treatment of choice.
- Endoscopic dilatation may also be considered, though recurrence is common. (84–86)

Long-term PPI use

Many adults born with OA/TOF have been on PPI for many years, and some since their inception in the 1980s. These adults may approach the GP to discuss concerns about side-effects of long-term use of PPIs, which, whilst certainly present, need weighing against the risks of possible lifelong untreated acid reflux disease.

Risks of untreated acid reflux/GORD

- Oesophageal ulcers
- Oesophageal haemorrhage
- Anaemia secondary to chronic blood loss from oesophagitis
- Oesophageal strictures
- Barratt's oesophagus
- Oesophageal cancer

Long-term side effects of PPIs

- Increased fracture/osteoporosis risk. There are several reasons to suspect PPIs might be associated with fractures. The most plausible theory is that a decrease in stomach acid production might reduce calcium absorption in the small intestine. Over a long period, this could be followed by a decrease in bone mineral density. This mechanism remains largely theoretical and several studies have failed to show any reduction in bone mineral density in adults taking PPIs. Bone mineral density and fractures in adults and children taking PPIs long term has been (and still is) the subject of a large number of studies. The results are conflicting. The main problem with all these studies is that people who take PPIs are likely to be older and sicker than people who don't. People who are old and frail have other risk factors for fractures that are far more important than PPIs. Nearly all of the published studies have tried to correct for this confounding effect but it is difficult to eliminate completely. (36,87) However, NICE advises careful monitoring for osteoporosis and risk of fracture in those at higher risk and on PPIs, and prescription of calcium and vitamin D supplementation if needed. This should be considered in the context of poor nutritional status in some born with OA/TOF. (88)
- Dementia. Here again, evidence is conflicting, and falls foul of the same issues that the fracture risk studies do, that the participants in studies taking PPIs will be older and sicker than those who don't.
- Clostridium difficile infection. Acid in the GI tract reduces susceptibility to this infection so high-dose PPI use is associated with increased numbers of this infection. (89)
- Hypomagnesemia (magnesium deficiency), B12 deficiency. NICE recommends checking magnesium levels before and intermittently during PPI treatment if other factors are present that increase risk of hypomagnesemia. (88)
- Anaemia due to PPIs reducing iron absorption. (90)
- Increase in gastric neuroendocrine tumours (GNETs). This is a very rare malignancy, but one has occurred in an Adult TOF who has been on high dose PPIs for 20+ years. However, these are indolent tumours and, unlike their non-PPI-induced counterparts, are usually superficial lesions which are easily removed. (91) It is impossible to compare the risk of oesophageal

malignancy and GNETs in adults born with OA/TOF, but the limited research and our knowledge of these two malignancies would suggest that it is better to prevent a much higher risk of Barratt's oesophagus and the risk of oesophageal cancer if left untreated, as this is a much more aggressive and difficult to manage malignancy, than to avoid PPIs for a miniscule risk of a rarer and better prognosis GNET.

Intermittent monitoring of iron, magnesium, B12, Vitamin D is recommended for those on long-term PPIs as those with OA/TOF may have other causes of malabsorption. Assessment of osteoporosis risk is also recommended. (92)

Long-gap OA with or without TOF

Those born with long-gap OA have a number of health issues specific to the long-term morbidity of oesophageal replacement, in addition to often more severe symptoms of the common OA/TOF long-term conditions. Whilst oesophageal replacement techniques have improved since the early days of successful repair, many of the older adults with oesophageal replacements have colonic transpositions which were originally developed in cancer patients intended to last five to ten years rather than five decades.

Gastric pull-up/gastric interposition

Adults with oesophaguses replaced by gastric pull-up have significantly worse levels of GI, respiratory and nutrition morbidity than found in short-gap OA closed by primary repair. Multiple factors are suggested for this, some related to the change in the position of the stomach by the surgery, such as displacement of the gastroesophageal junction. Others include delayed gastric emptying and negative intrathoracic pressure and positive intraluminal pressure in the transposed stomach. The presence of the stomach in the chest also reduces functional lung capacity.

GI symptoms

These are much increased in this population compared to primary repair patients.

- Vomiting – 16% report vomiting daily (compared with 3% primary repair (PR)), 30% weekly (10% PR) and 60% rarely (40% PR).
- Reflux – 25% report daily reflux (17% PR), 60% monthly (40% PR) and 70% monthly (65% PR).
- GI ulceration and/or bleeding found in 9%.
- Dumping syndrome – 12–34% had a formal diagnosis of dumping syndrome and 25% further had symptoms consistent with the diagnosis. (31,173)
- Delayed gastric emptying on endoscopy. (174)
- Anti-reflux medication in one study was prescribed to 71% and prokinetics to 14%.
- Anastomotic strictures can occur and need treatment in late childhood and adulthood. (48,50,175)
- Barratt's oesophagus can occur in the oesophageal stump, as discussed above.(31,50)

Respiratory symptoms

Studies also show higher levels of respiratory symptoms than for those with jejunal interpositions and primary repair.

- Wheezing is reported in 57%.
- Dyspnoea on exertion is reported in 57%, and in infection in 14%.
- Noisy breathing is reported in 71% during infections.
- Recurrent pneumonia was reported in 14% and episodic in 14%; recurrent respiratory tract infection was reported in 14%.
- Lung function tests are also markedly abnormal in this group. Abnormal FEV1/FEV was found in 67%, FEV1 100%, PEF 100% and TLC is abnormal in 67%. (176)

Nutrition

Hannon et al. (31) reported that:

- BMI was significantly lower in gastric pull-up patients than PR.
- 19% required supplemental jejunal feeding.
- Anaemia was present in 47% and is attributed to poor iron absorption.

Jejunal interposition grafts

Respiratory symptoms

- Dyspnoea was reported in 62%, 25% during exertion, 37% in infection and 12% during stress.
- Noisy breathing was reported in 25%, continuous in 25% and during infection in 12%.
- Recurrent pneumonia was reported in 25% and episodic in 25%; 37% reported respiratory tract infections. (70)
- Lung function tests are also commonly abnormal – FEV1/FVC is abnormal in 29%, FEV1 in 71%, FVC in 43%, PEF in 43%, TLC in 29%.

These patients also have very high levels of respiratory morbidity, similar to gastric pull-up.

Gastrointestinal symptoms

- Dysphagia present in 50%.
- Choking present in 37%.
- Heartburn present in 12%.
- However, levels of medication in jejunal interposition is less than found in gastric pull-up, with only 12% in one study on anti-reflux medication and 12% prokinetics. (176)

Colonic interposition grafts

Colonic interposition has largely been superseded as an oesophageal replacement technique. (177–182) However, there remain adults born with long-gap OA with these grafts who are becoming increasingly troubled by complications from the graft. Burges et al. (183) found 27% of these patients had needed further procedures since repair. This is anticipated to increase as this patient cohort ages and the graft ages with them. There are a number of complications specific to colonic interpositions discussed below; however, many present with similar symptoms. Management of this complex patient group is best performed by tertiary care, though this varies in speciality from thoracic surgeons to upper gastrointestinal surgeons depending on who has a specialist interest in the condition in the region or country. The TOFS charity has a list of those known to have such experience in the UK.

Symptoms

Each patient's anatomy and symptoms are unique, but many of the complications with colonic interpositions present with similar symptoms.

- Severe and worsening dysphagia
- Worsening regurgitation
- Recurrent aspiration pneumonia
- Retrosternal and/or abdominal pain
- Weight loss
- Worsening cough
- Halitosis
- Dyspepsia
- Postprandial neck and chest swelling and oedema is only reported in graft redundancy

Late-onset colono-gastric anastamotic strictures

Anastomotic strictures are the commonest late complication in colonic interposition, and has been reported in between 27% and 30% of patients over their lifetime so far. (183,184) The aetiology of these strictures includes cologastric reflux and food pooling in the colonic conduit. Both cause inflammation and then scarring of the anastomosis site, triggering the stricture. This is usually managed by endoscopic dilatation, but surgical resection is necessary in some patients.

Graft redundancy

This is a recognised late complication of this technique and occurs in 5% of patients. This can also trigger worsening gastrocolic reflux, hastening the deterioration of the graft. The aetiology varies between patients. In some, the surgeon used a longer piece of colon than necessary due to fear of anastomosis tension; in other cases growth of the colon intrathoracically was greater than the growth of the thorax; lastly, there may be intrapleural herniation of graft, forming hiatus hernia and exposure of the graft to constant negative pressure. Treatment is complex due to the variety of surgical procedures and techniques carried out in this patient group. In some, the choice of past procedures and previous complications greatly limits treatment options. First-line treatment is always symptomatic and directed at alleviating presenting complaints with medication and lifestyle measures (see section on GI conditions above) or, if not manageable through medication, tube feeding has been necessary in those for whom surgery is not an option. Surgery is performed when other methods fail and methods in the literature include refashioning the colonic interposition, segmental resection, anastamotic revision, replacement with a supercharged jejunal tube, or a gastric tube or gastric pull-up. (178,179)

Very rare emergency complications of graft redundancy

1. **Colonic interposition volvulus**. This is intermittent twisting of the conduit causing intermittent ischaemia, secondary to redundancy. This is a medical emergency and needs admission, preferably to a tertiary centre with knowledge of this adult with repaired long-gap OA, though may still be managed conservatively with decompression, parenteral nutrition and antibiotics. This can happen on a number of occasions in the same patient. Surgery may be needed at a later date. (185,186)
2. **Cardiac compression**. There is a single case report of a dilated colonic conduit causing cardiac compression in adulthood. This presented as 24-hour history of inability to swallow, shortness of breath, and a left-sided non-reducible supraclavicular mass, accompanied by hypotension, tachycardia and tachypnoea. The authors attribute this to a progressive cycle of increased retention of liquid and particulate matter and low-grade ischemia ultimately leading to massive conduit dilatation and secondary cardiac compression. This was alleviated by emergency removal of the conduit to immediate effect. (187)

Cologastric reflux

Reflux here can cause bleeding, ulceration and scarring, and rarely can result in erosion of the colon wall, causing massive bleeding without pain as the transplant is insensate.

Treatment

- Surgical treatment, including an anti-reflux wrap
- Gastric resection
- Diversion of bile and acid

Obstruction

This is less common than bowel redundancy and strictures, with 5.6% of Burgos et al.'s cohort (183) reporting one or more incidents. Aetiology is very variable and dependant on the anatomy of the patients and their grafts, and includes volvulus and diaphragmatic hernia, and is more common in those with redundancy in the interposition. (76) Symptoms are as for other complications of these conduits, listed above, but with an acute onset of symptoms and rapidly progressive weight loss. This is a medical emergency, and again is best dealt with in a tertiary centre with prior knowledge of the patient. The obstruction is usually managed conservatively, with non-surgical decompression, parenteral nutrition and IV fluids, but surgical management is needed in some cases. This can be a recurrent phenomenon in some patients.

Bezoars

A bezoar is a tightly packed mass of foreign indigestible material in the gastrointestinal tract, usually in the stomach, but occasionally in the intestine. Bezoar composition varies, from phytobezoars mainly composed of fruit fibres but also vegetable fibres, skin and seeds. There are a small number of case reports of these developing in patients post repair of OA/TOF in childhood, and they have been reported in adults post colonic transposition in childhood.

Symptoms include abdominal pain, nausea, vomiting, early satiety, anorexia and weight loss. Uncommon presentations include gastrointestinal bleeding due to concurrent gastric ulcers and gastric outlet obstruction. Physical examination may include an abdominal bezoar mass and halitosis but it may be normal.

If suspected, investigation includes radiological investigations such as chest X-ray, abdominal ultrasound or CT. Gastroscopy can also be used, both to visualise the bezoar and remove it. However, many can be dissolved with either repeated drinking of Coca Cola, nasal lavage with Coca Cola, or incorporation of lavage and gastroscopy with Coca Cola. Surgical removal is occasionally needed. (177,188,189)

Blind stump/stagnant loop/blind loop syndrome

This is a rare but recognised long-term complication of gastrointestinal surgery. This is most commonly found post bariatric surgery, but has also been identified in patients who have had colonic interpositions, particularly those who have had multiple surgeries or interpositions. Uniquely to this group, the blind pouch may occur in either the interposition or (as is more usual) the operated remaining bowel.

In this condition, a small segment of the bowel is bypassed and cut off from the normal flow of food. This can lead to malabsorption and small intestinal bacterial overgrowth (SIBO) syndrome. Obstruction to the normal passage of food through the affected segment leads to ineffective bile salt digestion of fats and fat-soluble vitamins. The stagnant food ferments, with associated bacterial overgrowth. (190)

The blind stump can lead to fat malabsorption and steatorrhoea, and vitamin A and D deficiency from the fat malabsorption. If the bowel wall becomes inflamed, this can also cause malabsorption of carbohydrates and proteins. Vitamin B12, K and iron may become deficient.

Symptoms include bloating and early satiety, dyspepsia, flatulence, diarrhoea and steatorrhoeia, weight loss (sometimes extreme) and nausea. It can also rarely present with ulceration and melaena.

If blind loop syndrome or SIBO is suspected in this patient group, referral to a tertiary centre with knowledge of OA/TOF is recommended. The majority of testing will be done in the hospital setting, but blood testing for deficiencies associated with malabsorption should be done in primary care, including FBC, ferritin, vitamin D levels, INR and calcium levels.

SIBO breath testing is the first-line investigation, but these patients will need in-depth investigation to identify the blind loop, including flexible gastrointestinal endoscopy, capsule endoscopy for the small intestine, CT scans, abdominal X-ray and barium studies.

The ideal treatment is correction of the underlying cause, surgically, but many of these patients are too complex for this to be a safe option. Correction of any malabsorption and nutritional deficiencies is also vital. Long-term antibiotics are the mainstay of treatment, such as tetracyclines, rifaxamin, ciprofloxacin. (190,191,191–194)

Short bowel syndrome

Short bowel syndrome (SBS) is defined as ***loss of bowel mass from surgical removal, congenital anomaly or disease***. A small number of long-gap OA/TOF patients fall into this definition as a result of the jejunal and colonic interpositions undertaken to repair the OA, in particular those where complications meant that more than one such procedure was undertaken. It is estimated that having less than 200cm of functional intestine is needed to develop SBS and less than 35cm for intestinal failure (where oral feeding plus supplements are not sufficient to meet nutritional needs and parenteral nutrition is necessary). (195)

Symptoms

Whilst any adults with OA/TOF will have had loss of bowel since childhood and some adaptation will have occurred over this time, some may present with ongoing symptoms in adulthood, particularly if any further surgery to the bowel has occurred, and some may have worsening problems due to gastrointestinal infection or may be debilitated by the symptoms they have lived with for many years.

- Diarrhoea and steatorrhoea (fat in the stools, meaning they are bulky, difficult to flush, oily and are foul smelling)
- Fatigue, malaise and lethargy
- Weight loss
- Signs of vitamin deficiency (vitamins A, D, E, K, B12, thiamine, calcium, magnesium and zinc deficiency can occur) (196)

Management

1. The great majority with SBS are managed with diet. This is a specialist area, needing dietician and specialist gastrointestinal surgeon/gastroenterologist input, but in general drinking and eating around 1.5x more than their nutritional requirement is encouraged so that the relative malabsorption can be overcome and they should eat throughout the day, not just at the three meal times.
2. Vitamin supplementation may be needed:

- Thiamine (thiamine absorption can also be affected by blind loop syndrome/ small intestinal bacterial overgrowth)
- B12 in all patients who have had more than 30cm ileum removed due to malabsorption
- Fat-soluble vitamins such as A, D and E may also be deficient due to malabsorption
- Zinc deficiency may also occur due to diarrhoea losses in SBS patients

3. Control of diarrhoea – this can include opiates and loperamide.
4. Severely affected patients may need parenteral nutrition. (196)

Blind loop mucocoele

This is a very rare complication even in this patient subgroup, restricted to those in whom the oesophagus is both replaced and the distal segment closed at both ends and abandoned in the mediastinum. Here, secretions continue and accumulate in the closed segment. These are mainly asymptomatic if they remain small, but can rarely become enlarged and cause respiratory symptoms, even respiratory distress. This is due to tracheobronchial compression, causing coughing, chest and abdominal pain and vomiting. Infection, fistulisation and ulceration has also occurred. Drainage and stabilisation of the patient, then resection, is the treatment of choice. (197–199)

Neurodevelopmental issues

Imaging in infants born with long-gap OA show globally delayed or diminished brain growth in infants (in particular the corpus callosum) and reduced brain stem growth. (200,201) Motor studies at aged 8 are weaker than peers in 34% of cases, particularly in those with a longer time under anaesthetic. This particularly affects gross motor skills such as balance and ball skills, with normal manual dexterity. (202) The authors of research in these areas hypothesise this is the impact of long-term hospitalisation in infancy, and frequent surgery and prolonged general anaesthetic. Research in adolescents born with OA/TOF found motor skills deteriorated in adolescence – this was most common in teens who had had more than one thoracotomy, and it has been speculated that the musculoskeletal deformity thoracotomy can cause may trigger less trunk stability and poorer balance. Associated cardiac anomalies in those with OA/TOF are also strongly associated with poor motor skills in adolescence. (203)

Pubertal delay

Up to 22% of patients with long-gap OA/TOF have delayed puberty. This is attributed to the impact of chronic disease and low BMI and calorific intake due to the other long-term morbidities of the condition. This usually resolves by 18 but should be assessed and underlying causes managed in this patient group. (177)

VACTERL

The acronym VACTERL refers to a collection of anomalies that were first identified as occurring together in 1973. Prevalence of this syndrome is around 1/10,000–1/40,000 births and usually occurs sporadically, but there are some examples of familial inheritance. There is a small male preponderance of patients and most of those living with VACTERL were born after 2000 (around 75%) so this is a new and evolving patient group. It occurs across the world, with no increase in any ethnic population.

