Exploring the Relationship between Gestational Age and Gastrointestinal-Pulmonary Complications in Esophageal Atresia Patients

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TABLE OF CONTENTS:

ABSTRACT

Background. Esophageal atresia (EA) is a rare congenital anomaly frequently accompanied by additional birth defects, posing significant challenges to patient outcomes. Despite notable progress in treatment, EA patients without comorbidities still encounter significantly elevated mortality rates and endure long-term complications that severely impact their quality of life. This study aimed to investigate the impact of gestational age on post-repair gastroesophageal and respiratory complications in EA patients.

Aim. To investigate the impact of gestational age on the incidence of gastrointestinal and respiratory complications during the first 5 years after esophageal atresia repair.

Methods. A retrospective chart review was conducted, involving 137 patients who underwent primary EA repair at McGill University Health Centre between 2005 and 2023. Data was reviewed independently by research team members and entered into an electronic REDCap database. Descriptive and analytical statistics were compared and discussed in light of pre-existing literature, and the estimated impact of gestational age on gastrointestinal and respiratory outcomes during the first 5 years after surgical repair was explored.

Results. Demographic correlation was found between our study population and international reported outcomes. We found no association between gestational age and the incidence of respiratory complications within the first 5 years after primary surgical repair. An increased incidence in the reported use of anti-H2 blocker therapy was reported for the full-term study population (p=0.001; OR 15.75 [2.65;93.46]) while the incidence of need for force feeding (p=0.019; OR 0.15 [0.03;0.75] and stenosis (p=0.046; OR [0.05, 1.03]) was significantly higher in the premature population.

Conclusion. No impact of gestational age on respiratory complications was found during the first 5 years of life. In addition, the majority of gastrointestinal complications during the first 5 years of life were equally not impacted by gestational age. Due to the limited availability of substantial scientific data, actionable conclusions based on these results should be cautiously interpreted. This study emphasizes the need for broad international scientific collaborations with predefined variables and objectives. Further studies are needed to establish a comprehensive understanding of the impact of gestational age on respiratory and gastrointestinal complications.

RESUME

Contexte. L'atrésie de l'œsophage (AO) est une anomalie congénitale rare souvent accompagnée de malformations congénitales supplémentaires, ce qui pose d'importants défis pour les résultats des patients. Malgré des progrès notables dans le traitement, les patients atteints d'AO sans comorbidités présentent encore des taux de mortalité significativement élevés et souffrent de complications à long terme qui affectent considérablement leur qualité de vie. Cette étude visait à étudier l'impact de l'âge gestationnel sur les complications gastro-œsophagiennes et respiratoires après réparation de l'AO. Objectif Étudier l'impact de l'âge gestationnel sur l'incidence des complications gastro-intestinales et respiratoires au cours des 5 premières années après la réparation de l'atrésie de l'œsophage.

Méthodes. Une étude exhaustive de dossiers rétrospectifs a été réalisée, impliquant 137 patients ayant subi une réparation primaire de l'AO au Centre universitaire de santé McGill entre 2005 et 2023. Les données ont été examinées indépendamment par les membres de l'équipe de recherche et saisies dans une base de données électronique REDCap. Des statistiques descriptives et analytiques ont été comparées et discutées à la lumière de la littérature préexistante, et l'impact estimé de l'âge gestationnel sur les résultats gastro-intestinaux et respiratoires au cours des 5 premières années après la réparation chirurgicale a été exploré.

Résultats. Une corrélation démographique a été trouvée entre notre population d'étude et les résultats internationaux rapportés. Nous n'avons trouvé aucune association entre l'âge gestationnel et l'incidence des complications respiratoires au cours des 5 premières années après la réparation chirurgicale primaire. Une incidence accrue de l'utilisation rapportée d'un traitement par les anti-H2 a été observée pour la population à terme ($p = 0,001$; OR 15,75 [2,65 ; 93,46]), tandis que

l'incidence du besoin de nourriture forcée (p = 0,019 ; OR 0,15 [0,03 ; 0,75]) et de sténose (p = 0,046 ; OR [0,05, 1,03]) était significativement plus élevée dans la population prématurée.

