# Outcomes of the international database on SARS-CoV-2 infections in children with Esophageal Atresia/Tracheoesophageal Fistula

Jonathan O'Donnell E M[1], Usha Krishnan[1], and Christophe Faure[2]

[1]Sydney Children's Hospital
[2]Sainte- Justine Hospital

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**Abstract**

**Background and Aim** To assess the outcomes of children born with esophageal atresia/tracheoesophageal fistula (EA-TEF) with concomitant SARS-CoV-2 infection. **Methods** An international survey was circulated to the International Network of Esophageal Atresia **(**INoEA) members from April 2020 to May 2022. Information on demography, type of EA-TEF, comorbidities, complications, hospitalization, and therapies administered for SARS-CoV-2 infection was collected for all patients. **Results** Forty-two patients from April 2020-May 2022, with a mean age of 6.8 years were reported from Argentina, Switzerland, Netherlands, Canada, France, Italy, Australia and Turkey. 34 patients (81%) had a type C, EA-TEF. 30 had respiratory comorbidities, 14 had associated cardiac malformations and 14 had a history of recurrent anastomotic stricture. Reported medications included proton-pump inhibitors (n=14), inhaled bronchodilators (n=3) and inhaled corticosteroids (n=4). Six patients (14%) were hospitalised. Three required respiratory support and one required extra-corporal membranous oxygenation. There were no deaths. Respiratory, cardiac and gastrointestinal comorbidities were not associated with increased risk of hospitalization. Concomitant medication at time of infection was associated with increased risk for hospitalization with SARS-CoV-2 infection (p=0.0035), however PPI alone was not significantly associated with increased risk for hospitalization (p=0.16). **Conclusion** Rates of hospitalization with SARS-CoV-2 are higher for patients with EA-TEF than the general pediatric population, with increased risk in those on medication in patients. 67% of those admitted required respiratory support. Infection likely does not represent a risk for severe respiratory complications or severe outcome.

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[1] [2] Jonathan E M **O'Donnell BMed** , [1] [2] Usha **Krishnan MBBS** , [3] [4] Christophe **Faure MD**

1. Department of Pediatric Gastroenterology, Sydney Children's Hospital

2. Discipline of Paediatrics, School of Women's and Children's Health, University of New South Wales, Sydney, Australia

3. Division of Pediatric Gastroenterology, Sainte- Justine Hospital

4. Department of Pediatrics, Université de Montréal, Montreal, Canada

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Correspondence to:

Dr Jonathan O'Donnell, Sydney Children's Hospital, High Street, Randwick 2031, Australia. Phone number: +612 9382 1752, Fax: +612 9382 1787. jonathan.odonnell@health.nsw.gov.au

Leading research institute: Division of Pediatric Gastroenterology, Sainte- Justine Hospital

C.F. is the senior author

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Jonathan E M O'Donnell – analysis and interpretation of data for the work, drafting of the first draft, revisions based on feedback from other authors, final approval of version to be published, agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Usha Krishnan - contributed to the conception and design of the work, drafting the work, revising it critically for important intellectual content and final approval, agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Christophe Faure – contributed to the acquisition of data, contributed to the conception and design of the work, revising it critically for important intellectual content, final approval, agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

**Abstract**

**Background and Aim**

To assess the outcomes of children born with esophageal atresia/tracheoesophageal fistula (EA-TEF) with concomitant SARS-CoV-2 infection.

**Methods**

An international survey was circulated to the International Network of Esophageal Atresia **(** INoEA) members from April 2020 to May 2022.

Information on demography, type of EA-TEF, co-morbidities, complications, hospitalization, and therapies administered for SARS-CoV-2 infection was collected for all patients.

**Results**

Forty-two patients from April 2020-May 2022, with a mean age of 6.8 years were reported from Argentina, Switzerland, Netherlands, Canada, France, Italy, Australia and Turkey. 34 patients (81%) had a type C, EA-TEF. 30 had respiratory comorbidities, 14 had associated cardiac malformations and 14 had a history of recurrent anastomotic stricture. Reported medications included proton-pump inhibitors (n=14), inhaled bronchodilators (n=3) and inhaled corticosteroids (n=4).

Six patients (14%) were hospitalised. Three required respiratory support and one required extra-corporal membranous oxygenation. There were no deaths.

Respiratory, cardiac and gastrointestinal comorbidities were not associated with increased risk of hospitalization. Concomitant medication at time of infection was associated with increased risk for hospitalization with SARS-CoV-2 infection (p=0.0035), however PPI alone was not significantly associated with increased risk for hospitalization (p=0.16).