What is VACTERL syndrome?(151)

V = vertebral anomalies

A = anorectal malformations

C = cardiac anomalies

T= tracheo-oesophageal fistula

E = (o)esophageal atresia

R = renal anomalies and radial anomalies

L = limb anomalies

When is the diagnosis made?

Diagnosis is made if there are three or more of these features without evidence of an alternative diagnosis. (152)

Adult VACTERL health issues

Key points

- More people with VACTERL syndrome are surviving into adulthood.
- Most will have ongoing health problems as a result of VACTERL in adulthood.
- New diagnoses that are part of the syndrome may present in adulthood.
- Existing diagnoses (eg cardiac, renal, vertebral) may progress in adulthood.
- Older patients with OA/TOF may have VACTERL diagnosed in adulthood as awareness of the syndrome was not as widespread or screened for in those over 40.
- Adults with VACTERL are a high surgical risk due to airway, vertebral and other organ anomalies, and need careful assessment by anaesthetists.

Many born with VACTERL are seen by paediatric teams in childhood but not followed up in adulthood for VACTERL issues, either by single specialties or (ideally) a multidisciplinary team. More children are surviving to adulthood with the syndrome, as treatment has improved for congenital heart defects, OA/TOF and imperforate anus, and many will need lifelong medical input. These patients may also be diagnosed with new anomalies in adulthood. Raam et al. (153) found 40% of adult patients were diagnosed with vertebral anomalies in adulthood, 20% with cardiac anomalies and 20% with renal anomalies.

Vertebral

(60–80% patients)

Major anomalies (33% of patients diagnosed with VACTERL)

- Congenital scoliosis due to bony malformation including hemivertebrae, fusion and failure of segmentation with scoliosis
- Other congenital malformations of spine (excluding scoliosis)
- Combination of vertebral anomalies with rib anomalies

Minor anomalies (32.7%)

- Klippel Feil syndrome
- Cervical rib and other rib anomalies (accessory rib, rib absence, fusion rib)

Why might these present to the GP in adulthood?

The degree of vertebral issues in VACTERL is variable, and some patients will be under the care of orthopaedic surgeons, but many will be under the care of the GP for these issues. Older VACTERL patients may not have been thoroughly screened in childhood for such anomalies due to lack of awareness of the syndrome at this time. This may need GP attention for several reasons:

1. Chronic pain, which may worsen with age
2. 'New' vertebral anomalies may cause symptoms and need identifying and treating for the first time in adulthood
3. Osteoarthritis may develop either in the area of anomalies or due to compensation by other joints for these anomalies
4. Syrinx and tethered cord have been diagnosed in adulthood (153)

Recommendation: New or worsening back pain in VACTERL patients should be treated with caution and referred for specialist investigation, even if previous vertebral anomalies have not been diagnosed. VACTERL should also be considered in adults born with OA/TOF, even when not previously identified as having VACTERL association.

Anorectal

(55–90% patients)

Major anomalies (62.2%)

- Congenital absence, atresia and stenosis of the rectum with or without fistula
- Congenital absence, atresia and stenosis of anus with or without fistula, including congenital fistula of the rectum and anus, congenital rectovaginal fistula and congenital urethro-rectal fistula. Genito-urinary anomalies can occur in 25% of VACTERL patients and may be less obvious
- Ectopic anus

Minor anomalies (3%)

- Persistent cloaca
- Cloacal exstrophy

Why might these patients present to the GP in adulthood?

These patients represent a complex patient group with ongoing physical and psychological challenges in adulthood. For this group, the onset of adulthood means work, relationships and fertility will be faced for the first time and may mean previously unidentified medical problems are discovered or the known medical issues pose additional difficulties. For the patient and the GP, ongoing medical issues due to anorectal malformation (ARM) are complicated by the lack of experience managing this patient group in adult services. (154) Some may remain under the care of paediatric surgeons, but others are solely managed in general practice, though other specialities involved include urology and general surgery. There is also a lack of a multidisciplinary team approach in the adult setting, unlike management of patients with ARMs in the paediatric setting. Lack of awareness of ARM in adult providers means some patients are reluctant to seek medical support due to perceived lack of knowledge about their conditions. (154)

1. Faecal incontinence. Prevalence ranges from 16.7% to 76.7% Research into this patient group in adulthood shows that many with ARMs would like improved treatment and function, but had not received maximal optimal treatment, and had been told colostomy was the only treatment, despite other options available, and many have given up seeking treatment due to this. (155)
2. Chronic constipation. Prevalence ranges from 22.6% to 86.7%.
3. Urinary incontinence. Prevalence ranges from 1.7% to 30.5%. (156)
4. Sexual function. Genital anomalies may make sexual activity difficult and new anomalies may be discovered. Incontinence due to ARMs may cause issues during intercourse. There may also be a psychological impact of ARMs, with the anomalies causing a loss of self-esteem and self-confidence about sexual relationships. (157) For women, this can cause pain during intercourse, difficulties achieving penetration and incontinence of faeces during intercourse. For men, there can be erectile dysfunction (5.6–11.6%) and ejaculatory dysfunction (15.6–41.2%). (156)

5. Fertility issues. Patients may present to GPs after difficulties conceiving a child. In men this can result from the ARM or from the surgery to correct the ARM. (158) In case reports of pregnancies in women with ARMs, 3/18 needed assisted conception. (159)
6. Women with ARMs are high-risk pregnancies. A systematic review of obstetric outcomes in this patient group found the majority had Caesarean deliveries, although two had vaginal deliveries This is a result of desire to preserve the repaired anatomy during delivery, and anatomical anomalies that prevent vaginal delivery. (151,159,160) During pregnancy, frequency of UTIs (urinary tract infections) increased and, in some, kidney function was affected. Rarely, the disease is associated with Mayer-Rokitansky-Küster-Hauser syndrome, where there is aplasia of the uterus and part of the vagina, and may present to the GP with amenorrhoea (not starting periods) or failure to conceive. (161)
7. Mental health. In one study, 58% of adults with ARMs had mental health diagnoses, mainly depression and anxiety. This reflects the high impact of these anomalies on patients' quality of life and self-image. (162)

Cardiac

(40–80%)

Major anomalies (57.2%)

- Congenital malformation of the cardiac chambers and connections
- Congenital malformation of cardiac septa
- Congenital malformation of great arteries including patent ductus arteriosus and aortal anomalies

Minor anomalies (6.5%)

- Isomerism of atrial appendages
- Congenital valve malformations
- Congenital malformations of the great veins and other great arteries

Why might these patients present to the GP in adulthood?

Congenital heart defects (CHD) can have a lifetime impact on health, education, work and social outcomes. Gong et al. (163) found that life expectancy, disability-free years and QALYs (quality adjusted life years) were all lower in those with CHD compared to healthy peers. Lifetime earnings were also considerably less, and less likely to be employed and work for fewer years.

1. Poor transition to adult services. Between 50% and 80% of patients are lost to services at the time of transition, and this can impact on cardiac function. A lapse of two or more years is associated with a 3x increase in need for surgical or catheter intervention on reconnecting with the health system. (164)
2. New arrhythmias. This is a common reason for re-engagement with medical services when lost to transition. (164) These may be dysrhythmias, but also atrial and ventricular tachy and bradycardias.
3. Poor lung function. Separate from the effects of OA/TOF on the chest, abnormal lung function is common in adult patients with CHD, due to both CHD itself and the aftermath of cardiac surgery on lung function and growth (diaphragmatic palsy, musculoskeletal effects of thoracotomy) causing restrictive lung disease. CHD can also cause development of pulmonary hypertension in around 10% of adults with CHD. (165)
4. Renal dysfunction secondary to CHD. Nearly half of all adults with CHD have renal dysfunction, and 20% have moderate or severe renal dysfunction.
5. Cardiovascular comorbidities. Young adults with CHD have a higher rate of congestive cardiac failure (CCF) and stroke. (166) Oster et al. found 4.3% of adults between 20 and 38 years old with CHD had CCF compared to 0.2% general population, and 1.4% had had a stroke compared to 0.3% general population.
6. Peripheral vascular disease as an aftermath of vascular manipulations during cardiac surgeries. Neidenbach et al. found a rate of 12.4% in their adult CHD population. (165)
7. Pregnancy. Pregnancy induces cardiovascular haemodynamic changes in all mothers. However, if there is pre-existent CHD, this and the hormonal changes can increase risks of arrhythmias and the pro-thrombotic state of pregnancy increases thromboembolic

complications. This means pregnancy can worsen maternal cardiac function. Maternal CHD is associated with a higher risk of pregnancy complications, including emergency caesarean delivery, post-partum haemorrhage and cardiac complications, as well as preterm birth, small for gestational age birthweight, and maternal and infant mortality. It is recommended that women with CHD receive preconception and prenatal counselling to assess their structural lesion at birth, type of repair, residual lesions, current functional status, known risk factors, so that the best antenatal, intrapartum and postpartum care can be provided by a multidisciplinary team with expertise in CHD pregnancies. (167)

8. Mental health problems. Anxiety and depression are higher in adults with CHD, though it varies depending on the nature of their CHD. Both anxiety and depression are most common in those with cyanotic heart disease, transposition of the great arteries and Eisenmenger's syndrome. (168)
9. Non-cardiac surgery. Non-cardiac surgery carries a greater risk in CHD than their healthy peers. It is recommended that those with simple CHD can have non-cardiac surgery at a general hospital, moderate CHD should be assessed at a specialist centre prior to non-cardiac surgery at a general hospital, and complex CHD should undergo all non-cardiac surgery at a specialist cardiac centre.

Tracheo-oesophageal

(62%)

- **OA without fistula**
- **TOF with OA**
- **TOF without OA**

See rest of leaflet, however there is a case report of an adolescent with OA/TOF with VACTERL first diagnosed with H type TOF aged 15, so a history of VACTERL and recurrent pneumonia or chest infections should be investigated for missed TOF. (169)

Renal

(50–80%)

Major anomalies (50.9%)

- Renal agenesis
- Renal dysplasia
- Lobulated, fused and horseshoe kidneys

Minor anomalies (16.4%)

- Polycystic kidneys and other cystic kidney diseases
- Congenital obstructive defects of renal pelvis and malformations of the ureter

Why might these patients present to a GP as adults?

1. Known patients with renal disease. Those in whom renal conditions were diagnosed in infancy/ childhood. These patients may remain under adult renal physician surveillance, but if not, renal function and blood pressure should be regularly monitored, particularly in light of recurrent UTIs.
2. Undiagnosed patients with renal anomalies. Some patients may be diagnosed later on with renal anomalies, especially vesico-ureteric reflux, and this late diagnosis can increase risk of repeated UTIs, renal scarring and renal damage.
3. Nephrolithiasis (kidney stones). The combination of renal and urological anomalies increases risk of kidney stones and in turn risk of renal damage.
4. Progression of known kidney disease. VACTERL patients with known renal anomalies develop end-stage renal failure and require transplantation more frequently than those with renal anomalies without VACTERL.

Recommendation: Recurrent UTI, kidney stones and pyelonephritis need to be carefully investigated and monitored in VACTERL population to preserve renal function, and VACTERL patients with renal anomalies ideally should remain under monitoring of renal and/or urological adult specialists. (161,170–172)

Limb

(Upper) (40–50%)

Major anomalies (24.7%)

- Accessory thumbs
- Congenital absence of hands and fingers, thumb
- Longitudinal reduction of radius including club hand
- Other upper limb defects

Minor anomalies (6.8%)

- Congenital deformity of fingers and hands
- Accessory fingers
- Fused or webbed fingers or polysyndactyly
- Congenital absence of parts of upper limbs

Why might these issues present to GPs in adulthood?

As for vertebral anomalies, pain and wear and tear may progress with age. Compensatory use of other joints may trigger osteoarthritis in these joints and it may of course develop in the anomalous joints.

Nutrition and weight

Low BMI is NOT 'normal' for those with OA/TOF and is a sign of poor nutrition as a result of difficulties eating and/or malabsorption.

Food intake can be an ongoing problem post OA/TOF repair. Multiple studies have shown that adults born with OA/TOF have lower BMIs, with one showing 24.3% had a BMI less than 18.5. (97) This can follow on from a childhood of poor nutrition, with growth stunting found in between 5% and 15% of adults. (94,95) Birketvedt et al. (94) found 71% of adolescents were eating less calories than the recommended calorie intake for their age and a third less than their basal metabolic rate. They posit two causes for this: dysphagia and severe postprandial fullness. Dysphagia leads to selective eating, avoiding foods like meat, bread and other foods which are difficult to swallow. Hyperalimentation (excessive drinking to expedite food down the oesophagus) and oesophageal stasis and gastroparesis lead to severe postprandial fullness with lower quantities of macronutrients consumed.

Malnutrition is related to surgical factors/type of OA – delayed primary anastomosis of long-gap OA, jejunostomy, gastric pull-up and pyloromyotomy all have a poorer prognosis for malnutrition. (96) However, poor growth and weight is commonest in early childhood, with catch up around age 8, so for many adults born with OA/TOF, any such issues will likely be historical. Nonetheless, none of the Adult TOFs in the study by Presse et al. were classified as 'tall', suggesting that whilst many TOFs reach a normal height, they may not reach their full height potential if they had not had OA/TOF. (96,97)

There is also low intake of micronutrients such as vitamin D, riboflavin, calcium and iron, as well as reduced intake of macronutrients, particularly carbohydrates. (94) Nutrition and weight are a particular issue for those with repaired long-gap OA/TOF. (31) Post gastric transposition, 47% of adults are anaemic, compared with 9% with primary repair, and 19% still need supplemental feeding.

Signs of malnutrition/wasting in OA/TOF patients:

- Low BMI
- Continued weight loss
- Persistent inflammatory state
- Failure to respond to adequate nutritional support

Issues to monitor

- BMI/weight
- Ask patient about eating/swallowing difficulties. Are they drinking more than usual for them to help food down? Have they had increasing issues with foods getting 'stuck'?
- Consider referral for indirect calorimetry measurement
- Vitamin D levels
- Haemoglobin/FBC, ferritin, consider iron saturation.
- Magnesium, calcium, B12 levels if signs of deficiency

- Assess for osteoporosis due to poor calcium and vitamin D absorption and long-term PPI use.

Recommended actions

- Dietician input if nutritional status directs – this supportive care would also need referrals as below.
- Upper GI surgeon referral/gastroenterology referral to investigate dysphagia, preferably one with experience in long-term effects of OA/TOF. (94,96)

Ear, nose and throat problems in adults with OA/TOF

The majority of ear, nose and throat (ENT) issues in adults born with OA/TOF are related to GORD. However, structural issues can also cause problems, both as part of the original anomaly, or as an after effect of surgery.

Structural airway issues

Laryngeal cleft

Vocal cord paralysis

Laryngopharyngeal Reflux

Chronic rhinosinusitis

Laryngeal cleft

A high proportion of babies born with OA/TOF also have laryngeal clefts, with a prevalence of 8.3% to 19.6%. (7,93,98) A further 8.3% have oropharyngeal anomalies. Both of these add to dysphagia and aspiration and are often underdiagnosed in patients with OA/TOF compared to their non-TOF counterparts, due to these symptoms already existing due to this anomaly. Whilst many are picked up in childhood, some are not detected until worsening aspiration and dysphagia symptoms in adulthood. (7) Secretions can 'pool' in the cleft and tip over into the airways, often when lying down.

Symptoms

- Known history of OA/TOF
- Recurrent wheeze
- Recurrent aspiration
- Dysphagia
- Aspiration pneumonia

Diagnosis

This is diagnosed by endoscopy, laryngoscopy and bronchoscopy under general anaesthetic.

Treatment

This is usually repaired surgically.