Conclusion. Aucun impact de l'âge gestationnel sur les complications respiratoires n'a été observé au cours des 5 premières années de vie. De plus, la majorité des complications gastro-intestinales au cours des 5 premières années de vie n'ont pas été influencées de manière significative par l'âge gestationnel. En raison de la disponibilité limitée de données scientifiques substantielles, les conclusions pratiques basées sur ces résultats doivent être interprétées avec prudence. Cette étude souligne la nécessité de collaborations scientifiques internationales étendues avec des variables et des objectifs prédéfinis. Des études supplémentaires sont nécessaires pour établir une compréhension globale de l'impact de l'âge gestationnel sur les complications respiratoires et gastro-intestinales.

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CONTRIBUTION OF AUTHORS

Each author has made significant contributions to the manuscript. The contributions of the authors are as follows:

The primary author, Dr. Mathias Johansen, was responsible for the conception and design of the study, data collection, analysis, and interpretation. The primary author was also responsible for writing the manuscript.

Dr. Dan Poenaru supervised and provided methodological guidance throughout all phases of the entire project.

Dr. Sam Daniel, Dr. Pablo Ingelmo and Dr. Thomas Engelhardt provided academic support and funding

Sam Wasserman, research assistant from the Department of Pediatric Anesthesia, assisted in data collection and statistical analysis.

ABBREVIATIONS

EA	Esophageal atresia
CHARGE	Coloboma of the eye, Heart defects, Atresia of the nasal choanae, Retardation of growth and/or development, Genital and/or urinary abnormalities, and Ear abnormalities and deafness.
GA	Gestational age
MCH	Montreal Children's Hospital
MUHC	McGill University Health Centre
TEF	Tracheo-esophageal fistula
LGEA	Long-gap esophageal atresia
VACTERL	Vertebrae Anus Cardiac Trachea Esophagus Renal Limb

CHAPTER 1 - INTRODUCTION

1.1 Background

Anatomy. The anatomy of the esophagus begins at the level of the cricoid cartilage in the neck and extends downward through the mediastinum, passing through the diaphragm, and terminating at the gastroesophageal junction in the abdomen. It is approximately 25-30 cm long in adults and has four distinct anatomical parts: cervical, thoracic, abdominal, and gastroesophageal junction. Several layers of smooth muscle fibers, which enable peristaltic contractions to propel food from the mouth to the stomach during the process of swallowing, are organized in inner circular and outer longitudinal layers. The end of the esophagus is anatomically marked by the gastroesophageal junction and gastrointestinal sphincter muscle, of which the latter plays an important role in the prevention of gastric contents propelling back into the esophagus.[1,2,3] The newborn esophagus differs physiologically and anatomically from the adult. The length is around 10-12 cm with an approximate outer diameter of one to eight millimeters. The muscle layers are underdeveloped resulting in limited coordination of peristaltic movements which compromises swallowing and digestion as well as increases the risk of reflux. A normal physiological trait in a newborn baby.[4,5,6]

Embryonic development. During the early stages of embryonic development, the primitive gut tube forms as a result of folding and fusion of the endodermal layer. Around the fourth week of gestation, the gut tube undergoes regional differentiation, leading to the establishment of the foregut, midgut, and hindgut.[6,7] In the following weeks organogenesis leads to the development of specific structures within the foregut such as the esophagus and stomach. Under normal circumstances the foregut will detach from the trachea and continuous growth, development and

differentiation of cells will lead to a normal anatomical presentation of the gastrointestinal and respiratory system.[6,7] In the case of esophageal atresia, disruptions occur during the differentiation and elongation of the esophagus. The tracheoesophageal septum which usually separates the esophagus and the respiratory tract is defective, resulting in an abnormal development, connection and/or communication between the trachea and esophagus known as a transesophageal fistula (TEF). Simultaneously, the growth of the esophagus is equally compromised resulting in an upper "pouch" and a distal segment which connects to the stomach.[8,9,10]

