

# Predictors of poor outcomes in children with tracheoesophageal fistula/oesophageal atresia: an Australian experience

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## ABSTRACT

**Objective** The aim of this study is to characterize long-term morbidities of oesophageal atresia (OA) with or without tracheoesophageal fistula (TOF).

**Methods** Infants born with OA/TOF from 2000 to 2016 in Western Australia were included for analysis. Infants were categorized into high-risk and low-risk groups based on the presence of one or more perioperative risk factors [low birth weight, vertebral defects, anal atresia, cardiac defects, TOF, renal anomalies, limb abnormalities (VACTERL), anastomotic leak, long gap OA, and failure to establish oral feeds within the first month] identified by a previous Canadian study. Frequency of morbidities in infants with perioperative risk factors was compared.

**Results** Of 102 patients, 88 (86%) had OA with distal TOF (type C). The most common morbidities in our cohort were anastomotic oesophageal strictures (AS) (n=53, 52%), tracheomalacia (n=48, 47%), gastroesophageal reflux disease (GORD) (n=42, 41%) and recurrent respiratory tract infections (n=40, 39%). Presence of GORD (30/59 vs 12/43, p=0.04) and median frequency of AS dilatations (8 vs 3, n=59, p=0.03) were greater in the high-risk group. This study further confirmed that inability to be fed orally within the first month was associated with high morbidities.

**Conclusions** Gastrointestinal and respiratory morbidities remain high in OA/TOF regardless of perioperative risk factors. Inability to be fed orally within the first month is a predictor of poor outcomes with high frequency of gastrointestinal and respiratory comorbidities.

## INTRODUCTION

Oesophageal atresia (OA) and/or tracheoesophageal fistula (TOF) have a worldwide estimated prevalence of 2.44 per 10 000 births<sup>1 2</sup> worldwide and an estimated prevalence of 2.63/10 000 birth in Western Australia (WA).<sup>3</sup> Advances in surgical technique and perioperative care have made a significant improvement in survival, now approaching nearly 100%.<sup>4 5</sup> However, high morbidity remains a challenge.<sup>6 7</sup>

Previous data suggest that low birth weight <2500 g, vertebral defects, anal atresia, cardiac

## Key messages

### What is already known on this topic?

- ▶ Long-term gastrointestinal and respiratory morbidities remain high in children with oesophageal atresia/tracheoesophageal fistula.
- ▶ Children with high-risk perioperative factors have greater incidence of long-term morbidities.

### What this study adds?

- ▶ Inability to be fed orally within the first month is a predictor of poor outcome.
- ▶ Gastroesophageal reflux disease is significantly associated with anastomotic oesophageal strictures and recurrent respiratory tract infections.
- ▶ Eosinophilic oesophagitis may be poorly recognised and sub optimally treated with second line medical therapies.

defects, TOF, renal anomalies, limb abnormalities (VACTERL), anastomotic leak, long gap OA and failure to establish oral feeds during the first month are predictors of poor outcomes.<sup>8 9</sup> This study aims to examine the impact of previously reported perioperative risk factors on outcomes of OA/TOF and on frequency of gastrointestinal (GI) and respiratory comorbidities in our population-based cohort.

## METHODS

### Patients

All infants with live births undergoing surgical repair of OA/TOF at Princess Margaret Hospital for Children (PMH) from 2000 to 2016 were included. Death in the first month of life due to event unrelated to TOF was excluded. Patients were identified using an electronic operation theater database. The following information was collected: demographics (gestational age, sex, birth weight), type of OA/TOF, long gap, anastomotic leak, days to

**Table 1** Patient demographic (n=102)

Variables	Value
Female:male (n)	35:67
Birth weight (g), mean (range)	2740 (825–4044)
Low birth weight (<2500 g), n (%)	38 (37)
Gestational age (wk), mean (range)	37 (26–41)
Prematurity (<37 wk), n (%)	35 (34)
VACTERL, n (%)	14 (14)
Type of TOF/OA, n (%)	
Type A	0
Type B	7 (7)
Type C	88 (86)
Type H	4 (4)
Type D	3 (3)

TOF/OA, tracheoesophageal fistula/oesophageal atresia; VACTERL, vertebral defects, anal atresia, cardiac defects, tracheoesophageal fistula, renal anomalies, limb abnormalities.

oral feeds, GI complications [gastroesophageal reflux disease (GORD), dysmotility, oesophageal strictures, frequency of balloon dilatations, TOF recurrence] and respiratory complications [tracheomalacia, aortopexy, tracheostomy, recurrent respiratory tract infections (RRTIs), structural airway abnormalities]. Infants were categorized into high-risk or low-risk groups based on the presence of perioperative risk factors identified by a Canadian observational study and morbidity outcomes were compared.<sup>8</sup>