**Conclusion**

Rates of hospitalization with SARS-CoV-2 are higher for patients with EA-TEF than the general pediatric population, with increased risk in those on medication in patients. 67% of those admitted required respiratory support. Infection likely does not represent a risk for severe respiratory complications or severe outcome.

Word count: 234

**What is known**

Children with EA-TEF are at increased risk of respiratory infections due to airway abnormalities

Rates of hospitalization with SARS-CoV-2 infection are low in the pediatric population

**What is new**

- This is the first study to describe outcomes of the international database on SARS-CoV-2 infections in children with Esophageal Atresia/Tracheoesophageal Fistula (EA-TEF)
- Overall, this study showed that children with EA-TEF had increased rates of hospitalization with SARS-CoV-2 infection
- The majority of those admitted required respiratory support, with no severe outcomes recorded.

**Introduction:**

The coronavirus-19 (COVID-19) pandemic to date has accounted for over 6.9 million deaths and 530 million cases[1]. Most children have asymptomatic or mild symptoms of SARS-CoV-2 infection comparative to adults, with lower rates of hospitalization[2-4]. Hospitalization rates have been quoted between 0.04-1.26%[4-6]

Approximately 4-6% of children admitted to hospital develop severe disease[4, 6] with risk factors for severe disease being any pre-existing medical conditions[2, 6] (particularly chronic lung disease, cardiovascular disease, airway abnormality[6, 7]) male sex[2, 6], age less than 1 month[2], viral coinfection[2] and obesity[7]. Increased incidence of severe disease has been noted in adults on immunosuppressive medications, proton pump inhibitors[8]and famotidine[8], however these relationships are less clear in children[9, 10]

Knowledge of patients at risk for increased mortality and morbidity is essential to inform public health measures, clinical decision making and recommendations for vaccination.

Esophageal atresia-Tracheoesophageal fistula (EA-TEF) is one of the most common congenital malformations of the aerodigestive tract affecting 1 in 2500 to 1 in 4500 live births[11, 12]. Improved operative and perioperative care has resulted in survival rates between 90-100%[13], with management of EA-TEF patients now focused on improving management of associated symptoms and complications. Children with EA-TEF are at increased risk of respiratory infections due to airway abnormalities (tracheomalacia, impaired airway clearance and aspiration from impaired swallow and gastro-esophageal reflux)[14], with recurrent respiratory tract infections increase the risk of chronic lung disease. Half of EA-TEF patients have an underlying syndrome, such as VACTERL, CHARGE syndrome and chromosomal abnormalities and there is an frequency of congenital cardiovascular disease[14]. Finally, EA-TEF patients are often on acid suppressing medications. These comorbidities and treatments may potentially increase these patient's risk of severe SARS-CoV-2 infection and epidemiological data is required to inform medical care.

**Materials and Methods**

To capture epidemiological data on children with EA-TEF with concurrent SARS-CoV-2 infection, a 24-question survey was created by the International Network of Esophageal Atresia (INoEA). Links to this survey were published on the Esophageal Atresia Global Support Groups, European Reference Networks for Rare and Inherited and congenital anomalies (ERNICA). In addition, members of INoEA were emailed survey links. Membership of these groups consist of clinicians involved in the care of EA-TEF patients, including gastroenterologists, surgeons and pulmonologists and otolaryngologists.

This survey was authorised by the Ethics Committee of the CHU Sainte-Justine, Université de Montréal, Canada (#2020-2877), with waiver of consent approved.

Clinicians were asked to report baseline data regarding patient age, gender, type of EA-TEF as well as known associated cardiac malformations, respiratory comorbidities and gastrointestinal comorbidities and medication the patient was taking at baseline at time of SARS-CoV-2 infection. Outcomes post infection

were then recorded, including whether the patient required hospitalization, intensive care admission, disease complications or other treatments administered acutely during infection

Fischer Exact Test was used to determine variables that were significantly associated with hospitalization for SARS-CoV-2.

The survey ran from April 2020 and data was collected until April 2022.

**Results**

Data was captured from eleven countries, with 37 cases of SARS-CoV-2 submitted. The highest number of cases was submitted from Europe (19), followed by Asia (8), Oceania (5), South America (3) and North America (2).

Figure 1 – Cases by location

The average age of patients was 7 years with the majority of children having Type C, EA- TEF (81%). Respiratory comorbidities such as tracheomalacia, asthma, recurrent pulmonary infections were present in 71% of patients, cardiac comorbidities in 32% of patients and gastrointestinal comorbidities such as strictures, gastro-oesophageal reflux disease, eosinophilic oesophagitis present in 57% of patients. Only 4 patients did not have any reported comorbidities.