Vocal cord paralysis

Vocal cord paralysis (VCP) also occurs at a high prevalence in patients with repaired OA/TOF, with figures ranging from 3% to 20%. Whilst it is usually managed conservatively, it does aggravate dysphagia, and some TOFs never achieve a safe swallow and remain tube fed in adulthood. It also poses a risk in any future intubation as there is a heightened risk of damage to the other cord. (7,93) This is usually unilateral and can affect either vocal cord, but one study of children born with OA/TOF presenting to an ENT clinic found nearly half had bilateral immobility. However, it is likely that those referred to an ENT clinic are the most severe cases, as many go undiagnosed as their body adapts to compensate for the damage. (99)

VCP impacts voice quality, with the voice being breathy and weak, and causing dyspnoea on talking, particularly on the telephone and in noisy areas. The severity of this can be assessed using the Voice Outcome Survey. (100)

Poor voice quality has an impact on those with VCP both socially and in choice of employment. Qualitative research shows people with VCP report frustration with communication difficulties (difficulty being understood, having to repeat themselves and other peoples' impatience) and at work due to their voice. It can also lead to social isolation as sufferers limit long conversation, talk on telephones, Bluetooth, Zoom/Discord/WebEx etc due to the added effort and strain this puts on the voice. This all can in turn lead to depression as a result of the social isolation. Work is often also an issue – those jobs that rely on the voice such as teaching, singing, call centres are unlikely to be feasible in this condition, and those with voice problems have considerably higher sickness absence in these professions. There is also a negative impact on job satisfaction and performance. Even in those professions less reliant on speech, sickness absence is higher in those with VCP. (101–103)

Laryngopharyngeal reflux

Causes of symptoms

Direct and indirect contact with gastric and duodenal content causes mucosal irritation to the upper aerodigestive tract. Mucosal lesions in this area are primarily caused by pepsin, and this has been found throughout this area in symptomatic patients, in the nose and sinuses of patients with chronic rhinosinusitis, larynx/throat of those with chronic laryngitis and ears of those with chronic otitis media. (104)

Laryngeal symptoms

Chronic but intermittent complaints of:

- Need to clear throat excessively
- Hoarseness
- Voice changes/hoarseness – particularly weakness of the voice worst in the mornings (105)
- Chronic cough
- Painful swallowing/odynophagia
- Ear pressure
- Globus/sensation of a lump in the throat
- Post-nasal drip
- Laryngeal spasm (101)
- Nasal symptoms can lead to insomnia or frequent waking
- Bad breath/halitosis (106)

All of the above can exist in the absence of typical GORD symptoms like heartburn. Symptoms are worst at night when lying down and can wake the patient with choking and coughing. (107)

Laryngeal conditions that GORD can cause

1. **Laryngitis**. This is persistent irritation of the larynx. Up to 60% of hard-to-treat sore throats and recurrent laryngitis may be due to GORD. It is caused by direct mucosal injury from the acid and pepsin.
2. **Laryngeal ulcers**.
3. **Laryngeal granulomas**. Rounded benign masses of inflammatory tissue on the larynx – they may be asymptomatic or cause voice changes, throat discomfort or dyspnoea. GORD is responsible for up to 25% of laryngeal granulomas, and responds to pharmacological treatment in 75% (inhaled steroids, PPIs and alginates). (108)
4. **Vocal cord polyps**. Whilst voice misuse is the main cause of such lesions, alongside smoking, GORD is also implicated in polyp development. In one study, 50% of patients with polyps also had GORD and 60% had pepsin detected on the area affected. The chronic mucosal damage from the reflux is thought to be responsible for their development. For the most part, these can be managed with either no treatment or treatment of reflux, but 5% require surgery. (109)

Investigations

None may be needed and the patient can be treated empirically on the basis of typical symptoms. However, those treatment-resistant symptoms may need referral to ENT or gastroenterology for consideration of:

1. Laryngoscopy – inflammation, hypertrophy and oedema of the larynx can be seen. Granulomas can also develop. Excess mucus may be visible, as can ulceration. (110,111)
2. Gastroscopy.
3. pH monitoring and impedance studies.
4. Oesophageal manometry.

Treatment

- **Diet changes**. Fried and fatty foods, citrus fruit, tomatoes, mint, acidic dressings, caffeine, carbonated drinks, alcohol can all aggravate LPR. (107)
- **Lifestyle change**. Smoking cessation, eating slower, regular meal times, eating more than three hours before bed. Sleeping in a left lateral sleeping position and elevation of the head of the bed may also alleviate GORD and LPR. (112) There is some evidence for alkaline water consumption denaturing pepsin in the pharynx and it is a harmless intervention that can be safely tried. (105)
- **PPIs**. Twice daily PPIs half an hour before meals for at least three months.
- **Sodium alginate liquids or tablets** such as Gaviscon Advance, three times a day after meals neutralise the pepsin on the throat, minimising mucosal damage. (107)
- **Surgical anti-reflux surgery**.
- **Inhaled steroids are used to treat laryngeal granuloma**. (108)
- **Voice education may be useful in some patients**.
- **Surgery to remove polyps and granulomas**.

Chronic rhinosinusitis

This is defined as chronic inflammation of the nose and sinuses for at least 12 weeks. Whilst there are a number of different factors involved in this common condition, such as environmental factors (allergy and pollution) and individual anatomy and past surgery, GORD is a recognised factor in its aetiology.

Symptoms

- Nasal obstruction, stuffiness and congestion
- Nasal discharge
- Post-nasal drip
- Facial fullness, headache, pressure
- Loss of sense of smell
- Poor sleep
- Halitosis
- Chronic cough
- Sore throat
- Sneezing

Treatment

The aim is to reduce mucosal swelling, encourage sinus drainage and clear any concurrent infection.

1. Symptomatic treatment – steam inhalation and nasal saline irrigation.
2. Control of predisposing factors – reduction of exposure to environmental irritants like dust, mould, cigarette smoke.
3. Management of GORD.
4. Management of asthma if co-existent – leukotriene inhibitors may be helpful here such as montelukast, 10mg nocte.
5. Topical steroid spray, eg mometasone or fluticasone for up to three months.
6. Sodium cromoglycate drops or spray – one spray two to four times per day.
7. Oral steroids may occasionally be necessary.
8. Surgery and ENT referral may be considered in refractory cases. (113)

Dental complications of GORD

Enamel hypoplasia

Formation of tooth enamel can be disrupted by early severe health issues such as OA/TOF repair, premature birth, NICU stay. This is usually most evident on the first permanent molars, which erupt aged 6. These need careful monitoring throughout life, with good diet, brushing twice daily with an electric toothbrush, fluoride toothpaste and fissure sealants.

Tooth wear

Progressive loss of the tooth's surface due to erosion caused by GORD. Acid reflux causes the enamel to dissolve, initially causing a glassiness of the surface appearance, then leading to stripping of the enamel down to the dentine. It classically affects the back of the upper front teeth as this is where the reflux hits the teeth. In time, if untreated, this can lead to cosmetic changes, chipping and sensitivity, and, if severe, death of the nerve and possible infection. (114) There may also be loss of enamel from the back of posterior teeth, especially molars, and loss of cusps of posterior teeth (molars) exposing yellow dentine and causing visible cupping. (115) Eventually, this can result in tooth loss if not managed.

Dental caries

Acid erosion, tooth wearing and enamel hypoplasia all increase the risk of caries. (116)

M**anagement**

- If dental changes are noted by a GP, this should lead to consideration of whether the patient's GORD is properly managed.
- Lifestyle changes – avoid food that aggravates reflux, avoid fizzy drinks and fruit juices, or use a straw if drinking an acidic drink.
- Avoid toothbrushing for up to 30 minutes after an acidic drink.
- Use fluoride toothpaste, particularly a desensitising one if sensitivity is present.
- Avoid scrubbing with the toothbrush.

Dentine bonding agents and resin composite restorations can all be used to protect teeth against acid damage. Porcelain crowns may also replace individual teeth that are lost or severely damaged. (117) However, long-standing acid reflux can lead to extreme tooth wear and destruction and may need reconstructive dentistry.

If noted by GP, in a patient born with OA/TOF this should lead to consideration of whether GORD is adequately managed and encouragement of patient to seek dental care. (115) Ideally, management of OA/TOF patients' teeth to protect against reflux damage should start in childhood, but fluoride toothpaste and mouthwash, fissure sealing of teeth, dentine bonding agents and resin composite restorations can all be used to protect teeth against acid damage. (117) However, long-standing acid reflux can lead to extreme tooth wear and destruction and may need reconstructive dentistry.

Oral aversion and eating difficulties

Oral aversion is defined as a sensitivity or fear of food, drink and/or other implements (toothbrushes for example) entering the mouth. This usually has its roots in infancy, and by adulthood the food and drink aspect has largely been managed successfully in those born with OA/TOF. However, some will still struggle with certain foods, drinks and textures due to oral aversion (rather than simply due to dysphagia) or will find instrumentation of the mouth (dentists, suction devices in other settings, NG tubes, endoscopy, tongue depressors) very difficult.

Those born with OA/TOF are at high risk of development of oral aversion in childhood. Many of the risk factors for oral aversion exist in those born with OA/TOF. These include the following:

- Intubation and suctioning post diagnosis and surgery in the NICU.
- Enteral feeding occurs in all born with OA/TOF post birth and repair, but is usually short term in short-gap OA. However, it can be for years in long-gap OA. Enteral feeding into the weaning period may cause the child to miss the 'learning to eat' cognitive window and also fulfils the child's nutritional requirements so hunger doesn't occur.
- GORD can make eating painful and the infant (and adult) brain may rightly link this with eating and make them unwilling to do so.
- Dysphagia and unsafe swallows lead to choking events and food bolus obstructions in children and adults.
- Forced medication – many born with OA/TOF have frequent medications in childhood, and this can mean another aversive experience to make sure this is given.
- Aggressive attempts to encourage oral consumption can produce negative feeding experiences and worsen the issue. (118)

Eating difficulties documented in children born with OA/TOF (95)

There is a wide body of research into eating difficulties found in children with OA/TOF. While we are lacking similar research in adults, some of these factors persist into adulthood and may limit the total intake of all food and/or intake of specific foods. This in turn impacts the nutritional status of adults born with OA/TOF. Eating difficulties identified in childhood that can still apply in adulthood include:

- Selective eating (avoiding hard-to-eat foods or foods that exacerbate GORD or are associated with prior choking episodes)
- Slow eating and lengthy meal times
- Regurgitation of food
- Food impaction
- Coughing and choking during meals
- Texture avoidance (119–122)

How may this present to healthcare professionals?

1. Nutrition and growth issues (see that section)
2. Oral aversion to toothbrushing and dentistry may lead to dental problems (see dental section)

3. Anxiety and/or avoidance of procedures involving instrumentalisation – a survey of adults born with OA/TOF revealed NG tubes, endoscopy, suction devices etc lead to post traumatic stress disorder (PTSD) symptoms of panic, anxiety, tachycardia in some individuals.

Mental health in OA/TOF

Most adults born with OA/TOF go on to live normal, healthy lives. Many also feel grateful for having survived their difficult beginning and describe resilience that carries on throughout their lives. However, for some adults born with OA/TOF, physical health problems and complications related to OA/TOF can be ongoing and impact the quality of life and psychological wellbeing. Some adults born with OA/TOF report increased levels of anxiety and depression, whilst some have also described trauma responses to medical interventions and hospital admissions. There is very limited research on the mental health of adults born with OA/TOF but below are some examples of preliminary findings. (126)

Experience of adults born with OA/TOF

- Many adults born with OA/TOF report a lack of understanding and support from medical professionals. This can lead to some people feeling isolated, dismissed and angry when dealing with healthcare providers. (94) They may also feel frustrated, trying to navigate a complex medical illness whilst locating professionals with knowledge and experience of their anomalies to treat their symptoms effectively.
- The appearance of surgical scars from OA/TOF operations vary greatly. All adults born with OA/TOF have at least one surgical scar. More complex patients may have multiple scars, some of which can be cosmetically unsightly. Whilst some adults regard these scars in a positive light, and a sign of their achievement in surviving, the scars might impact others negatively, particularly in social and public situations.
- Most adults born with OA/TOF have experienced coughing and clearing their oesophagus in public. The loud and unusual nature of the 'TOF cough' and choking episodes can sometimes elicit public comments and stares. This can, understandably, increase anxiety and avoidance of eating in front of others.

The mental health of those affected by OA/TOF can be impacted in a number of ways. Early childhood (0–5 years) is a vital time for neurological development, formation of attachment, cognitive development and emotional regulation. Adverse experiences during this time may affect brain development, pain sensitivity and attachment. (127,128) To date there is limited research on the mental health consequences of OA/TOF in childhood but the following are examples of preliminary research findings in this area.

Children born with OA/TOF 40 to 50 years ago were likely to have been hospitalised for long periods of time and as such separated from their families. Advances in neonatal surgery and anaesthesiology, an increased knowledge and understanding of attachment issues and the promotion of family-centred care have gone some way to reducing the emotional impact of hospitalisation on the TOF child and their families. (129) Despite the promotion of evidence-based holistic care, many invasive procedures experienced by the sick child are associated with pain and anxiety. These interventions and experiences can have an impact on both the child and families' wellbeing and mental health attachment. (132)

Dysphagia, GORD symptoms, Nissen fundoplication and higher number of days on ventilator might increase the risk of developing traumatic stress. (134)

Multiple hospital admissions and uncomfortable medical procedures in childhood might increase a child's anxiety towards medical procedures and professionals. This apprehension and in some cases fear can continue into adulthood

Parents who care for a child with a chronic health condition, compared to parents of a well child, are more likely to report increased levels of anxiety and depression.

Parents may experience trauma responses such as increased anxiety, hypervigilance and avoidance about their child's health. (94) Fear that their child may die can continue for many years. PTSD may present in both the TOF child and their parents.

Treatment

GPs should, if appropriate, make a referral to suitable mental health services. Or, recommend that patients make a self-referral to NHS talking therapies if OA/TOF-related anxiety, depression or trauma symptoms are impacting on the individual's quality of life, or ability to cope with day-to-day life.

Mental health difficulties in adulthood

Even though research into mental health difficulties in adults born with OA/TOF is limited, it is known that living with childhood chronic illness has an impact on mental health and quality of life of family members. It is likely that several factors influence the impact, including severity of health condition, (31) pain, presence of associated complications, such as dysphagia and GORD symptoms (and its surgical treatment), and invasive hospital treatments, such as number of days on ventilator. (134)

- Pain during hospital admission is associated with subsequent chronic stress in children, and may trigger PTSD in some cases. (151)
- Multiple hospital admissions in childhood and multiple procedures leave some with a fear of hospitals and medical professionals.
- Lack of awareness of OA/TOF in healthcare professionals in childhood can deter individuals from seeking medical treatment as adults. (213)

Sleep

Adults born with OA/TOF may have many different reasons to sleep poorly, both anatomical related to their congenital anomalies and the long-term possible sequelae of these. GORD is well recognised to affect sleep – 79% of those with GORD report nocturnal symptoms, 63% poor sleep quality due to heartburn and 40% poor daytime functioning the next day after night-time symptoms. (135) Chronic cough, aspiration and choking episodes and chronic rhinosinusitis symptoms secondary to reflux may also affect sleep in this group of patients.

Treatment

- Identify and address underlying causes – GORD, LPR, respiratory.
- Treat as for other patients with sleep disorders if underlying causes addressed and sleep problems continue.

Musculoskeletal abnormalities

OA/TOF patients have musculoskeletal abnormalities as a result of thoracotomy as well as those discussed due to the VACTERL association. Of those who had open thoracotomy, 33% had sequaelae.(8) These include:

- Scapula winging
- Thoracic wall asymmetry
- Scoliosis – in keeping with other causes of scoliosis, these usually present in adolescence with the growth spurt (136)

This can be symptomatic, with more than 75% reporting shoulder height differences, 20% limited movement of the right arm and 14% asymmetry of the chest wall and breast asymmetry. These anomalies are often mild, but a proportion will need surgical treatment and referral to orthopaedics or breast surgeons.

Scarring

All patients born with OA/TOF have at least one surgical scar, and many have multiple scars. The majority of newborns with OA/TOF are repaired via a thoracotomy approach, with a curved horizontal excision below the scapula or laporoscopic route, both of which minimise scar issues. However, adults with OA/TOF may have had one or more of a different surgical approach, including vertical thoracotomy scar or vertical substernal scar. Most will also have scars from previous chest drains and gastrostomy scars. Those who had long-gap OA may have multiple surgical scars, and may also have oesophagostomy and/or tracheostomy scars in the neck.

Keloid scars

Some with OA/TOF, as with all surgical procedures, will develop keloid scarring. These are raised, firm, itchy scars that can be unsightly.

Treatment

The aim here is to see the scar slowly softening then flattening, but this can take many months. They also may recur post any treatment.

- Silicone dressings such as dermatix or cicacare worn 24/7 for six months plus, washing underneath daily and changing dressings weekly.
- Intralesional triamcinolone injections (usually done in dermatology in secondary care).
- Pressure dressings (usually fitted and prescribed in secondary or tertiary care plastic surgery departments). (137)
- Surgical excision of the scar is often commonly requested by patients, but keloid scarring returns in almost all cases after simple re-excision, unless accompanied by steroid injection into the area.

Tethered/depressed scars

These are scars in which adhesion/scarring in the collagen can cause the scar to lie below the surrounding skin. This may pose a cosmetic problem, but can also cause physical problems with sweat pooling in the scar triggering maceration or fungal infections due to the moist environment. Most adults with OA/TOF needed chest drains and gastrostomies during infancy and these frequently caused indented scars as these were closed with purse suturing.

Treatment

Indented scars can be treated surgically, with subcision incision in the dermal plane or deeper undermining may be necessary. The scar could also be fully excised and refashioned surgically. However, recurrence of tethering can occur with both approaches and UK NHS funding for surgical management of these scars is usually not available. (138,139)

Unsightly scars

Some adults with OA/TOF may be distressed by the appearance of their scars even without the scars being abnormal, and these may limit their choice of clothing, activities and intimate relationships. This may be due to the number of scars they have, the quality of the scar (dog earring, stretching),

patient skin characteristics (ethnicity, genetics, other skin disease), and whether the scar became infected or broke down during healing.

Treatment

In some cases, these can be refashioned surgically to improve the appearance. However, this would usually require an individual funding request from the local clinical commissioning group (CCG) for referral to plastic surgery in the UK and may need to be a private referral.