### Definition of variables

#### *Gastroesophageal reflux disease*

Presence of irritability, poor weight gain and/or hematemesis with or without documented oesophagitis on endoscopy or biopsy was defined as GORD.<sup>6,8</sup>

#### *Non-eosinophilic, eosinophilic-dominant oesophagitis and proton pump inhibitor (PPI) response*

We characterized oesophagitis as non-eosinophilic-dominant (if the total eosinophils counts were <15/hpf) and eosinophilic-dominant oesophagitis. Eosinophilic oesophagitis (EoE) was defined as symptoms of oesophageal dysfunction with a biopsy demonstrating >15 eosinophils per high-powered field. This was further subclassified as responsive or non-responsive to PPI despite adequately dosed treatment with PPI.<sup>10,11</sup> Response to PPI was defined by histological remission with reduction in eosinophils count <15/hpf associated with clinical improvement.

#### *Long gap OA*

“Long gap OA” was defined as a gap longer than 3 cm, approximately greater than the height of two

vertebral bodies or described as “moderate-high” or “excessive” tension by surgeons.<sup>6,8,12</sup>

#### *Anastomotic oesophageal stricture*

Anastomotic oesophageal stricture (AS) was defined as an intrinsic luminal narrowing associated with presence of clinical symptoms (dysphagia, feeding difficulties, regurgitation, foreign body obstruction, heartburn and poor weight gain) detected by barium contrast study and/or endoscopy.<sup>6,13,14</sup>

#### *Refractory oesophageal stricture*

Refractory oesophageal stricture (ROS) was defined according to the ESPGHAN-ESGE Guidelines as “the inability to successfully remediate the anatomic problem to obtain age-appropriate feeding possibilities after a maximum of 5 dilatations with maximal 4 week intervals”.<sup>6,15</sup>

**Table 2** TOF/OA complication profile of infants in WA from 2000 to 2016

Complications	n (%)
<b>Gastrointestinal</b>	
AS	53 (52)
ROS	37 (36)
Acute food bolus obstruction	13 (13)
GORD	42 (41)
Normal biopsy	8 (19)
Non-EoE	18 (43)
EoE	16 (38)
PPI non-response	11 (69)
PPI response	5 (31)
<b>GORD management (n=42)</b>	
Medical therapy	36 (86)
Fundoplication	6 (14)
Dysphagia	29 (28)
Oesophageal dysmotility	31 (30)
TOF recurrence	4 (4)
<b>Respiratory</b>	
Tracheomalacia	48 (47)
Severe tracheomalacia	5 (5)
Aortopexy	1 (1)
Tracheostomy	4 (4)
Vocal cord palsy	2 (2)
RRTI	40 (39)
Ventilatory defects (TOF cough)	37 (36)
Tracheal narrowing	2 (2)

AS, anastomotic oesophageal stricture; EoE, eosinophilic oesophagitis; GORD, gastroesophageal reflux disease; OA, oesophageal atresia; PPI, proton pump inhibitor; ROS, refractory oesophageal stricture; RRTI, recurrent respiratory tract infection; TOF, tracheoesophageal fistula; WA, Western Australia.

**Table 3** Predictor variables of high-risk group (n=59) of infants with TOF/OA in WA from 2000 to 2016

Variables, n (%)	Value
Birth weight <2500g	38 (64)
VACTERL	14 (23)
Long gap	19 (32)
Anastomotic leak	7 (12)
Inability to be fed orally by end of first mon	9 (15)

OA, oesophageal atresia; TOF, tracheoesophageal fistula; VACTERL, vertebral defects, anal atresia, cardiac defects, tracheoesophageal fistula, renal anomalies, limb abnormalities; WA, Western Australia.

### Statistical analysis

Statistical analyses were performed using GraphPad Prism (GraphPad Software, San Diego, California, USA). Univariate analysis was presented as mean and median. Unpaired t-test was used to compare continuous variables and Fisher's exact test for categorical variables for those in high-risk and low-risk groups. Univariate analysis was utilized to characterize performance of established risk factors in our cohort. Multivariable logistic regression analysis was used to calculate odd ratio (OR) of individual risk factors on TOF complications. A p value of less than 0.05 was considered statistically significant.

### RESULTS

A total of 103 infants with a diagnosis of OA/TOF were identified (table 1). One patient was excluded due to death within the first month as a result of cardiac event unrelated to TOF. Of 102 patients, 38 (37%) had low birth weight (<2500 g). The most frequent OA/TOF was OA with distal fistula (type C) (86%) followed by type B with proximal fistula (7%). Long gap was noted in 19% (19/102) of infants and postoperative anastomotic leak was detected in 7% (7/102). The median time to commence oral feed was 8 days (range 2–119 days), 91% infants established oral feeds within the first month of life. Median follow-up was 5 years (range 0.08–15 years).