Table 1 – Baseline characteristics

Six patients were admitted to hospital (16%), with four patients (67%) requiring respiratory support, including one patient admitted to Intensive Care requiring extra-corporal membrane oxygenation, on a background of previous cytomegalovirus pneumonia and esophageal replacement with cologastric anastomosis for long gap esophageal atresia.

The majority of patients hospitalised (66%) were admitted during the first 12 months of the database. Rates of hospitalization in the first 12 months were 18%, compared to a rate of 10% in the second 12 months of the database.

Medication use alone was associated with increased risk of hospitalization. Subgroup analysis demonstrated that proton pump inhibitors, bronchodilators and inhaled steroids were not associated with an increased risk of hospitalization. Cardiac comorbidities and gastrointestinal comorbidities also did not increase the risk of hospitalization. Overall, having a respiratory comorbidity also did not increase the risk of hospitalization – and on subgroup analysis, there was no association between tracheomalacia, asthma or recurrent chest infections on risk of hospitalization.

Table 2 – Factors associated with hospitalization

Figure 2 - Timeline of cases.

**Discussion**

This is the first international database to examine complications of SARS-CoV-2 infection in children with EA-TEF. Our dataset was representative of a normal EA-TEF cohort with 81% of patients having Type C, EA-TEF, comparative to 78-90% rates in the literature[11, 15, 16], cardiovascular anomalies in 33% , comparative to 29% reported in the literature[17].

19% of our cohort were on inhaled bronchodilators, inhaled corticosteroids or montelukast, consistent with reported rates of asthma of 10-30%[18, 19] and 25% of our cohort had tracheomalacia, comparative to rates of 17%-78%[20].

Recurrent strictures were noted in 33% of our cohort and third of patients were on proton pump inhibitor (PPI), again, comparative to rates of 18-50%[21] and gastroesophageal reflux disease (GERD) rates of 15-66%[22-24] respectively.

Our population had a high rate of admission to hospital comparative to a pediatric population, where rates of hospitalization have been documented at 1.2-2.9%[25]. This high rate is likely reflective of the fact that patients with EA-TEF are more susceptible to respiratory deterioration given high rates of comorbidities such as chronic lung disease (a known risk factor for severe SARS-CoV-2 infection[26]) secondary to airway anomalies, reactive airway disease or chronic aspiration; and be reflective of decreased respiratory reserve.

It is paramount for the clinician and carers to be mindful of this increased acute morbidity with respiratory tract infections in those with EA-TEF, and longer-term morbidity with recurrent lower respiratory tract infections leading to bronchiectasis, poor lung function and lower quality of life in adulthood[14]. Concomitant infections may also impact on oral intake and nutrition. For these reasons, it is important that EA-TEF patients continue to receive multidisciplinary care, for early detection and management of risk factors for chronic lung disease as well as advocacy for access to primary prevention mechanisms, such as vaccination.

It is interesting to note that medication use for any reason was associated with an increased risk of hospitalization, however that individual medication use was not. This may be due to that fact that those on medications are likely to have more severe comorbidities and therefore risk factors for chronic lung disease than those not on medications.

We did not see an association with PPI use and hospitalization. PPI use has been postulated to be associated with more severe infection[8, 27], possibly secondary to increased virus survival in those with higher gastric pH, although this has not been demonstrated in children.

Our study had several limitations. As EA-TEF is a rare disease, only 42 patients were able to be included in this cohort. There is the possibility that patients may have under-reported infections if asymptomatic or well, thereby skewing this dataset towards patients with more severe SARS-CoV-2. Demographic data such as birthweight, gestational age at birth – traditionally associated with more severe morbidity were not included to focus on other modifiable risk factors. Finally, there was an increased rate of hospitalization in the first 12 months of the database, which may represent worse outcomes before widespread pediatric vaccination or increased caution early in the pandemic from clinicians.

Future avenues for research include long term pulmonary and extra-pulmonary outcomes for those infected with SARS-CoV-2 as well as risk factors for 'long covid' or PIMS-TS in the EA/TEF population.

## Conclusion

In patients with EA-TEF, the SARS-CoV-2 infection results in higher rates of hospitalization are higher than the general pediatric population, with increased risk in those on concomitant medication. Infection likely does not represent a risk for acute severe respiratory complications or severe outcomes.

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