Intraabdominal adhesions

Adhesions are bands of scar tissue which form (in this case) in the abdominal cavity after surgery. Over 95% of those who have abdominal surgery have adhesions, but for the great majority, they cause no problems unless further surgery in the abdomen is needed at a later stage. However, for a small minority, this can lead to bowel obstruction and chronic pain. The numbers of adhesions increase with increasing numbers of abdominal procedures a patient has undergone. These adhesions can cause symptoms years post surgery.

Diagnosis

Unless there is bowel obstruction, there is no way to see these radiologically, and they are usually only found during later surgery.

Treatment

Unless they are symptomatic, adhesions don't need treatment. Even if they are symptomatic, treatment may not be a cure – around 10% to 30% have new adhesions formed by surgical adhesolysis. However, in patients with chronic pain or obstruction due to adhesions, most achieve some benefit from adhesolysis. (140)

Surgical and anaesthetic risks in adults born with OA/TOF

All patients born with OA/TOF are regarded as high-risk patients for general anaesthetic and need careful assessment by an anaesthetist pre-surgery. Whilst this is outside the purview of primary care, it is worth highlighting key risk factors covered elsewhere in the leaflet so that these can be discussed with any surgeon when referring for routine surgery. Not all risk factors will be present in all patients, and severity varies between patients.

- Vocal cord paralysis. As discussed elsewhere, many adults with OA/TOF have this, and this makes intubation more difficult and riskier, as any further damage can be catastrophic.
- Unsafe swallow and severe GORD. Some adults with OA/TOF will choke on their own secretions, and this as well as GORD and gastroparesis increases risk of aspiration under anaesthetic.
- Tracheobronchomalacia. This makes maintenance of a patent airway during anaesthetic more difficult.
- Adhesions. Adhesions from childhood surgery can mean simple surgeries become much more complex, such as gall bladder removal. The number of adhesions will also become more pronounced with increasing number of childhood surgeries.

Latex allergy

Individuals with repaired OA/TOF are at increased risk of latex allergy. This is similar to all patient groups with multiple surgeries and medical procedures in childhood, such as spina bifida, where these bring about repeated exposure to latex. In one study, 25% were positive on prick testing and 13% symptomatic. Risk of allergy increases with increased number of procedures, longer stay in hospital and length of time the patient had a central venous catheter in. (141,142)

Pregnancy, conception and OA/TOF

As adults born with OA/TOF start families, they may seek medical advice about recurrence risk in their children. In those with isolated OA/TOF and those with non-isolated OA/TOF who aren't part of a known genetic syndrome, recurrence risk is between 2% and 4%. (143) However, for those with genetic syndromes, the recurrence risk depends on the mode of inheritance of the syndrome and genetic counselling is advised.

Maternal health during pregnancy and delivery for women born with OA/TOF

There is no published research in this area, but from research in the Adult TOF support group, there are a few common themes of problems that can arise, mainly due to aggravation of existing issues by the increased demands on the body by pregnancy or the pressure of the foetus in the abdomen and pressure on the thorax.

- Worsening reflux. This is clearly a common feature in many pregnancies, but the majority of adult mothers born with OA/TOF reported exacerbation of reflux.
- Hyperemesis gravidarum. A number of our adult members reported hyperemesis in pregnancy. It is difficult without formal research to know if there is an increased risk in adults born with OA/TOF but one can see how this might be the case. Adults born with OA/TOF report vomiting more frequently than the healthy population, especially those with gastric pull-ups, and the impact of pregnancy hormones and the pressure of the foetus on the stomach and oesophagus later in pregnancy would exacerbate this.
- Worsening/new respiratory problems. If there is already small lung volume or restricted lung volume, this may aggravate symptoms or unmask previously well-compensated patients due to the increased pressure on the thoracic cavity and additional demands on the maternal system. This is also the case for those with respiratory conditions such as bronchiectasis.
- Nutritional support. Pregnancy may unmask or aggravate previously undiagnosed malnutrition and micronutrient deficiencies, especially in long-gap OA due to the additional demands of the pregnancy.
- Breast asymmetry and difficulties breast feeding on the thoracotomy side. A number of our members reported this, and this correlates with the research into musculoskeletal effects of thoracotomy in this patient group.
- Anaesthetic risk. As mentioned previously, adults born with OA/TOF may be high risk for general anaesthetic, and planned spinal anaesthesia may be preferred if Caesarean is needed.

The genetics of OA/TOF

OA/TOF can sometimes run in families. The role of a clinical geneticist is to give advice to families on the likelihood that a medical condition that has happened once could happen again in the same family. This requires knowledge of the precise diagnosis, and clinical geneticists are often concerned with achieving this important step. Fully understanding the diagnosis is vital before the question of what caused the condition can be addressed.

Sometimes DNA analysis reveals the precise genetic change that has led to the condition, and this can be the basis for a pre-natal genetic test carried out on an unborn child. Alternatively – and just as likely – the genetic basis of a condition may be poorly understood or not known, in which case a geneticist has to rely on other sources of information to provide the family with a recurrence risk.

Syndromic or non-syndromic?

Although oesophageal atresia and tracheo-oesophageal fistula refer to two different malformations, for the purposes of genetic counselling they can be considered the same. Either separately or together, OA and/or TOF occur with an incidence of approximately 1 in 3,500 births. There is no difference in the incidence in boys and girls.

In around half of cases additional malformations are present, most commonly a congenital heart malformation. Malformations of the vertebral column, kidneys and limbs also occur, and may lead to a diagnosis of VACTERL association.

Where additional features such as these are present, geneticists refer to this as syndromic OA/TOF, whereas OA/TOF occurring in the absence of other anomalies is known as isolated. (215)

What causes OA/TOF?

It is useful to classify OA/TOF into different groups based on what we currently know about possible causes. The first two in the list below are non-genetic causes, the remainder are genetic causes. These causative factors are summarised in the table below.

OA/TOF may occur because of an exposure to a substance known to be damaging during early development

This would have to occur during the first few weeks of pregnancy. Alcohol, certain drugs (an example is the anti-thyroid drug methimazole) and exposure to high levels of glucose in a mother with poorly controlled diabetes are all known examples.

The case of *maternal diabetes* is actually a likely rather than a definitely proven example. Poorly controlled diabetes is known to be as- sociated with a high risk of several congenital malformations, including spina bifida and mal- formations of the heart. Direct evidence for an increased incidence of OA/TOF is lacking, but neither has the possibility been excluded.

Twinning

This may be an under-appreciated cause of many different congenital malformations, including OA/TOF. Data from one study showed that a child from a twin pregnancy is nearly three times more likely to have OA/TOF than a child from a singleton pregnancy. Why this should be the case is not fully understood, perhaps to do with the blood supply to the twins, has been suggested as the cause, but the reason is not really understood at all. It is possible that some cases of OA/TOF occur in one twin where the co-twin was lost at an early stage of pregnancy, and whose existence may not have been appreciated either by the mother or the doctors looking after her. The incidence of significant bleeding in the first trimester of pregnancy, followed by the delivery of a child with OA/TOF could signify that a twin had been lost early in pregnancy, although obtaining proof in this situation can be difficult if not impossible. (215)

Category	Examples	Syndromic or isolated TOF?	Proportion of OA/TOF cases
Exposure	Maternal diabetes, exposure to medicines in pregnancy e.g. methimazole	Usually syndromic, possibly some isolated cases?	Likely low proportion, but not really known
Twinning	Identical twins; apparently singleton pregnancy with possible early pregnancy loss	Not known	Likely low proportion, but not really known
Chromosomal diagnosis	Down's syndrome (trisomy 21) Edwards syndrome (trisomy 18)	Always syndromic	Around 5%
Single gene disorder	*See table on facing page*	Syndromic	Likely <1%
Unknown cause	The majority of cases of OA/TOF	More likely to be isolated OA/TOF	Majority

Different categories of causes for OA/TOF

OA/TOF due to Chromosome disorders

Around 10% of cases of OA/TOF occur in children with a chromosome imbalance. This is usually either *Down's syndrome* (three copies of chromosome 21 instead of the usual two, also called *trisomy 21*) or *Edwards syndrome* (*trisomy 18*). A small proportion of cases are due to disorders of other chromosomes; for example, loss of genetic material from chromosome number 17 has been associated with OA/TOF.

Trisomy 21 Down's Syndrome- anomalies here include learning difficulties, delayed physical growth, typical facial characteristics, congenital heart diseases, thyroid, gastrointestinal, eye and hearing disorders. Inheritance is autosomal dominant. Only 0.5%-1.0% of individuals with Down's syndrome have OA/TOF.

Trisomy 18 Edward's syndrome- here there is severe neurological, motor and growth retardation, microcephaly, microphthalmia, malformed ears, and severe jaw anomalies. OA/TOF is present in 25% of these patients. (150)

Trisomy 13 Patau syndrome. Anomalies include severe learning difficulties, microcephaly, structural eye defects, meningo-myelocele, polydactyly, cleft palate. OA/TOF is very rarely present in this anomaly.

Trisomy X This is the commonest female congenital anomaly, found in 1/1000 female births, but as it is often very mild, it is only diagnosed in 10% of patients. Physical features include tall stature, epicanthal folds, hypotonia and clinodactyly. Seizures, renal and genitourinary abnormalities, and premature ovarian failure can also be associated findings. Learning difficulties and psychological diagnoses are more common. OA/TOF is very rarely associated with this chromosomal anomaly.(149)

OA/TOF due to single gene disorders

In the same way that cystic fibrosis is caused by mutations in a single gene, single gene disorders may can cause OA/TOF. In this situation, there are usually other malformations as well. Considerable progress has been made in understanding single gene disorders causing OA/TOF in the last ten years.

One syndrome, named *Feingold syndrome* after the doctor who first described it, has been shown to be caused by mutations in a gene called *N-MYC*, and may be associated with other clinical features such as small head size and subtle changes in the fingers and toes.

Feingold syndrome is one of the few conditions which may cause OA/TOF to appear in several generations of the same family (*autosomal dominant inheritance*).

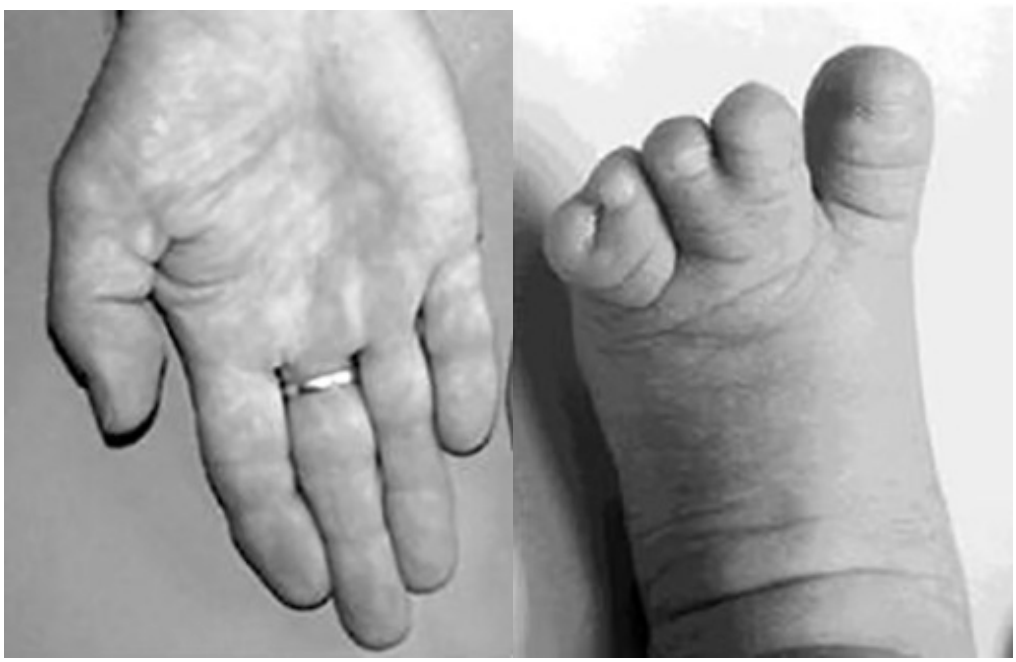
In *autosomal dominant inheritance*, a misprint or fault in just one of the two copies of a gene is sufficient to cause the condition.

When an affected individual has a child, the child has a 50% (1 in 2) chance of inheriting the faulty gene from his or her affected parent.

This applies equally to males and females.

If the child does not inherit the faulty gene, then of course he or she cannot pass it on to his or her own children.

On the other hand, if the child does inherit the faulty gene, then his or her own children in the future are at risk of inheriting it.



Subtle changes in the fingers and toes in Feingold syndrome. In the hand, there is incurving (clinodactyly) of the index and little fingers.There may also be a narrowing of the distance between the finger creases in the index finger compared with the middle and ring fingers. In the foot, some of the toes may also be fused (syndactyly).

The genetic basis of other syndromal forms of OA/TOF has now been worked out. These include *CHARGE syndrome*, *OA/TOF with anophthalmia* (congenital absence of the eyes), and a rare condition called *Mandibulofacial dysostosis with micro cephaly*. Genetic testing is available in the UK for each of these conditions through the *Regional Genetics Services*. (214,143,216)

Name	**Inheritance pattern**	**Gene**	**Clinical features besides OA/TOF**
Feingold syndrome	Autosomal dominant	MYCN	Small head size, unusual configuration of fingers and toes. Heart and kidney malformations may be associated. May be mild developmental delay/learning difficulties.
CHARGE syndrome	Autosomal dominant	CHD7	Coloboma of the eye, failure to thrive/poor growth, heart and kidney malformations, deafness.
Mandibulo-facial dysostosis with microcephaly	Autosomal dominant	EFTUD2	Extremely small head size, unusual facial features, developmental delay/learning difficulties.

Anophthalmia-esophageal-genital syndrome	Autosomal dominant	SOX2	Absent or very small eyes; hypospadias. Extremely rare.

Single gene causes of OA/TOF

Rare syndromic causes of OA/TOF

Here, OA/TOF is very rarely found with these syndromes but these have been included as some anomalies may be diagnosed in adulthood and individuals with these syndromes may be undiagnosed in the community if born prior to the syndromes' discovery or ability to genetically screen for.

Opitz G/BBB syndrome.
This is due to mutations in MID1/Xp22 gene and is X linked recessive inheritance. Anomalies include hypertelorism, hypospadias, cleft lip/palate, laryngotracheoesophageal abnormalities, imperforate anus, and developmental anomalies.

15q11 deletion.
This is due to deletions in UBE3A, NDN,SNRPN genes. Anomalies include mental retardation, movement and behaviour disorders, facial dysmorphisms, and genital anomalies. Mode of inheritance is uncertain.

2q11.2 del/dup.
This is associated with parathyroid hypoplasia, thymic hypoplasia, outflow-tract defects of the heart, cleft palate, facial dysmorphism, hypocalcaemia, hypertelorism, and midline defects.

Renal dysplasia; Potter; CAKUT
Genes involved here include 10q24.31, 17q12,1q32, 3p12.3,8q11.23, 16p13.3 These are associated with kidney anomalies (renal dysplasia, duplex kidney, and hydronephrosis) and ureter anomalies (vesicoureteral reflux, megaureter, and ureterovesical junction (UVJ) vesicoureteral reflux obstruction.

Alveolar Capillary Dysplasia syndrome
This is due to a mutation in the FOXF1 gene, and anomalies include alveolar capillary dysplasia, and VACTERL-associated defects

Klippel-Feil syndrome
This is due to mutations in 8q22, 12p13.3, 17q21. These mutations are associated with fused cervical vertebrae, short neck, low posterior hairline, limited neck movement, cardiac defects, craniofacial anomalies, skeletal and ocular anomalies, malformation of the larynx.

Pallister-Hall syndrome
This is due to a mutation in 7p13. This mutation is associated with hypothalamic hamartoma, pituitary dysfunction, central polydactyly and organ malformations, anal atresia and occasionally laryngotracheoesophageal cleft.

Mandibulofacialdysostosis with microcephaly
This is due to a mutation in 17q21. This causes Microcephaly, midface and malarhypoplasia, micrognathia, microtia, dysplastic ears, preauricular skin tags, significant developmental delay, and speech delay.

Thrombocytopenia-absent radius
This is due to a mutation in 1q21 and causes low platelets, limb malformations, cardiac and renal anomalies.(217)

What are the chances of recurrence of OA/TOF in the same family?

A study was carried out in the 1970s to determine whether or not OA/TOF can run in families. The study was designed to determine what the chance was for a male or female adult who was born with OA/TOF of having an affected child. This study only became possible in the 1970s because this was the first time that children born with OA/TOF were able to survive long enough to have their own children.(217)

The results were reassuring: the chance of having a child affected with OA/TOF was about 1% – or, put another way, the chance of their child not being affected was 99%.

This study seems to suggest that OA/TOF is not a genetic condition, and this is mainly true. However, there are rare cases where OA/TOF does occur for genetic reasons, as explored above.

Where OA/TOF occurs in isolation (non-syndromic the recurrence risk is low, of the order of 1%, and specialist genetic advice need not be sought.

In order to show that someone born with OA/TOF does indeed have isolated OA/TOF, a careful clinical examination must be performed by the clinician to rule out other malformations. The patient will have the following investigations:

- echocardiogram (ultrasound scan of the heart)
- ultrasound of the kidneys
- x-ray of the vertebral column
- some kind of imaging of the brain (either an ultrasound or an MRI scan)
- an analysis of chromosomes.