### Frequency of GI and respiratory morbidities

#### GI morbidities

The most frequent GI complication in our cohort was AS, present in just over half of our cohort (n=53, 52%); almost 70% of those with AS fulfilled the criteria of ROS (n=37/53, 70%) with an overall incidence of ROS in our TOF cohort as 36% (table 2).

GORD was present in 42/102 (41%) with histological evidence of oesophagitis in 34/42 (81%). Of 34 with oesophagitis, 16/34 (47%) had EoE. Of 16 with EoE, 11/16 failed to demonstrate histological response to dose-optimised PPI (1.5–2.0 mg/kg/day). Six of 42 patients required fundoplication due to refractory GORD (14%). A strong association

between GORD and AS was observed (29/42 69% vs 24/60 40%, p=0.004).

#### Respiratory morbidities

Tracheomalacia was common (48/102, 47%), and of those with tracheomalacia, 5/48 (10%) required tracheostomy (n=4) or aortopexy (n=1). Recurrent TOF was seen in 4/102 patients (4%), requiring a second surgery. RRTIs occurred in 40 patients. RRTI was significantly associated with GORD (22/40 55% vs 20/62 32%, p=0.02), but no associations were observed with tracheomalacia (p=1.00), vocal cord palsy (p=0.47) or TOF recurrence (p=1.00).

#### High-risk vs low-risk group outcomes

A total of 59 patients were categorized as high risk due to presence of at least one or more high-risk factors and 43 were categorized as low-risk based on previously published risk factors by Castilloux *et al*<sup>8</sup> (table 3). In the high-risk group, higher rates of GORD (30 vs 12, p=0.041) and frequency of AS dilatations (8 vs 3, p=0.039) were recorded (table 4). However, median time to the first dilatation, overall frequency of ROS and RRTI were similar in both groups.

#### Morbidities in those with perioperative high-risk factors

Multivariable regression analysis of the effect of individual risk factor on TOF complications showed that inability to be fed orally within the first month was associated with higher rates of RRTI [OR=6.32, 95% confidence interval (CI) 1.23 to 32.32; p=0.02] (table 5). The mean frequency of anastomotic dilatation was greater in those with long gap OA. However, there was no significant association between ROS and

**Table 4** Comparison of outcomes between high-risk (n=59) and low-risk (n=43) group of infants with TOF/OA in WA from 2000 to 2016

Characteristics	High risk	Low risk	P value
AS	35 (59)	18 (42)	0.16
Frequency of AS dilatations*	8	3	0.0392
ROS	26 (44)	11 (28)	0.24
First dilatation (wk)*	9	9.5	0.40
RRTI	25 (42)	15 (35)	0.68
GORD	30 (51)	12 (28)	0.0410
Oesophagitis	26 (44)	12 (28)	0.20
Non-EoE	11 (19)	7 (16)	0.48

P<0.05 is statistically significant.

Data were shown as n (%).

\*Data were presented as median.

AS, anastomotic oesophageal stricture; EoE, eosinophilic oesophagitis; GORD, gastroesophageal reflux disease; IQR, interquartile range; OA, oesophageal atresia; ROS, refractory oesophageal stricture; RRTI, recurrent respiratory tract infection; TOF, tracheoesophageal fistula; WA, Western Australia.

**Table 5** Effect of individual risk factor on TOF complications of infants with TOF/OA in WA from 2000 to 2016

Risk factor	AS			ROS			GORD			RRTI		
	n (%)	OR (95% CI)	P value	n (%)	OR (95% CI)	P value	n (%)	OR (95% CI)	P value	n (%)	OR (95% CI)	P value
Low birth weight (n=38)	23 (61)	1.74 (0.77 to 3.92)	0.32	2 (5)	1.49 (0.65 to 3.41)	0.16	19 (50)	1.67 (0.74 to 3.75)	0.24	16 (42)	1.21 (0.53 to 2.75)	0.56
VACTERL (n=14)	6 (43)	0.65 (0.21 to 2.04)	0.50	3 (21)	0.43 (0.11 to 1.66)	0.70	5 (36)	0.73 (0.22 to 2.36)	0.70	6 (43)	1.19 (0.38 to 3.73)	0.70
Long gap (n=19)	12 (63)	1.75 (0.63 to 4.90)	0.31	10 (53)	1.07 (0.37 to 3.05)	0.30	10 (53)	1.68 (0.62 to 4.58)	0.31	9 (47)	1.51 (0.55 to 4.12)	0.44
Anastomotic leak (n=7)	5 (71)	2.44 (0.45 to 13.24)	0.42	3 (43)	0.68 (0.12 to 3.72)	0.68	5 (71)	3.75 (0.69 to 20.33)	0.14	3 (43)	1.17 (0.25 to 5.55)	1.00
Inability to be fed orally within the first mon (n=9)	7 (77)	3.12 (0.61 to 15.87)	0.29	3 (33)	0.78 (0.18 to 3.33)	0.14	5 (55)	1.77 (0.44 to 7.05)	0.50	7 (77)	6.32 (1.23 to 32.32)	0.02

AS, anastomotic oesophageal stricture; CI, confidence interval; GORD, gastroesophageal reflux disease; OA, oesophageal atresia; OR, odd ratio; ROS, refractory oesophageal stricture; RRTI, recurrent respiratory tract infection; TOF, tracheoesophageal fistula; VACTERL, vertebral defects, anal atresia, cardiac defects, tracheoesophageal fistula, renal anomalies, limb abnormalities; WA, Western Australia.