Diagnostics. Esophageal atresia patients are usually diagnosed prenatal by ultrasound examination. Key findings include the absence or small size of the fetal stomach bubble and the presence of polyhydramnios (excessive amniotic fluid) due to the inability of the fetus to swallow and absorb amniotic fluid properly.[11] Due to the increased risk of concomitant comorbidities such as genetic syndromes or chromosomal abnormalities the ultrasound examination is usually supplemented with genetic testing.[11] Due to an extensive prenatal screening program in most high income countries, EA is often diagnosed prior to birth. This ensures that clinicians are able to prepare for the immediate perioperative management of the newborn with EA. In particular, the coordination among the obstetric team, neonatal specialists, and pediatric surgeons, ensures a well-planned approach to the delivery and subsequent care of the affected newborn.[11] Postpartum, the immediate priority is to establish a patent airway for the newborn.[12] Depending on the specific type of EA, a tracheoesophageal fistula (TEF) may be present, leading to respiratory complications. In an attempt to mask ventilate the newborn EA patient, air will be able to pass through the TEF into the stomach. This will increase intragastric pressures making continuous ventilation difficult due to an increased trans diaphragmatic pressure affecting the lung capacity. A suction is inserted into the upper blind

pouch of the esophagus. Though closed distally, this upper pouch can equally generate secretions which will then spill over to the trachea and result in respiratory complications.

Anatomical configuration. Esophageal atresia (EA) can present in various anatomical configurations, each with its own specific characteristics. This was anatomically described in 1939 by Vogt et al. and reviewed by Gross et al. in 1953 which now remains the predominant classification used internationally.[13,14] The initial risk classification of EA patients was provided by Waterson et al. in 1962, and was based on the presence of other congenital anomalies and pneumonia.[15] The risk classification was following revised by Spitz et al. in 1994 and continues to be the most commonly utilized risk classification systems for EA demonstrating a birth weight dependent survival rate of 97% (>1500g without major cardiac anomaly), 59% (<1500 g or major cardiac anomaly) and 22% (Birth weight <1500 g and major cardiac anomaly)[16,17]:

Type A: Isolated esophageal atresia. The upper and lower segments of the esophagus do not connect, resulting in a complete interruption or atresia of the esophageal lumen. There is no associated TEF. This presentation accounts for about 8% of cases.[14]

Type B: Esophageal atresia with proximal TEF. One of the two rarest forms of EA accounting for <1% of cases. In this particular setting the upper esophageal pouch connects via a tracheoesophageal fistula to the trachea.[14]

Type C: Esophageal atresia with distal TEF. This is the most common form (86%) characterized by a proximal esophageal pouch and a distal esophageal segment, which connects to the trachea via a TEF.[14]

Type D: Esophageal atresia with double TEF: This is the second rarest form of EA, representing <1% of cases. Both the proximal and distal esophageal segment has a connection to the trachea through a TEF.[14]

Type E: H-Type fistula. This type is characterized by a small fistula or communication between the trachea and esophagus without any associated esophageal atresia. It is considered a separate entity from traditional EA but is included in the classification due to its similar clinical presentation. The H-type fistula may present with varying degrees of severity.[14]

In addition to the above mentioned categories, the long gap esophageal atresia (LGEA) represent a specific subtype of esophageal atresia where there is a significant separation between the proximal and distal ends of the esophagus, making primary anastomosis challenging or impossible.[18,19] This population of esophageal atresia patients are less likely to have a TEF, but are more likely to be related to trisomy 21. For these patients surgery will take place once the esophagus has had time to grow to an appropriate length. This can either be achieved by passively awaiting growth of the esophagus or facilitated by use of the Foker process in which case a surgical intervention places sutures in the proximal and distal end of the esophagus. These sutures are then connected to an exterior traction device to allow for stretching of the muscle and connective tissue fibers.[20]

Treatment. Final surgical correction for esophageal atresia usually takes place within the first days of life depending on the need for diagnostic evaluation and preoperative optimization. Various approaches (open surgery vs laparoscopic surgery) exist depending on the specific anatomic presentation, comorbidity and the possible presence of a TEF.[21] The essence of the surgical correction is to make an anastomosis in order to connect the proximal and distal end of the esophagus, and to close any presence of a TEF to avoid respiratory complications and allow for a

normal anatomical presentation.[22] If surgery and postoperative care is uncomplicated the patient should be able to start feeding around 1 week post surgical correction.