This is usually performed in childhood. However, in older individuals born with OA/TOF, these were not routine and thus some anomalies may be missed until a later age.

Who should seek genetic counselling?

Within the UK, anyone interested in the possibly genetic nature and likely recurrence risk of a medical condition may seek genetic counselling simply by asking their GP or primary care physician to refer them to a Genetic Counselling Service.

The whole of the UK is covered by a network of twenty or so Regional Genetics Centres, located in hospitals of major towns and cities.

Advice is usually sought for one of these reasons:

- There is doubt over the precise diagnosis, and this would be helpful in management of the patient.

- Adults not formerly thought to be syndromic who have been diagnosed with new conditions that raise this as a possibility.
- There is thought to be a significant chance of recurrence of the condition and the family wish to have information about this, including possible advice about pre-natal diagnostic testing for a subsequent child.
- Adults born with OA/TOF wishing to have information about their risk of recurrence of OA/TOF in their children

In the event that additional malformations besides OA/TOF are identified, it is reasonable to seek the advice of a clinical geneticist to determine whether the pattern of malformations conforms to a known syndrome or association.

During a consultation with a clinical geneticist, a detailed family history will be taken; the child's case history will be taken and a careful examination performed. Further imaging investigations may be needed, depending upon which the child has had already. Genetic tests may also be requested. If investigations are required, a second consultation is used to feed back the results of the tests, and information about recurrence risk, to the family. (215,143,216)

The causes of VACTERL association

What causes VACTERL association? Clinical geneticists use the word association when they appreciate that one or more malformations can appear together, but they don't know the underlying cause. When they do understand the cause, then the condition is re-designated as a syndrome. For example, another acronym, CHARGE, was considered to be an association until 2004, when it was shown that this condition, which sometimes features oesophageal atresia, was due to mutations in a gene called CHD7. Now it is called CHARGE syndrome. Before this information was known, clinicians sometimes had difficulty in distinguishing between CHARGE and VACTERL, because certain malformations (cardiac, renal) are common to both. Now that doctors can test for gene faults or mutations in CHD7, it is possible to make a clear separation between these cases and VACTERL association. The same is true of a condition called Feingold syndrome, another condition resembling the VACTERL association. The discovery of mutations in a gene called N-MYC in patients with Feingold syndrome in 2005 cemented the status of this condition as a syndrome of known cause, although clinicians had before that time clearly delineated it as a syndrome based on its characteristic features and tendency to run in families. As time goes on, other causes of VACTERL association will be identified – and once this has happened, the new condition can be given a name that reflects the cause and clinical features.

As with oesophageal atresia, non-genetic causes of VACTERL association are recognised, including

- exposure to alcohol
- exposure to certain medicines
- exposure of the developing embryo in the womb to too much sugar in mothers who have diabetes.
- the presence of a twin, who may be lost in early pregnancy and therefore never identified, may also lead to VACTERL association, but our knowledge here is very incomplete, mainly

because of the difficulty of carrying out the type of epidemiological study needed to establish a definite link.

Genetic Counselling in VACTERL association

It is fair to say that any child diagnosed with VACTERL association should be referred to a clinical geneticist, where the question of the underlying cause of the malformations can be addressed in detail. In the scenario where the child is growing and developing normally, with no suggestion of delayed milestones, a syndromic cause is less likely, and the recurrence risk is similar to or lower than that for isolated oesophageal atresia, that is, around a 1% chance of recurrence in the family. If the child's growth or development are not normal, then a syndromic cause should be carefully sought by the clinical geneticist. One UK-based study has suggested that there is an increased incidence of VACTERL-type malformations in first degree relatives of individuals with OA/TOF, and similar findings were reported in an American study. Adults born with VACTERL may also ask to be referred for genetic counselling pre or during pregnancy to explore the risk of VACTERL being diagnosed in future children. If the person with VACTERL also has ano-rectal malformations, pre-conception appointments with gynaecology or urology should also be considered to explore whether there are any physical barriers to conception.(218)

Radiation exposure in the adult OA/TOF population

There is a growing pool of research addressing the burden of radiation exposure in infants born with OA/TOF. Babies born with OA/TOF undergo a series of medical imaging both pre and post surgery as part of diagnosis, monitoring and therapeutic intervention.

Children are more vulnerable to the potentially carcinogenic effects of such radiation than adults as their tissues are still rapidly dividing and growing, plus they have a much longer lifespan than adults. Whilst the levels of exposure are less than those children treated for paediatric cancers, they are greater than those infants born prematurely or with necrotising enterocolitis. (144) Zamiara et al. (145) found their cohort underwent numerous imaging, including multiple chest X-rays, abdominal X-rays and oesophagrams. Their population group received the equivalent of seven years of background radiation in the first year of life. However, this is extremely variable, depending on the complexity of the patient, with Gottrand et al. (214) finding an estimated increase in cancer mortality varying between a 130-fold average to a maximum of 1,575-fold in one complex patient.

There isn't an equivalent pool of research for adults born with OA/TOF, but one can safely say that this patient group had increased exposure to radiation in infancy. An additional factor is that those born with OA/TOF with ongoing respiratory or gastrointestinal symptoms will likely have had further X-rays, barium swallows, CT scans etc across their lifespan. Whilst the data is lacking as to whether this will in turn lead to malignancy in this population, the cumulative radiation exposure is worth consideration in this patient group. This will be particularly true in long-gap OA patients and those with VACTERL syndrome or other syndromic or genetic conditions that may necessitate radiological imaging.

Enteral Feeding

Enteral feeding allows long-term delivery of nutrition into the stomach or intestines of those who are unable to maintain sufficient oral intake to maintain their nutritional needs. (204) A small minority of those born with OA/TOF need enteral feeding in adulthood, either due to associated co-morbidities or due to the complications of OA/TOF. The latter group include those who have never managed to sustain their nutritional needs with oral intake alone and those who have previously been able to eat and drink to maintain their nutritional needs in childhood and adulthood, but this is no longer possible. (31)

There are a number of indications for enteral feeding. These include impaired swallowing, obstructions to swallowing, fistulae in the neck or digestive tract, malnutrition. (204) All of these may occur (albeit rarely severe enough to need enteral feeding) in those born with OA/TOF. The NICE guidelines concerning nutritional support for adults suggest nutritional support from enteral feeding should be considered in those with a BMI of less than 18.5kg/m2, unintentional weight loss of more than 10% in the last three to six months, a BMI of less than 20kg/m2 and unintentional weight loss within the last three to six months. (205)

Whilst the initiation and management of enteral feeding falls solidly within the purview of secondary and tertiary care, those healthcare professionals in primary care may still be approached for advice about the management and difficulties with enteral feeding. However, NICE recommends that those receiving enteral tube feeding in the community should be monitored by those who are trained in enteral feeding and nutritional monitoring and they should also train the patient and their carers in management of their equipment and possible adverse signs to report. This monitoring should be by a multidisciplinary team of dieticians, district nurses, GPs community pharmacists and gastroenterologists/upper GI surgeons and other healthcare professionals as needed. (205)

Types of enteral tube feeding

Nasogastric (NG) tube: This is a flexible tube passed into the stomach or jejunum via the nostril.

Percutaneous gastrostomy: Toussaint et al. define this as the 'establishment of an artificial access in the stomach, through the abdominal wall, which can be performed surgically (PSG), endoscopically (PEG) or with image guidance. Insertion of the gastrostomy tube can be done via the oral or the abdominal route'. (204)

Percutaneous gastrostomy with jejunal extension: Here, the access into the stomach is used to insert a feeding tube into the jejunum.

Percutaneous jejunostomy: As with gastrostomy, there is the establishment of artificial access to the jejunum through the abdominal wall, either surgically or endoscopically. These are preferred to gastrostomy feeding if there is gastroparesis, altered anatomy, severe GORD or gastric or duodenal access obstruction.

The only published data about enterally fed adults born with OA/TOF is contained within Hannon et al.'s (31) paper 'Outcomes in adulthood of gastric transposition for complex and long gap esophageal atresia'. In their patient group, all of the 13% of their patients whose long-gap OA was repaired with gastric transposition who still needed enteral feeding were fed through jejunostomy. However,

surveying the adult members of a Facebook support group for those born with OA/TOF showed that those who needed enteral feeding starting in adulthood were initially trialled on NG tubes, and some then progressed to gastrostomy tubes with a jejunostomy extension as well as jejunostomy feeding. This would correlate with the many reasons jejunostomy access is preferred, as one or more will be present in all born with OA/TOF needing enteral feeding.

Complications

Here, the focus is on complications that may present in the community, due to long-term placement, rather than due to the procedure itself.

NG tube

- Discomfort
- Epistaxis/nose bleeds
- Sinusitis
- Tube malposition
- Oesophageal injury

Gastrostomy

1. **Peristomal leakage of gastric contents.**

Risk factors

- Skin infection
- Irritant contact dermatitis due to excess use of cleaning products
- Increased gastric acid secretion
- Gastroparesis
- Tube torsion
- Buried bumper
- Granuloma tissue in the tract

Treatment

- PPIs and prokinetics can reduce acid secretion and improve gastric emptying. (204)
- Sucralfate powder onto erosions. (206)
- Zinc oxide application.
- Topical steroid cream, eg clobetasone valearate or betamethasone valearate cream, or topical immunomodulators such as tacrolimus or pimecrolimus. (206)
- Fungal superinfection can be treated with a topical antifungal cream such as clotrimazole cream or a mixed cream containing an antifungal and hydrocortisone. (206)

2. **Infection of the site**. This can occur in up to 30% of patients but is rarely serious. The majority can be managed with oral broad-spectrum antibiotics, though IV antibiotics may be needed if there are signs of sepsis.
3. **Buried bumper syndrome**. Here the gastric mucosa overgrows the internal part of the PEG, and can occur in up to 3% of PEG patients.

Symptoms

- Peristomal leakage or infection
- Tube difficult to mobilise
- Abdominal pain
- Resistance when formula infused

Risk factors

- Previous malnutrition
- Excess tension on the gastrostomy
- Significant weight gain
- Prior malnutrition
- Poor nursing care of gastrostomy

Management

- Endoscopy or CT scan to confirm diagnosis
- Endoscopic surgery to release the overgrowth and remove the tube part that is overgrown (bumper)
- Open surgery may be needed if overgrowth is severe. (204)

4. **Gastric ulcer or erosion of the wall under the internal part of the PEG.** This can develop in up to 1%.
5. **Fistulae** between stomach, colon and skin which may present as long as months after initial placement.

PEG-J

These are similar to PEG complications. Additional problems include the extension tube moving back into the stomach, and the tube clogging more frequently as it is smaller in diameter.

PEJ

These are similar to PEG complications. (204)

Complications due to enteral feeding

The British Association of Parenteral and Enteric Nutrition (BAPEN) recommends the following assessment and management. (207)

1. **Vomiting and reflux**

Consider acutely:

- Is the patient feeding at 45 degrees or sat up to minimise reflux?
- Is the patient at risk of dehydration – do they need IV rehydration?
- Consider stopping the feed.

If vomiting persists:

- Ask the patient to create a diary of their vomiting.
- Is the feeding regime right for the patient – method, rate, volume, concentration of feed?
- Is the feed the correct temperature?
- Is the patient on any medications that may cause this?
- Is the feeding tube in the right place?

2. **Abdominal pain and distension**

Causes:

- Constipation
- Build up of gas
- Gastrointestinal obstruction

Consider:

- Check bowel function
- Reduce air going into the feeding tube
- Is the feeding regime right for the patient – method, rate, volume, concentration of feed?
- Consider gastric venting – release gas by attaching an open-ended large syringe to the feeding tube.
- Is the feed the correct temperature?
- Would promotility agents help, or are they the cause of the discomfort?

3. **Diarrhoea**

Causes:

- Infection
- Medications
- Rate of feeding
- Intolerance to feed
- Migration of the tube

Management:

- Maintain feeding regime unless changed recently
- Electrolyte and hydration replacement
- Stool diary
- Stool culture

Consider possible causes:

- Has the feed been changed recently and can any changes be made to improve symptoms (rate, volume, concentration)?
- Feed temperature
- Tube migration

- Sorbitol content of medication, medications that may cause diarrhoea or alleviate it
- Tube and feed hygiene
- Faecal impaction
- Malabsorption

4. **Constipation**

This occurs for the same reason as in other situations, due to lack of fluid, immobility, lack of fibre or due to medications.

Administering medication through feeding tubes

Most medications are not licensed for use through feeding tubes, so administration of drugs through this route relies on the clinical judgement of the prescribing doctor and advice of community or hospital pharmacists. BAPEN advises the following approach. (208)

Consider:

- Is this medication needed?
- Can an alternative method of administration be used, eg topical, sublingual, rectal, intravenous Orodispersable tablets are not suitable for sublingual administration.
- Can a drug with an alternative method of administration in the same class be used instead?
- Can the medication be given safely orally instead?
- What is the site and size of feeding tube?

Formulations administered through feeding tubes

1. Liquid – this is easy to measure and administer and ready to use. However, excipients may cause side effects (eg sorbitol), large volumes may be needed, and some may cause GI side effects if hyperosmolar. **Preferred formulation.**
2. Liquid suspension – this is easy to measure and administer and ready to use. However, granules in the suspension may block tubes, they can be expensive special prescriptions, and adequate mixing is needed.
3. Soluble tablets (in water) – drug is in solution/liquid form, easy to administer, relatively cheap, dosing accurate. However, the drugs may take a while to disperse. **Preferred.**
4. Effervescent tablets – Convenient and accurate dosing, but may have high salt content, need a large volume of water and take a while to disperse.
5. Opening capsules – cheap, readily available, convenient. However, they may not disperse in water, may cause contact skin allergies and can be tricky to manage. **Last resort.**

Do not crush:

- Modified release preparations
- Enteric coated tablets
- Cytotoxics
- Hormones

NJ tubes and medication:

BAPEN advises: 'NJ tubes have greater potential to block due to longer length and smaller lumen. Some medicines are unsuitable for NJ administration as this bypasses gastric and duodenal absorption. Hyperosmolar medicines can cause GI side effects as the diluting effect of the stomach is bypassed. Advice from a pharmacist should always be taken before medication is administered via an NJ tube.' (208)

Psychological impact

Whilst enteral feeding provides a lot of health benefits for those that need it, it does have a psychological impact. There is no published research on those adults born with OA/TOF who are enterally fed, but literature on adults with other reasons for enteral feeding has shown a number of common themes. These include:

- Taking away the pleasure of eating and drinking
- Feeling trapped by the equipment, with a restriction of their social milieu due to fear of damaging the NG tube or PEG. This can include exercise, physical activities/work, taking public transport. The time needed for feeds and maintenance of the tube is also restrictive for some.
- Impact on socialising with others – some struggle with meals out with others. Family members and friends may not understand their changed situation with eating and drinking. Some are reluctant to initiate new relationships or struggle with physical intimacy with existing partners due to concerns about the equipment.
- Social stigma. The NG tube may be commented on by others when out in public or make the individual themselves feel different to others.

Possible strategies that may help

- Choosing the best way to administer the feed that gives them the most control and allows them to integrate it into their life – eg syringe feeding for speed or backpack for others.
- Arranging their activities around their feeding routine so they can live a full life.
- PEG feeding is less visible and allows patients to feel more confident in undertaking their daily routine and socialising with others. (209)

About the author

Dr Caroline Love qualified as a doctor in 1998 from the University of Liverpool. After an initial foray into psychiatry, her career has been spent in dermatology, and she has worked as an Associate Specialist at York Hospitals Trust since 2008. She has a Masters in Allergy from Imperial College London and specialist interests in telemedicine and psychodermatology.

Caroline was born in 1975 with type C OA/TOF and repaired by Miss Kapila at City Hospital, Nottingham. She has ongoing respiratory issues related to reflux and tracheomalacia, from infancy to the current day. The experience of navigating a healthcare system that is underinformed about OA/TOF and the long-term health issues that may occur caused her to become involved in the TOFS charity, and prompted the writing of the original leaflet for health professionals treating adults born with OA/TOF (along with another adult patient with OA/TOF, Sophie Smallwood). In consultation with the Adult TOF working group, Caroline has subsequently rewritten the content for the health professionals' pamphlet (available in hard copy), along with this much more detailed online material.

Caroline continues to volunteer for TOFS, and makes a valuable contribution to the Medical Liaison and Research sub-committee, Pastoral Support sub-committee and the Adult TOF working group.

About the Reviewers

This document has been peer reviewed by the following specialists.