GORD, presence of long gap and/or anastomotic leak ( $p>0.05$ ).

## DISCUSSION

To our knowledge, recent reviews of GI, respiratory outcomes and predictive factors in patients with OA/TOF have been few in the Australian setting. Chetcuti and Phelan<sup>16</sup> reported one of the largest series of long-term outcomes across childhood to adulthood in Melbourne. More recent cohort-based Australian studies were mainly centered on growth and neurodevelopmental outcomes.<sup>17 18</sup> We report GI and respiratory morbidity outcomes in our population-based cohort focusing on identification of perioperative risk factors associated with poor disease outcomes.

The frequency of AS (52%) in our TOF cohort is similar to results previously documented in the literature.<sup>1 4 5 7 13 19–23</sup> Overall frequency of ROS (38/102, 36%) was also consistent with previous reports.<sup>5 6</sup> We hypothesized that time to first dilatation might reduce future ROS but no significant difference in the outcomes was noted in the study. This concurs with current literature, that there is no difference in long-term outcomes between selective dilatations (performed in presence of symptoms) or routine scheduled dilatations.<sup>24 25</sup>

The prevalence of GORD (41%) in our cohort was similar to that in other studies (27%–63%).<sup>1 13 22 26–29</sup> Our study reaffirms that GORD is frequently associated with AS (29/42, 69%,  $p=0.004$ ) and is prevalent in patients with perioperative risk factors (51% vs 28%,  $p=0.041$ ). We also confirmed that frequency of repeated dilatations was greater in the high-risk group ( $p=0.039$ ).

As evident from recent studies, there are no endoscopic or histological differentiation between GORD and EoE. Among those with oesophagitis 34/42 (81%), nearly half 16/34 (47%) were EoE with majority of cohort (11/16) failed to demonstrate histological response to dose-optimized PPI (1.5–2.0 mg/kg/day). Although overall frequency of EoE (16%) is consistent with some recent reports,<sup>30</sup> however, only 1/11 patient with EoE (6%) was treated with topical steroids in our cohort. Therefore, it is important to consider EoE as a potential diagnosis and a trial of topical steroids and elimination diet should be commenced. We noted that frequency of EoE was greater in patients with ROS (12/59, 20% vs 4/43 9%) but this was non-significant. Only 14% of patients underwent fundoplication, which was lower compared with other studies (median 46%, range 13%–70%).<sup>1 25 31–34</sup>

The incidence of RRTI in our cohort (39%) was lower than that of other studies (range 46%–70%, mean 54%).<sup>1 4 35–37</sup> In the large Melbourne series by Chetcuti and Phelan<sup>38</sup> involving 334 patients, over half the patients over 15 years had persisting but

minor respiratory symptoms likely attributed to family history of atopy and early childhood respiratory illness, but there was a lack of relationship between GORD and respiratory symptoms. Our study demonstrated significantly higher rates of RRTI observed in patients with GORD (22/42, 52%,  $p=0.02$ ). Previous studies have also observed this association, but no direct analysis was done to determine its significance.<sup>34-36</sup> It remains unclear if this risk is contributed by GORD-related microaspirations or possibly related to chronic PPI use contributing to increased infections.

The main strength of our study is that all neonates in WA are exclusively managed in a single tertiary center. Hence, this is a complete representation of the general population in WA. On the contrary, lack of nutritional and neurodevelopmental outcomes are also a shortfall of our study, particularly comparing outcomes of premature infants, low-birth-weight babies and those with VACTERL. TOF/OA is a rare birth defect and hence authors suggest multicenter network studies to generate data of greater statistical significance.

In conclusion, we further established that inability to feed orally within the first month is associated with high comorbidities making long gap OA, low birth weight, VACTERL and anastomotic leak less significant risk factors for GI and respiratory comorbidities, thus warranting close monitoring in these patients. However, long gap OA, low birth weight, VACTERL anomalies and prematurity may be relevant for long-term growth and neurodevelopmental outcomes, which were not analyzed in our study. This study demonstrated that ROS remains problematic in infants with high perioperative risk factors, morbidity remains high even in those with no perioperative high risk factors, and GORD is common in patients with ROS and is significantly associated with RRTI.

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