Complications. Despite the extensive multidisciplinary approach right after birth this is just the beginning of a long encounter for the EA patient with the health care system. From prenatal diagnostic evaluation to being born with a congenital defect, corrected surgically and discharged from hospital the majority of patients will on repeated occasions need an entire team of dedicated clinicians and healthcare professionals ready to assure a proper treatment and follow up of short- and long term complications. These include but are not limited to tracheomalacia, aspiration pneumonia, asthmatic symptoms, chronic cough, wheezing, gastroesophageal reflux, esophagitis, anti-reflux medication / surgical procedures and much more.[23,24,25]

Increased fetal, surgical and perioperative medical care has resulted in an almost 100% survival rate for full term EA patients born without comorbidity[26]. However, standardized mortality rates for all EA patients is still 12 times greater compared to the background population with a peak incidence within the first five years of life.[26,27,28] Representing a rare congenital anomaly with an incidence of approximately 1.2 to 4.5 per 10,000 births, esophageal atresia is frequently associated with other congenital anomalies such as tracheoesophageal fistula (TEF), anal atresia, vertebral defects as well as cardiac, renal and limb malformations (e.g., VACTERL sequence).[27] Depending on the number and gravity of comorbidity these patients will be severely challenged in short- and long term outcomes. In the short term, individuals with EA and associated anomalies may face challenges related to feeding difficulties, respiratory problems, surgical complications, and the need for specialized care in a neonatal intensive care unit (NICU) setting. Long-term outcomes can vary widely depending on the specific anomalies involved, and include issues related to growth and

development, gastrointestinal function, respiratory health, cardiac function, renal function, and musculoskeletal abnormalities. Comprehensive and ongoing medical care, including surgical interventions, rehabilitation, and multidisciplinary support, is crucial to optimize the quality of life for these individuals.[24,28]

Throughout an entire lifespan EA patients are submitted to multiple admissions, investigations, surgeries and long term medication therapy related to respiratory and gastrointestinal complications.[25] Initially, breathing disorders are most often caused by congenital conditions such as tracheomalacia or a tracheoesophageal fistula. Tracheomalacia is a pathological condition characterized by abnormal weakening of the tissue surrounding the trachea and the tracheal walls, resulting in compromised structural airway integrity. It represents a complex respiratory condition that necessitates a multidisciplinary approach involving specialists in pediatric pulmonology, otolaryngology, and sometimes even thoracic surgery.[29] For most EA patients tracheomalacia will ameliorate with time as they continue to grow and develop but for some patients this will remain a lifelong challenge and complication.[30,31,32] The presence of a transesophageal fistula (TEF) significantly affects respiration, ventilation and oxygenation in EA patients. Aspiration of gastric contents to the lungs causes inflammation, infection, and damage to the lungs, contributing to atelectasis, chemical induced pneumonia, respiratory distress, impaired respiratory function, desaturation and hypoxemia. In worst cases acute respiratory distress syndrome (ARDS) will develop and necessitate intubation and mechanical ventilation due to an impaired ventilation/perfusion mismatch. Later in life, despite adequate surgical correction, persisting respiratory complications are most often characterized by asthma-like symptoms (e.g. wheezing), chronic cough and chronic restrictive lung disease as a result of recurrent pulmonary infections.[33,34]

Chronic motility disorders, strictures, esophagitis, dysphagia, feeding disorders and intestinal metaplasia are some of the most common gastrointestinal complications of EA surgery, mandating multiple esophageal dilations and long term anti-reflux medication therapy. These comorbidities follow the patient long into adulthood, with gastroesophageal reflux disease reported in up to 48% of adult EA patients.[29] The extent of medical and surgical anti-reflux treatment following primary EA repair is currently not well documented. This is also the case regarding the impact of medical anti-reflux treatment on positive endoscopic findings later in life. Managing long-term gastrointestinal complications in EA patients requires a multidisciplinary approach involving gastroenterologists, nutritionists, and other healthcare professionals. Treatment strategies may include medication to control reflux and promote gastric emptying, dietary modifications, esophageal dilation, surgical interventions, and long-term monitoring to ensure adequate nutrition and optimize gastrointestinal function.[28,29,33]

With a consistent 'high' survival rate and optimized medical treatment of comorbidities, quality of life and patient reported outcomes have become an area of increased interest. Understanding the physical, psychological, and social aspects of living with EA is important to allow for a continuous understanding.[35]