Professor Alyn Morice Professor Morice is Head of Respiratory Medicine at HYMS, based at the University of Hull. He is also an Honorary Consultant Physician at Hull and East Yorkshire Hospitals NHS Trust. Professor Morice specialises in the diagnosis and treatment of cough and runs the Hull Cough Clinic. He also runs the Hull Respiratory Clinical Trials Unit, specialising in the treatment of asthma and COPD. Professor Morice has led the European Respiratory Society and British Thoracic Society Taskforces on Cough.	
Mr Nick Maynard Mr Maynard is a Consultant Upper GI Surgeon at Oxford University Hospitals NHS Trust and set up the Oxford Oesophagogastric Centre in 1997. He trained at Oxford University, Guy's Hospital, London and Melbourne, Australia. He is Chair of Clinical Services and Audit for the Association of Upper Gastrointestinal Surgeons (AUGIS) and Surgical Lead for the National Oesophagogastric Cancer Audit. He is also Cancer Lead for Oxford University Hospitals.	
Dr Vuokko Wallace Dr Wallace is a clinical psychologist, lecturer and clinical tutor on the University of Bath's Clinical Psychology doctorate course. Dr Wallace, also works as a patient-led researcher exploring the congenital birth defect oesophageal atresia (OA) after being born with the condition herself.	
Ms Julia Faulkner Ms Faulkner is a Paediatric Dietitian at Somerset Foundation NHS Trust. Ms Faulkner is also a member of the TOFS Medical Liaison and Research Sub-committee, a board member of EAT, ERNICA patient journey nutrition task-force lead, and Member (in professional capacity) of the TOFS Medical Advisory Group. Ms Faulkner is also a parent of a child born with OA/TOF.	

Mr Charles Shaw-Smith Charles Shaw-Smith is a Consultant in Clinical Genetics at Royal Devon and Exeter Hospital, and Honorary Senior Lecturer at Peninsula Medical School, Exeter. He was, from 2006 to 2010, a Wellcome Trust Intermediate Clinical Fellow, based at the Sanger Institute and Department of Clinical Genetics at Addenbrooke's Hospital in Cambridge. This four-year award enabled him to focus attention on his main research interests of genetic factors in oesophageal atresia and the VACTERL association. Since 2010 Dr Shaw-Smith has been based at the Royal Devon and Exeter Hospital and Peninsula Medical School in Exeter, where he continues to have a clinical interest in oesophageal atresia and related malformations. He provided input into the recent new edition of The TOF Book and has also published a book about gastrointestinal tract malformations: ("Molecular Basis of Developmental Anomalies of the Human Gastrointestinal Tract"), as well as research articles on the subject. His current interest is the investigation of a possible link between a 'lost twin' and a baby born with TOF/OA.	

TOFS would like to thank them all for their contributions in putting this handbook together.

References

1. Comella, A, Tan Tanny, SP, Hutson, JM, Omari, TI, Teague, WJ, Nataraja, RM & King, SK 2021, 'Esophageal morbidity in patients following repair of esophageal atresia: A systematic review', Journal of Pediatric Surgery, vol. 56, no. 9, pp. 1555-1563

2. Baldwin D, Yadav D. Esophageal Atresia. In: StatPearls. Treasure Island (FL): StatPearls Publishing; August 1, 2021

3. Spitz L. Oesophageal atresia. Orphanet J Rare Dis. 2007 May 11;2(1):24.

4. Gatzinsky V, Jönsson L, Ekerljung L, Friberg L-G, Wennergren G. Long-term respiratory symptoms following oesophageal atresia. Acta Paediatr. 2011;100(9):1222–5.

5. Rintala RJ, Sistonen S, Pakarinen MP. Outcome of Oesophageal Atresia Beyond Childhood. J Pediatr Gastroenterol Nutr. 2011 May;52:S35.

6. Sadreameli SC, McGrath-Morrow SA. Respiratory Care of Infants and Children with Congenital Tracheo-Oesophageal Fistula and Oesophageal Atresia. Paediatr Respir Rev. 2016 Jan 1;17:16–23.

7. Baxter KJ, Baxter LM, Landry AM, Wulkan ML, Bhatia AM. Structural airway abnormalities contribute to dysphagia in children with esophageal atresia and tracheoesophageal fistula. J Pediatr Surg. 2018 Sep;53(9):1655–9.

8. Roberts K, Karpelowsky J, Fitzgerald DA, Soundappan SS. Outcomes of oesophageal atresia and tracheo-oesophageal fistula repair. J Paediatr Child Health. 2016 Jul;52(7):694–8.

9. Shah AR, Lazar EL, Atlas AB. Tracheal diverticula after tracheoesophageal fistula repair: case series and review of the literature. J Pediatr Surg. 2009 Nov;44(11):2107–11.

10. BNF: British National Formulary – NICE [Internet]. NICE; [cited 2021 Aug 2]. Available from: https://bnf.nice.org.uk/

11. Morice AH, Millqvist E, Bieksiene K, Birring SS, Dicpinigaitis P, Ribas CD, et al. ERS guidelines on the diagnosis and treatment of chronic cough in adults and children. Eur Respir J [Internet]. 2020 Jan 1 [cited 2021 Aug 2];55(1). Available from: https://erj.ersjournals.com/content/55/1/1901136

12. Koumbourlis AC, Belessis Y, Cataletto M, Cutrera R, DeBoer E, Kazachkov M, et al. Care recommendations for the respiratory complications of esophageal atresia-tracheoesophageal fistula. Pediatr Pulmonol. 2020;55(10):2713–29.

13. McDermott S, Barry SC, Judge EE, Collins S, de Jong PA, Tiddens HAWM, et al. Tracheomalacia in Adults with Cystic Fibrosis: Determination of Prevalence and Severity with Dynamic Cine CT. Radiology. 2009 Aug;252(2):577–86.

14. Sistonen S, Malmberg P, Malmström K, Haahtela T, Sarna S, Rintala RJ, et al. Repaired oesophageal atresia: respiratory morbidity and pulmonary function in adults. Eur Respir J. 2010 Nov 1;36(5):1106–12.

15. Mirra V, Maglione M, Di Micco LL, Montella S, Santamaria F. Longitudinal Follow-up of Chronic Pulmonary Manifestations in Esophageal Atresia: A Clinical Algorithm and Review of the Literature. Pediatr Neonatol. 2017 Feb;58(1):8–15.

16. Son YG, Shin J, Ryu HG. Pneumonitis and pneumonia after aspiration. J Dent Anesth Pain Med. 2017 Mar;17(1):1–12.

17. Kovesi T. Aspiration Risk and Respiratory Complications in Patients with Esophageal Atresia. Front Pediatr [Internet]. 2017 [cited 2021 Aug 2];0. Available from: https://www.frontiersin.org/articles/10.3389/fped.2017.00062/full

18. Deurloo JA, Klinkenberg EC, Ekkelkamp S, Heij HA, Aronson DC. Adults with corrected oesophageal atresia: is oesophageal function associated with complaints and/or quality of life? Pediatr Surg Int. 2008 May 1;24(5):537–41.

19. Hamid M, Ullah W, Ur Rashid M, Amjad W, Mukhtar M, Hurairah A. An Esophagogram or Tracheobronchogram? A Review of Barium Sulfate Aspiration. J Investig Med High Impact Case Rep. 2018 Jan 1;6:2324709618802872.

20. Yoshimatsu Y, Tobino K, Ooi R, Sueyasu T, Nishizawa S, Yoshimine K, et al. A Need for a Diagnostic Management Protocol in Barium Aspiration. Intern Med. 2021 Oct 15;60(20):3285–7.

21. Yan G-W, Deng J-F, Bhetuwal A, Yang G-Q, Fu Q-S, Chen H, et al. A case report and literature review of barium sulphate aspiration during upper gastrointestinal examination. Medicine (Baltimore). 2017 Nov 27;96(47):e8821.

22. Venkatraman B, Rehman HA, Abdul-Wahab A. High resolution computed tomography appearances of late sequelae of barium aspiration in an asymptomatic young child. Saudi Med J. 2005 Apr;26(4):665–7.

23. Gendeh HS, Hashim ND, Mohammad Yunus MR, Gendeh BS, Kosai NR. The sequelae of barium aspiration. ANZ J Surg. 2018;88(9):937–8.

24. Frontiers | Barium Aspiration in an Infant: A Case Report and Review of Management | Pediatrics [Internet]. [cited 2022 Mar 11]. Available from: https://www.frontiersin.org/articles/10.3389/fped.2014.00037/full

25. Voloudaki A, Ergazakis N, Gourtsoyiannis N. Late changes in barium sulfate aspiration: HRCT features. Eur Radiol. 2003 Sep;13(9):2226–9.

26. Bronchiectasis: Practice Essentials, Background, Pathophysiology [Internet]. [cited 2021 Aug 2]. Available from: https://emedicine.medscape.com/article/296961-overview

27. T Hill A, L Sullivan A, D Chalmers J, De Soyza A, Stuart Elborn J, Andres Floto R, et al. British Thoracic Society Guideline for bronchiectasis in adults. Thorax. 2019 Jan;74(Suppl 1):1–69.

28. Althoff MD, Ghincea A, Wood LG, Holguin F, Sharma S. Asthma and Three Colinear Comorbidities: Obesity, OSA, and GERD. J Allergy Clin Immunol Pract. 2021 Nov;9(11):3877–84.

29. Brinke A ten, Sterk PJ, Masclee A a. M, Spinhoven P, Schmidt JT, Zwinderman AH, et al. Risk factors of frequent exacerbations in difficult-to-treat asthma. Eur Respir J. 2005 Nov 1;26(5):812–8.

30. Song W-J, Chang Y-S, Morice AH. Changing the paradigm for cough: does "cough hypersensitivity" aid our understanding? Asia Pac Allergy. 2014 Jan;4(1):3–13.

31. Hannon E, Eaton S, Curry JI, Kiely EM, Spitz L, De Coppi P. Outcomes in adulthood of gastric transposition for complex and long gap esophageal atresia. J Pediatr Surg. 2020 Apr;55(4):639–45.

32. Arneitz C, Windhaber J, Castellani C, Kienesberger B, Klymiuk I, Fasching G, et al. Cardiorespiratory performance capacity and airway microbiome in patients following primary repair of esophageal atresia. Pediatr Res. 2020 Nov 6;

33. Vergouwe FWT, IJsselstijn H, Wijnen RMH, Bruno MJ, Spaander MCW. Screening and Surveillance in Esophageal Atresia Patients: Current Knowledge and Future Perspectives. Eur J Pediatr Surg. 2015 Aug 1;25(4):345–52.

34. Lin J-H, Deng L, Li X. Recurrent tracheoesophageal fistula in an adolescent without persistent symptoms: A case report. Medicine (Baltimore). 2017 Nov;96(46):e8668.

35. Downey P, Middlesworth W, Bacchetta M, Sonett J. Recurrent and congenital tracheoesophageal fistula in adults. Eur J Cardio-Thorac Surg Off J Eur Assoc Cardio-Thorac Surg. 2017 Dec 1;52(6):1218–22.

36. Maynard, Nick, Crabbe, David, Martin Vicki. Oesophageal Problems in Adult Life. In: The TOF Book [Internet]. 2nd ed. TOFS; [cited 2021 Aug 2]. Available from: https://www.tofs.org.uk/buy-the-tof-book.aspx

37. Cartabuke RH, Lopez R, Thota PN. Long-term esophageal and respiratory outcomes in children with esophageal atresia and tracheoesophageal fistula. Gastroenterol Rep. 2016 Nov;4(4):310–4.

38. Koivusalo AI, Pakarinen MP, Lindahl HG, Rintala RJ. Endoscopic Surveillance After Repair of Oesophageal Atresia: Longitudinal Study in 209 Patients. J Pediatr Gastroenterol Nutr. 2016 Apr;62(4):562–6.

39. Krishnan U, Mousa H, Dall'Oglio L, Homaira N, Rosen R, Faure C, et al. ESPGHAN-NASPGHAN Guidelines for the Evaluation and Treatment of Gastrointestinal and Nutritional Complications in Children With Esophageal Atresia-Tracheoesophageal Fistula. J Pediatr Gastroenterol Nutr. 2016 Nov;63(5):550–70.

40. Ikenberry SO, Jue TL, Anderson MA, Appalaneni V, Banerjee S, Ben-Menachem T, et al. Management of ingested foreign bodies and food impactions. Gastrointest Endosc. 2011 Jun;73(6):1085–91.

41. Leopard D, Fishpool S, Winter S. The management of oesophageal soft food bolus obstruction: a systematic review. Ann R Coll Surg Engl. 2011 Sep;93(6):441–4.

42. Connor MJ, Springford LR, Kapetanakis VV, Giuliani S. Esophageal atresia and transitional care—step 1: a systematic review and meta-analysis of the literature to define the prevalence of chronic long-term problems. Am J Surg. 2015 Apr 1;209(4):747–59.

43. Overview | Gastro-oesophageal reflux disease and dyspepsia in adults: investigation and management | Guidance | NICE [Internet]. NICE; [cited 2021 Aug 2]. Available from: https://www.nice.org.uk/Guidance/CG184

44. Barrett Esophagus: Practice Essentials, Background, Etiology. 2019 Nov 21 [cited 2021 Aug 2]; Available from: https://emedicine.medscape.com/article/171002-overview

45. Schneider A, Michaud L, Gottrand F. Esophageal atresia: metaplasia, Barrett. Dis Esophagus. 2013 May 1;26(4):425–7.

46. Sistonen SJ, Koivusalo A, Nieminen U, Lindahl H, Lohi J, Kero M, et al. Esophageal morbidity and function in adults with repaired esophageal atresia with tracheoesophageal fistula: a population-based long-term follow-up. Ann Surg. 2010 Jun;251(6):1167–73.

47. Vergouwe FWT, IJsselstijn H, Biermann K, Erler NS, Wijnen RMH, Bruno MJ, et al. High Prevalence of Barrett's Esophagus and Esophageal Squamous Cell Carcinoma After Repair of Esophageal Atresia. Clin Gastroenterol Hepatol Off Clin Pract J Am Gastroenterol Assoc. 2018 Apr;16(4):513-521.e6.

48. Taylor ACF, Breen KJ, Auldist A, Catto–Smith A, Clarnette T, Crameri J, et al. Gastroesophageal Reflux and Related Pathology in Adults Who Were Born With Esophageal Atresia: A Long-Term Follow-up Study. Clin Gastroenterol Hepatol. 2007 Jun 1;5(6):702–6.

49. Chantal A. ten Kate, Anne-Fleur R.L. van Hal, , Nicole S. Erler, Michail Doukas, , Suzan Nikkessen, , John Vlot, et al. Recommendations for endoscopic surveillance after esophageal atresia repair in adults (In press).

50. Awad K, Jaffray B. Oesophageal replacement with stomach: A personal series and review of published experience. J Paediatr Child Health. 2017 Dec;53(12):1159–66.

51. Adzick NS, Fisher JH, Winter HS, Sandler RH, Hendren WH. Esophageal adenocarcinoma 20 years after esophageal atresia repair. J Pediatr Surg. 1989 Aug 1;24(8):741–4.

52. Alfaro L, Bermas H, Fenoglio M, Parker R, Janik JS. Are patients who have had a tracheoesophageal fistula repair during infancy at risk for esophageal adenocarcinoma during adulthood? J Pediatr Surg. 2005 Apr 1;40(4):719–20.

53. Pultrum BB, Bijleveld CM, de Langen ZJ, Plukker JThM. Development of an adenocarcinoma of the esophagus 22 years after primary repair of a congenital atresia. J Pediatr Surg. 2005 Dec 1;40(12):e1–4.

54. Deurloo JA, van Lanschot JJB, Drillenburg P, Aronson DC. Esophageal squamous cell carcinoma 38 years after primary repair of esophageal atresia. J Pediatr Surg. 2001 Apr 1;36(4):629–30.

55. Vergouwe FW, Gottrand M, Wijnhoven BP, IJsselstijn H, Piessen G, Bruno MJ, et al. Four cancer cases after esophageal atresia repair: Time to start screening the upper gastrointestinal tract. World J Gastroenterol. 2018 Mar 7;24(9):1056–62.

56. Jayasekera CS, Desmond PV, Holmes JA, Kitson M, Taylor ACF. Cluster of 4 cases of esophageal squamous cell cancer developing in adults with surgically corrected esophageal atresia—time for screening to start. J Pediatr Surg. 2012 Apr 1;47(4):646–51.

57. Ng DWJ, Ching Tan GH, Teo MCC. Malignancy arising in a 41-year-old colonic interposition graft. Asian J Surg. 2016 Jan;39(1):45–7.

58. Shersher DD, Hong E, Warren W, Penfield Faber L, Liptay MJ. Adenocarcinoma in a 40-Year-Old Colonic Interposition Treated With Ivor Lewis Esophagectomy and Esophagogastric Anastomosis. Ann Thorac Surg. 2011 Dec 1;92(6):e113–4.

59. Michaud L, Sfeir R, Couttenier F, Turck D, Gottrand F. Dumping syndrome after esophageal atresia repair without antireflux surgery. J Pediatr Surg. 2010 Apr 1;45(4):e13–5.

60. Dumping Syndrome: Background, Pathophysiology, Etiology. 2021 Apr 23 [cited 2021 Aug 2]; Available from: https://emedicine.medscape.com/article/173594-overview

61. Scarpellini E, Arts J, Karamanolis G, Laurenius A, Siquini W, Suzuki H, et al. International consensus on the diagnosis and management of dumping syndrome. Nat Rev Endocrinol. 2020 Aug;16(8):448–66.

62. Longley KJ, Ho V. Practical management approach to gastroparesis. Intern Med J. 2020;50(8):909–17.

63. Keld R, Kinsey L, Athwal V, Lal S. Pathogenesis, investigation and dietary and medical management of gastroparesis. J Hum Nutr Diet. 2011;24(5):421–30.

64. Achalasia: Practice Essentials, Background, Pathophysiology [Internet]. [cited 2021 Oct 31]. Available from: https://reference.medscape.com/article/169974-overview

65. Cheng W, Poon KH, Lui VCH, Yong JL, Law S, So KT, et al. Esophageal atresia and achalasialike esophageal dysmotility. J Pediatr Surg. 2004 Oct 1;39(10):1581–3.

66. Marinello FG, Targarona EM, Poca M, Mones J, Hernández-Ballesteros C. Late-onset achalasia after esophageal atresia repair. Dis Esophagus. 2013 Apr 1;26(3):311–3.

67. Sabaté JM, Gaudric M, Dousset B, Chaussade S, Couturier D. [Dysphagia in a trisomic adult operated on for esophageal atresia: achalasia or pseudo-achalasia?]. Gastroenterol Clin Biol. 1999 May;23(5):573–6.

68. Chen GC, Cheng DW, Enayati PJ, Chen G, Conklin JL, Soffer EE. Concurrent Findings of Achalasia and Duodenal Duplication in a Down Syndrome Patient. J Formos Med Assoc. 2009 Jan 1;108(1):78–81.

69. Vaezi MF, Pandolfino JE, Yadlapati RH, Greer KB, Kavitt RT. ACG Clinical Guidelines: Diagnosis and Management of Achalasia. Off J Am Coll Gastroenterol ACG. 2020 Sep;115(9):1393–411.

70. Harvey PR, Thomas T, Chandan JS, Mytton J, Coupland B, Bhala N, et al. Incidence, morbidity and mortality of patients with achalasia in England: findings from a study of nationwide hospital and primary care data. Gut. 2019 May;68(5):790–5.

71. Pachl M, Eaton S, Kiely EM, Drake D, Cross K, Curry JI, et al. Esophageal atresia and malrotation: what association? Pediatr Surg Int. 2015 Feb;31(2):181–5.

72. Upadhyay V, Hea CM, Matthews RD. Oesophageal Atresia: A Handshake with Malrotation. Eur J Pediatr Surg. 2001 Dec;11(06):368–70.

73. Cieri MV, Arnold GL, Torfs CP. Malrotation in conjunction with esophageal atresia/tracheo-esophageal fistula. Teratology. 1999;60(3):114–6.

74. Eccleston JL, Su H, Ling A, Heller T, Koh C. Adult Presentation of Intestinal Malrotation. J Gastroenterol Hepatol. 2016 Aug;31(8):1382.

75. Albertson MJ. Intestinal Malrotation in an adult patient. Proceedings of UCLA Healthcare.2016 Vol 20.

76. Acute Mesenteric Ischemia Clinical Presentation: History, Physical Examination, Complications [Internet]. [cited 2021 Oct 31]. Available from: https://emedicine.medscape.com/article/189146-clinical

77. Small-Bowel Obstruction Clinical Presentation: History, Physical Examination [Internet]. [cited 2021 Oct 31]. Available from: https://emedicine.medscape.com/article/774140-clinical

78. Sigmoid and Cecal Volvulus Clinical Presentation: History, Physical Examination [Internet]. [cited 2021 Oct 31]. Available from: https://emedicine.medscape.com/article/2048554-clinical

79. Intestinal malrotation – Symptoms, diagnosis and treatment | BMJ Best Practice [Internet]. [cited 2021 Oct 31]. Available from: https://bestpractice.bmj.com/topics/en-gb/753

80. Liacouras CA, Furuta GT, Hirano I, Atkins D, Attwood SE, Bonis PA, et al. Eosinophilic esophagitis: Updated consensus recommendations for children and adults. J Allergy Clin Immunol. 2011 Jul;128(1):3-20.e6.

81. Lardenois E, Michaud L, Schneider A, Onea M, Rebeuh J, Gottrand-Aumar M, et al. Prevalence of Eosinophilic Esophagitis in Adolescents With Esophageal Atresia. J Pediatr Gastroenterol Nutr. 2019 Jul 1;Publish Ahead of Print:1.

82. Eosinophilic oesophagitis – Symptoms, diagnosis and treatment | BMJ Best Practice [Internet]. [cited 2021 Aug 7]. Available from: https://bestpractice.bmj.com/topics/en-gb/1304

83. ten Kate CA, Brouwer RWW, van Bever Y, Martens VK, Brands T, van Beelen NWG, et al. Infantile hypertrophic pyloric stenosis in patients with esophageal atresia. Birth Defects Res. 2020;112(9):670–87.

84. Hassan SM, Mubarik A, Muddassir S, Haq F. Adult idiopathic hypertrophic pyloric stenosis – a common presentation with an uncommon diagnosis. J Community Hosp Intern Med Perspect. 2018 Apr 17;8(2):64–7.

85. Lin H-P, Lin Y-C, Kuo C-Y. Adult idiopathic hypertrophic pyloric stenosis. J Formos Med Assoc. 2015 Jul 1;114(7):659–62.

86. Graadt van Roggen JF, van Krieken JH. Adult hypertrophic pyloric stenosis: case report and review. J Clin Pathol. 1998 Jun;51(6):479–80.

87. Briganti SI, Naciu AM, Tabacco G, Cesareo R, Napoli N, Trimboli P, et al. Proton Pump Inhibitors and Fractures in Adults: A Critical Appraisal and Review of the Literature. Int J Endocrinol. 2021 Jan 15;2021:8902367.

88. Proton pump inhibitors | Prescribing information | Dyspepsia – proven functional | CKS | NICE [Internet]. [cited 2021 Oct 31]. Available from: https://cks.nice.org.uk/topics/dyspepsia-proven-functional/prescribing-information/proton-pump-inhibitors/

89. Yibirin M, De Oliveira D, Valera R, Plitt AE, Lutgen S. Adverse Effects Associated with Proton Pump Inhibitor Use. Cureus. 13(1):e12759.

90. Menabawey TE, Dluzewski S, Phillpotts S, Preedy R, Besherdas K. PTU-112 Proton Pump Inhibitors – A Risk for Micronutrient Deficiency. But Are We Looking Out for This? Gut. 2016 Jun 1;65(Suppl 1):A111–A111.

91. Trinh VQ-H, Shi C, Ma C. Gastric neuroendocrine tumours from long-term proton pump inhibitor users are indolent tumours with good prognosis. Histopathology. 2020;77(6):865–76.

92. Tran-Duy A, Connell NJ, Vanmolkot FH, Souverein PC, de Wit NJ, Stehouwer CDA, et al. Use of proton pump inhibitors and risk of iron deficiency: a population-based case–control study. J Intern Med. 2019;285(2):205–14.

93. Fayoux P, Morisse M, Sfeir R, Michaud L, Daniel S. Laryngotracheal anomalies associated with esophageal atresia: importance of early diagnosis. Eur Arch Otorhinolaryngol. 2018 Feb 1;275(2):477–81.

94. Birketvedt K, Mikkelsen A, Klingen LL, Henriksen C, Helland IB, Emblem R. Nutritional Status in Adolescents with Esophageal Atresia. J Pediatr. 2020 Mar;218:130–7.

95. Traini I, Menzies J, Hughes J, Leach ST, Krishnan U. Oesophageal atresia: The growth gap. World J Gastroenterol. 2020 Mar 28;26(12):1262–72.

96. Pelizzo G, Destro F, Selvaggio GGO, Maestri L, Roveri M, Bosetti A, et al. Esophageal Atresia: Nutritional Status and Energy Metabolism to Maximize Growth Outcome. Child Basel Switz. 2020 Nov 14;7(11):E228.

97. Presse N, Taillefer J, Maynard S, Bouin M. Insufficient Body Weight of Adults Born With Esophageal Atresia. J Pediatr Gastroenterol Nutr. 2016 Mar;62(3):469–73.

98. Londahl M, Irace AL, Kawai K, Dombrowski ND, Jennings R, Rahbar R. Prevalence of Laryngeal Cleft in Pediatric Patients With Esophageal Atresia. JAMA Otolaryngol – Head Neck Surg. 2018 Feb 1;144(2):164–8.

99. Hseu A, Recko T, Jennings R, Nuss R. Upper Airway Anomalies in Congenital Tracheoesophageal Fistula and Esophageal Atresia Patients. Ann Otol Rhinol Laryngol. 2015 Oct;124(10):808–13.

100. Richard EG, Robert MG, William WM. Validation of a Voice Outcome Survey for Unilateral Vocal Cord Paralysis. Otolaryngol Neck Surg. 1999 Feb 1;120(2):153–8.

101. Carrau RL, Khidr A, Crawley JA, Hillson EM, Davis JK, Pashos CL. The Impact of Laryngopharyngeal Reflux on Patient-Reported Quality of Life. The Laryngoscope. 2004;114(4):670–4.

102. Francis DO, Sherman AE, Hovis KL, Bonnet K, Schlundt D, Garrett CG, et al. Life Experience of Patients With Unilateral Vocal Fold Paralysis. JAMA Otolaryngol – Head Neck Surg. 2018 May;144(5):433–9.

103. Cohen SM, Kim J, Roy N, Asche C, Courey M. The impact of laryngeal disorders on work-related dysfunction. The Laryngoscope. 2012;122(7):1589–94.

104. Lechien JR, Hans S, Bobin F, Calvo-Henriquez C, Saussez S, Karkos PD. Atypical Clinical Presentation of Laryngopharyngeal Reflux: A 5-Year Case Series. J Clin Med. 2021 May 31;10(11):2439.

105. Carroll TL. Reflux and the Voice: Getting Smarter About Laryngopharyngeal Reflux. Otolaryngol Clin North Am. 2019 Aug 1;52(4):723–33.

106. Moshkowitz M, Horowitz N, Leshno M, Halpern Z. Halitosis and gastroesophageal reflux disease: a possible association. Oral Dis. 2007 Nov;13(6):581–5.

107. Hamilton NJI, Wilcock J, Hannan SA. A lump in the throat: laryngopharyngeal reflux. BMJ. 2020 Nov 2;371:m4091.

108. Martins RHG, Dias NH, Soares CSP, Gramuglia ACJ. Treatment of Laryngeal Granulomas. Int Arch Otorhinolaryngol. 2019 Jul;23(3):e322–4.

109. Zou Y, Deng D, Li X, Yang Z. Association between gastroesophageal reflux disease and vocal fold polyps. Medicine (Baltimore). 2021 May 21;100(20):e25787.

110. Lechien JR, Akst LM, Hamdan AL, Schindler A, Karkos PD, Barillari MR, et al. Evaluation and Management of Laryngopharyngeal Reflux Disease: State of the Art Review. Otolaryngol Neck Surg. 2019 May 1;160(5):762–82.

111. Kotby MN, Hassan O, El-Makhzangy AMN, Farahat M, Milad P. Gastroesophageal reflux/laryngopharyngeal reflux disease: a critical analysis of the literature. Eur Arch Oto-Rhino-Larngol Off J Eur Fed Oto-Rhino-Laryngol Soc EUFOS Affil Ger Soc Oto-Rhino-Laryngol – Head Neck Surg. 2010 Feb;267(2):171–9.

112. Huestis MJ, Keefe KR, Kahn CI, Tracy LF, Levi JR. Alternatives to Acid Suppression Treatment for Laryngopharyngeal Reflux. Ann Otol Rhinol Laryngol. 2020 Oct 1;129(10):1030–9.

113. Chronic Sinusitis: Background, Anatomy, Pathophysiology. 2021 Jul 20 [cited 2021 Jul 26]; Available from: https://emedicine.medscape.com/article/232791-overview#a3

114. Lewis, Alison. Tooth wear in Adult TOFs. Chew TOFS Charity Publ.

115. Lee RJ, Aminian A, Brunton P. Dental complications of gastro-oesophageal reflux disease: guidance for physicians. Intern Med J. 2017;47(6):619–23.

116. Lewis, Alison. TOF teeth. Chew. TOFS charity publication94.

117. Moazzez R, Austin R. Medical conditions and erosive tooth wear. Br Dent J. 2018 Mar;224(5):326–32.

118. Byars KC, Burklow KA, Ferguson K, O'Flaherty T, Santoro K, Kaul A. A Multicomponent Behavioral Program for Oral Aversion in Children Dependent on Gastrostomy Feedings. J Pediatr Gastroenterol Nutr. 2003 Oct;37(4):473–80.

119. Menzies J, Hughes J, Leach S, Belessis Y, Krishnan U. Prevalence of Malnutrition and Feeding Difficulties in Children With Esophageal Atresia. J Pediatr Gastroenterol Nutr. 2017 Apr;64(4):e100.

120. Baird R, Levesque D, Birnbaum R, Ramsay M. A pilot investigation of feeding problems in children with esophageal atresia. Dis Esophagus Off J Int Soc Dis Esophagus. 2015 Apr;28(3):224–8.

121. Andrassy RJ, Patterson RS, Ashley J, Patrissi G, Mahour GH. Long-term nutritional assessment of patients with esophageal atresia and/or tracheoesophageal fistula. J Pediatr Surg. 1983 Aug 1;14):431–5.

122. Ramsay M, Birnbaum R. Feeding difficulties in children with esophageal atresia: treatment by a multidisciplinary team. Dis Esophagus Off J Int Soc Dis Esophagus. 2013 Jun;26(4):410–2.

123. Naik RD, Vaezi MF. Extra-esophageal manifestations of GERD: who responds to GERD therapy? Curr Gastroenterol Rep. 2013 Apr;15(4):318.

124. Primary Care Focus – Evaluation of Noncardiac Chest Pain [Internet]. Medscape. [cited 2021 Jul 25]. Available from: http://www.medscape.com/viewarticle/407980

125. Esophageal Spasm: Background, Pathophysiology, Epidemiology. 2019 Nov 10 [cited 2021 Jul 26]; Available from: https://emedicine.medscape.com/article/174975-overview

126. Rabone C, Wallace V. A thematic analysis exploring the psychological well-being of adults born with esophageal atresia. J Psychosom Res. 2021 Jun 1;145:110474.

127. De Young AC, Paterson RS, Brown EA, Egberts MR, Le Brocque RM, Kenardy JA, et al. Topical Review: Medical Trauma During Early Childhood. J Pediatr Psychol. 2021 Aug 1;46(7):739–46.

128. Shonkoff JP, Garner AS, The Committee on Psychosocial Aspects of Child and Family Health C on EC, Siegel BS, Dobbins MI, Earls MF, et al. The Lifelong Effects of Early Childhood Adversity and Toxic Stress. Pediatrics. 2012 Jan 1;129(1):e232–46.

129. Bowlby J. Preface. Bull World Health Organ. 1951;3(3):357–8.

130. Douglas WB. Early Hospital Admissions and Later Disturbances of Behaviour and Learning. Dev Med Child Neurol. 2008 Nov 12;17(4):456–80.

131. Rennick JE, Dougherty G, Chambers C, Stremler R, Childerhose JE, Stack DM, et al. Children's psychological and behavioral responses following pediatric intensive care unit hospitalization: the caring intensively study. BMC Pediatr. 2014 Oct 26;14:276.

132. Ben-Ari A, Benarroch F, Sela Y, Margalit D. Risk factors for the development of medical stress syndrome following surgical intervention. J Pediatr Surg. 2020 Sep 1;55(9):1685–90.

133. ten Kate CA, Rietman AB, Kamphuis LS, Gischler S, Lee D, Fruithof J, et al. Patient-driven healthcare recommendations for adults with esophageal atresia and their families. J Pediatr Surg. 2021 Jan;S0022346821000063.

134. Mikkelsen A, Boye B, Diseth TH, Malt U, Mørkrid L, IJsselstijn H, et al. Traumatic stress, mental health and quality of life in adolescents with esophageal atresia. J Pediatr Surg [Internet]. 2020 Nov 7 [cited 2021 Aug 7]; Available from: https://www.sciencedirect.com/science/article/pii/S002234682030782X

135. Lim KG, Morgenthaler TI, Katzka DA. Sleep and Nocturnal Gastroesophageal Reflux: An Update. Chest. 2018 Oct;154(4):963–71.

136. Mishra PR, Tinawi GK, Stringer MD. Scoliosis after thoracotomy repair of esophageal atresia: a systematic review. Pediatr Surg Int. 2020 Jul 1;36(7):755–61.

137. Keloids and hypertrophic scars | DermNet NZ [Internet]. [cited 2021 Nov 3]. Available from: https://dermnetnz.org/topics/keloids-and-hypertrophic-scar

138. Inchingolo F, Tatullo M, Abenavoli FM, Marrelli M, Inchingolo AD, Corelli R, et al. Surgical Treatment of Depressed Scar: A Simple Technique. Int J Med Sci. 2011 Jun 18;8(5):377–9.

139. Cartlidge PHT, Fox PE, Rutter N. The scars of newborn intensive care. Early Hum Dev. 1990 Jan 1;21(1):1–10.

140. Laparoscopic Adhesiolysis: Background, Indications, Contraindications. 2021 Jul 14 [cited 2021 Nov 3]; Available from: https://emedicine.medscape.com/article/1829759-overview

141. Cremer R, Lorbacher M, Hering F, Engelskirchen R. Natural rubber latex sensitisation and allergy in patients with spina bifida, urogenital disorders and oesophageal atresia compared with a normal paediatric population. Eur J Pediatr Surg Off J Austrian Assoc Pediatr Surg Al Z Kinderchir. 2007 Jun;17(3):194–8.

142. Gentili A, Ricci G, Lorenzo FPD, Pigna A, Masi M, Baroncini S. Latex allergy in children with oesophageal atresia. Pediatr Anesth. 2003;13(8):668–75.

143. Shaw-Smith C. Oesophageal atresia, tracheo-oesophageal fistula, and the VACTERL association: review of genetics and epidemiology. J Med Genet. 2006 Jul;43(7):545–54.

144. Roberts K, Karpelowsky J, Fitzgerald DA, Soundappan SSV. Radiation exposure in infants with oesophageal atresia and tracheo-oesophageal fistula. Pediatr Surg Int. 2019 Apr 1;35(4):509–15.

145. Zamiara P, Thomas KE, Connolly BL, Lane H, Marcon MA, Chiu PP. Long-term burden of care and radiation exposure in survivors of esophageal atresia. J Pediatr Surg. 2015 Oct 1;50(10):1686–90.

146. Yousef Y, Baird R. Radiation Exposure and Attributable Cancer Risk in Patients With Esophageal Atresia. J Pediatr Gastroenterol Nutr. 2018 Feb;66(2):234–8.

147. Scott DA. Esophageal Atresia / Tracheoesophageal Fistula Overview. In: Adam MP, Ardinger HH, Pagon RA, Wallace SE, Bean LJ, Mirzaa G, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993 [cited 2021 Aug 2]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK5192/

148. Brosens E, Ploeg M, van Bever Y, Koopmans AE, IJsselstijn H, Rottier RJ, et al. Clinical and etiological heterogeneity in patients with tracheo-esophageal malformations and associated anomalies. Eur J Med Genet. 2014 Aug 1;57(8):440–52.

149. Tartaglia NR, Howell S, Sutherland A, Wilson R, Wilson L. A review of trisomy X (47,XXX). Orphanet J Rare Dis. 2010 May 11;5:8.

150. Trisomy 18: Practice Essentials, Pathophysiology, Epidemiology [Internet]. [cited 2021 Aug 2]. Available from: https://emedicine.medscape.com/article/943463-overview

151. Solomon, B.D. VACTERL/VATER Association. Orphanet J Rare Dis 6, 56 (2011).

152. van de Putte R, van Rooij IALM, Marcelis CLM, Guo M, Brunner HG, Addor M-C, et al. Spectrum of congenital anomalies among VACTERL cases: a EUROCAT population-based study. Pediatr Res. 2020 Feb;87(3):541–9.

153. Raam MS, Pineda-Alvarez DE, Hadley DW, Solomon BD. Long-term outcomes of adults with features of VACTERL association. Eur J Med Genet. 2011;54(1):34–41.

154. van der Bent A, Duggan EM, Fishman LN, Dickie BH. Reality check: What happens when patients with anorectal malformations grow up? A pilot study of medical care transition from the adult patient perspective. J Pediatr Surg. 2018 Sep;53(9):1722–6.

155. Danielson J, Karlbom U, Graf W, Wester T. Outcome in adults with anorectal malformations in relation to modern classification — Which patients do we need to follow beyond childhood? J Pediatr Surg. 2017 Mar 1;52(3):463–8.

156. Rigueros Springford L, Connor MJ, Jones K, Kapetanakis VV, Giuliani S. Prevalence of Active Long-term Problems in Patients With Anorectal Malformations: A Systematic Review. Dis Colon Rectum. 2016 Jun;59(6):570–80.

157. Bicelli N, Trovalusci E, Zannol M, Gamba P, Bogana G, Zanatta C, et al. Gynecological and psycho-sexual aspects of women with history of anorectal malformations. Pediatr Surg Int. 2021 Aug;37(8):991–7.

158. Kyrklund K, Taskinen S, Rintala RJ, Pakarinen MP. Sexual Function, Fertility and Quality of Life after Modern Treatment of Anorectal Malformations. J Urol. 2016 Dec;196(6):1741–6.

159. Vilanova-Sanchez A, McCracken K, Halleran DR, Wood RJ, Reck-Burneo CA, Levitt MA, et al. Obstetrical Outcomes in Adult Patients Born with Complex Anorectal Malformations and Cloacal Anomalies: A Literature Review. J Pediatr Adolesc Gynecol. 2019 Feb;32(1):7–14.

160. Hilton G, Mihm F, Butwick A. Anesthetic management of a parturient with VACTERL association undergoing Cesarean delivery. Can J Anaesth J Can Anesth. 2013 Jun;60(6):570–6.

161. Bjørsum-Meyer T, Herlin M, Qvist N, Petersen MB. Vertebral defect, anal atresia, cardiac defect, tracheoesophageal fistula/esophageal atresia, renal defect, and limb defect association with Mayer-Rokitansky-Küster-Hauser syndrome in co-occurrence: two case reports and a review of the literature. J Med Case Reports. 2016 Dec 21;10(1):374.

162. Judd-Glossy L, Ariefdjohan M, Curry S, Ketzer J, Pena A, Bischoff A. A survey of adults with anorectal malformations: perspectives on educational, vocational, and psychosocial experiences. Pediatr Surg Int. 2019 Sep 1;35(9):953–61.

163. Gong CL, Zhao H, Wei Y, Tysinger B, Goldman DP, Williams RG. Lifetime Burden of Adult Congenital Heart Disease in the USA Using a Microsimulation Model. Pediatr Cardiol. 2020 Oct 1;41(7):1515–25.

164. Lei EL, Heggie J. Adult congenital heart disease and anesthesia: An educational review. Pediatr Anesth. 2021;31(2):123–31.

165. Neidenbach RC, Lummert E, Vigl M, Zachoval R, Fischereder M, Engelhardt A, et al. Non-cardiac comorbidities in adults with inherited and congenital heart disease: report from a single center experience of more than 800 consecutive patients. Cardiovasc Diagn Ther. 2018 Aug;8(4):423–31.

166. Oster ME, Riser AP, Andrews JG, Bolin EH, Galindo MK, Nembhard WN, et al. Comorbidities Among Young Adults with Congenital Heart Defects: Results from the Congenital Heart Survey To Recognize Outcomes, Needs, and well-being — Arizona, Arkansas, and Metropolitan Atlanta, 2016–2019. Morb Mortal Wkly Rep. 2021 Feb 12;70(6):197–201.

167. Ramage K, Grabowska K, Silversides C, Quan H, Metcalfe A. Association of Adult Congenital Heart Disease With Pregnancy, Maternal, and Neonatal Outcomes. JAMA Netw Open. 2019 May 10;2(5):e193667.

168. Moons P, Luyckx K, Thomet C, et al. Physical Functioning, Mental Health, and Quality of Life in Different Congenital Heart Defects: Comparative Analysis in 3538 Patients From 15 Countries. Can J Cardiol. 2021;37(2):215-223.

169. Stack M, Westmoreland T. Adolescent With VACTERL Association Presents With Recurrent Pneumonia. Cureus. 2020 Sep 10;12(9):e10365.

170. Ahn S-Y, Mendoza S, Kaplan G, Reznik V. Chronic kidney disease in the VACTERL association: clinical course and outcome. Pediatr Nephrol Berl Ger. 2009 May;24(5):1047–53.

171. Cimen S, Nantais J, Guler S, Lawen J. Kidney transplantation in an adult patient with VACTERL association. BMJ Case Reports. 2015 Jun;2015

172. Cunningham BK, Khromykh A, Martinez AF, Carney T, Hadley DW, Solomon BD. Analysis of renal anomalies in VACTERL association. Birt Defects Res A Clin Mol Teratol. 2014 Oct;100(10):801–5.

173. Irino T, Tsekrekos A, Coppola A, Scandavini CM, Shetye A, Lundell L, et al. Long-term functional outcomes after replacement of the esophagus with gastric, colonic, or jejunal conduits: a systematic literature review. Dis Esophagus. 2017 Dec 1;30(12):1–11.

174. Yajima K, Kosugi S, Kanda T, Matsuki A, Hatakeyama K. Risk Factors of Reflux Esophagitis in the Cervical Remnant Following Esophagectomy with Gastric Tube Reconstruction. World J Surg. 2008 Dec 13;33(2):284.

175. Foster JD, Hall NJ, Keys SC, Burge DM. Esophageal replacement by gastric transposition: A single surgeon's experience from a tertiary pediatric surgical center. J Pediatr Surg. 2018 Nov 1;53(11):2331–5.

176. Gallo G, Vrijlandt EJLE, Arets HGM, Koppelman GH, Van der Zee DC, Hulscher JBF, et al. Respiratory function after esophageal replacement in children. J Pediatr Surg. 2017 Nov 1;52(11):1736–41.

177. Coopman S, Michaud L, Halna-Tamine M, Bonnevalle M, Bourgois B, Turck D, et al. Long-term outcome of colon interposition after esophagectomy in children. J Pediatr Gastroenterol Nutr. 2008 Oct;47(4):458–62.

178. Shokrollahi K, Barham P, Blazeby JM, Alderson D. Surgical revision of dysfunctional colonic interposition after esophagoplasty. Ann Thorac Surg. 2002 Nov 1;74(5):1708–11.

179. Dhir R, Sutcliffe RP, Rohatgi A, Forshaw MJ, Strauss DC, Mason RC. Surgical management of late complications after colonic interposition for esophageal atresia. Ann Thorac Surg. 2008 Dec;86(6):1965–7.

180. Hartin CW, Escobar MA, Yamout SZ, Caty MG. Stapled tapering coloplasty to manage colon interposition graft redundancy for long gap esophageal atresia. J Pediatr Surg. 2008 Dec 1;43(12):2311–4.

181. Domreis JS, Jobe BA, Aye RW, Deveney KE, Sheppard BC, Deveney CW. Management of long-term failure after colon interposition for benign disease. Am J Surg. 183(5):544–6.

182. Vasseur Maurer S, Estremadoyro V, Reinberg O. Evaluation of an antireflux procedure for colonic interposition in pediatric esophageal replacements. J Pediatr Surg. 2011 Mar;46(3):594–600.

183. Burgos L, Barrena S, Andrés AM, Martínez L, Hernández F, Olivares P, et al. Colonic interposition for esophageal replacement in children remains a good choice: 33-year median follow-up of 65 patients. J Pediatr Surg. 2010 Feb 1;45(2):341–5.

184. Baggaley A, Reid T, Davidson J, de Coppi P, Botha A. Late life revision surgery for dilated colonic conduit in long gap oesophageal atresia. Ann R Coll Surg Engl. 2018 Sep;100(7):e185–7.

185. Henry CL, Reinerssman JM, Deb SJ. Substernal Colon Volvulus with Ischemia 43 Years after Reconstruction for Esophageal Atresia. Am Surg. 2017 Sep 1;83(9):396–7.

186. Sterling RP, Kuykendall RC, Carmichael MJ, Khalil K. Unusual Sequelae of Colon Interposition for Esophageal Reconstruction: Late Obstruction Requiring Reoperation. Ann Thorac Surg. 1984 Sep;38(3):292–5.

187. Khan BA, Ionescu RC, Halal AM, Kesler KA. Cardiac compression secondary to a massively dilated substernal colon conduit. J Pediatr Surg. 2012 Nov;47(11):2126–8.

188. Bos ME, Wijnen RMH, de Blaauw I. Gastric pneumatosis and rupture caused by lactobezoar. Pediatr Int Off J Jpn Pediatr Soc. 2013 Dec;55(6):757–60.

189. Chacko A, Masters BI, Isles A. Giant Gastric Bezoar Complicating Congenital Esophageal Atresia Repaired by Gastric Interposition – A Case Report. Front Pediatr. 2017 Jan 1;5:98.

190. Bures J, Cyrany J, Kohoutova D, Förstl M, Rejchrt S, Kvetina J, et al. Small intestinal bacterial overgrowth syndrome. World J Gastroenterol. 2010 Jun 28;16(24):2978–90.

191. Mallinson CN, Drasar BS, Trounce JR. Fat malabsorption associated with bacterial colonization of a colon transplant: a case report. Guys Hosp Rep. 1973 Jan 1;122(3–4):231–43.

192. Takiguchi S, Yano H, Sekimoto M, Taniguchi E, Monden T, Ohashi S, et al. Laparoscopic surgery for blind pouch syndrome following Roux-en Y gastrojejunostomy: report of a case. Surg Today. 1999;29(6):553–6.

193. Sawant AD, Shah R, Shah N, Gupta T. A Rare Cause of Chronic Life Threatening Bleeding in a Girl: The Ulcerated Blind Loops. APSP J Case Rep. 2016 Apr 24;7(2):13.

194. Pimentel M, Saad RJ, Long MD, Rao SSC. ACG Clinical Guideline: Small Intestinal Bacterial Overgrowth. Am J Gastroenterol. 2020 Feb;115(2):165–78.

195. Carroll RE, Benedetti E, Schowalter JP, Buchman AL. Management and Complications of Short Bowel Syndrome: an Updated Review. Curr Gastroenterol Rep. 2016 Jun 20;18(7):40.

196. Short-Bowel Syndrome: Background, Anatomy, Pathophysiology. 2021 Apr 29 [cited 2021 Jul 28]; Available from: https://emedicine.medscape.com/article/193391-overview

197. Haddad R, Teixeira Lima R, Henrique Boasquevisque C, Antonio Marsico G. Symptomatic mucocele after esophageal exclusion. Interact Cardiovasc Thorac Surg. 2008 Aug 1;7(4):742–4.

198. Kamath MV, Ellison RG, Rubin JW, Moore HV, Pai GP. Esophageal Mucocele: A Complication of Blind Loop Esophagus. Ann Thorac Surg. 1987 Mar 1;43(3):263–9.

199. Martínez L, Tovar JA. Ulcerated mucocele of the esophagus in a child. Ann Thorac Surg. 2003 Apr 1;75(4):1310–1.

200. Mongerson CRL, Jennings RW, Zurakowski D, Bajic D. QUANTITATIVE MRI STUDY OF INFANT REGIONAL BRAIN SIZE FOLLOWING SURGERY FOR LONG-GAP ESOPHAGEAL ATRESIA REQUIRING PROLONGED CRITICAL CARE. Int J Dev Neurosci Off J Int Soc Dev Neurosci. 2019 Dec;79:11–20.

201. Mongerson CRL, Jaimes C, Zurakowski D, Jennings RW, Bajic D. Infant Corpus Callosum Size After Surgery and Critical Care for Long-Gap Esophageal Atresia: Qualitative and Quantitative MRI. Sci Rep. 2020 Apr 14;10(1):6408.

202. Harmsen WJ, Aarsen FJ, Zijp MHM van der C, Rosmalen JM van, Wijnen RMH, Tibboel D, et al. Developmental problems in patients with oesophageal atresia: a longitudinal follow-up study. Arch Dis Child – Fetal Neonatal Ed. 2017 May 1;102(3):F214–9.

203. Møinichen UI, Mikkelsen A, Faugli A, Mørkrid L, IJsselstijn H, Emblem R. Impaired motor performance in adolescents with esophageal atresia. J Pediatr Surg [Internet]. 2020 Nov 27 [cited 2021 Aug 2]; Available from: https://www.sciencedirect.com/science/article/pii/S0022346820308587

204. Enteral access in adults – ClinicalKey [Internet]. [cited 2021 Nov 24]. Available from: https://www-clinicalkey-com.authproxy.bma.org.uk/#!/content/journal/1-s2.0-S0261561414002611

205. Toussaint E, Van Gossum A, Ballarin A, Arvanitakis M. Enteral access in adults. Clin Nutr. 2015 Jun;34(3):350-8.

206. Stoma skin problems | DermNet NZ [Internet]. [cited 2021 Nov 27]. Available from: https://dermnetnz.org/topics/skin-problems-from-stomas

207. Complication Management [Internet]. [cited 2021 Nov 27]. Available from: https://www.bapen.org.uk/nutrition-support/enteral-nutrition/complication-management

208. Medications [Internet]. [cited 2021 Nov 28]. Available from: https://www.bapen.org.uk/nutrition-support/enteral-nutrition/medications

209. Thomas A, Sowerbutts AM, Burden ST. The impact of home enteral feeding on the daily lives of people with head and neck cancer: a metasynthesis of qualitative studies. J Hum Nutr Diet Off J Br Diet Assoc. 2020 Aug;33(4):538–49.

210. Birk M, Bauerfeind P, Deprez PH, Häfner M, Hartmann D, Hassan C, Hucl T, Lesur G, Aabakken L, Meining A. Removal of foreign bodies in the upper gastrointestinal tract in adults: European Society of Gastrointestinal Endoscopy (ESGE) Clinical Guideline. Endoscopy. 2016 May;48(5):489–96. doi: 10.1055/s-0042-100456. Epub 2016 Feb 10. PMID: 26862844.

211. Becq A, Camus M, Dray X. Foreign body ingestion: dos and don'ts. Frontline Gastroenterology Published online First: 06 October 2020. Doi:10.1136/flgastro-2020-101450

212. Krishnan, U. Eosinophilic Esophagitis in Esophageal Atresia, https://www.frontiersin.org/articles/10.3389/fped.2019.00497/full

213. Hall, MF, Hall, SE (2017). *Managing the psychological impact of medical trauma: A guide for mental health and healthcare professionals.*Springer Publishing Co.

214. Gottrand, Frédéric; Avni, Freddy Can Patients With Neonatal Digestive Diseases Be Protected From Unnecessary Radiation?, Journal of Pediatric Gastroenterology and Nutrition: February 2018 - Volume 66 - Issue 2 - p 187