1.2 Rationale. Despite the extensive literature on complications related to EA repair, several research gaps still exist. These include, amongst others, long-term follow-up to understand the late-onset complications, such as gastroesophageal reflux (GER), respiratory aggravations and delayed growth and development.[36,37] There is a need for more comprehensive studies aiming to identify and understand risk factors associated with these complications after EA repair. In particular, the impact of gestational age, associated congenital anomalies, genetic factors, prenatal

exposures and perioperative management on the occurrence of complications is of interest and considered incomplete.[38,39] Finally, quality of life outcomes in individuals who have undergone EA repair is another underreported research area of interest. Studies evaluating risk factors in addition to the physical, cognitive, and psychosocial outcomes in these individuals can provide valuable insights into the overall impact of complications related to EA repair on the quality of life.[35,40]

1.3 Research question. Is there a correlation between gestational age (GA) in children with EA/TEF and the occurrence of gastrointestinal or respiratory complications within the first five years of life?

1.4 Hypothesis. Incidence of gastrointestinal and respiratory complications within 5 years of life after primary surgical repair for esophageal atresia is greater in preterm vs full-term infants.

1.5 Objective. The main objective of this study was to investigate the impact of gestational age on the incidence of gastrointestinal and respiratory complications during the first five years after esophageal atresia (EA) repair in a select population of children surgically treated at the Montreal Children's Hospital from 2005 to 2023.

CHAPTER 2 - MANUSCRIPT BASED THESIS

2.1 Article information.

Johansen M[1], Wasserman S[2], Engelhardt T[2], Laberge JM[3], Daniel S[3], Poenaru D[1].

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2.2 Abstract

Background. Esophageal atresia (EA) is a rare congenital anomaly frequently accompanied by additional birth defects, posing significant challenges to patient outcomes. Despite notable progress in treatment, EA patients without comorbidities still encounter significantly elevated mortality rates and endure long-term complications that severely impact their quality of life. This study aimed to investigate the impact of gestational age on post-repair gastroesophageal and respiratory complications in EA patients.

Methods. A retrospective chart review was conducted on 137 patients who underwent primary EA repair at Montreal Children's Hospital between 2005 and 2023. Data was reviewed independently by research team members and entered into an electronic REDCap database. Descriptive and analytical statistics were performed to compare the study population's outcomes to the literature and

the impact of gestational age on gastrointestinal and respiratory outcomes during the first 5 years after surgical repair.

Results. Our patient population included 39.4% females with a mean GA of 37.2 +/-3.2 weeks and a mean birth weight of 2679 +/-708 grams. The anatomical variations, stratified according to the EA Gross classification, showed the following distribution: Type A=3%, Type B=1.6%, Type C=82.2%, Type D=4.8% and Type E=8%. VACTERL syndrome was observed in 17 patients (27%) and CHARGE syndrome in one patient (1.6%). The categorical breakdown of congenital anomalies showed the following distribution: vertebral (23%), anorectal malformation (9.5%), cardiac (45.2%), distal esophageal fistula (95.1%), renal (27.9%), skeletal (11.1%), respiratory (8.6%), digestive (54.7%) and other (20.7%). The most frequent gastrointestinal complication observed in preterm and full term patients were use of anti-reflux medication (90.9% and 100% respectively) followed by need for dilatation (72.7% vs 50%), while need for force feeding was observed in 54.5% of preterm and 14.8% of full term patients. Full term patients demonstrated a significant increase in the use of anti-H2 blocker therapy compared to preterm patients (p=0.001; OR 15.75 [2.65,93.46]) while the incidence of force feeding (p=0.019; OR 1.5 [0.03,0.75]) and esophageal stenosis (p=0.46; OR [0.05, 1.03]) was significantly higher in the preterm population. The incidence of respiratory complications was found to be higher in the full term patient population (respiratory aggravations: 57.7% vs 33.3%; abnormal respiratory symptoms: 84.6% vs 66.7% and abnormal auscultation: 73.1% vs 46.7%) with the only exception exertional dyspnea which was higher in the preterm population (13.3% vs 7.7%). These results were all statistically non-significant with a p value >0.05. Also, no significant association between gestational age and the incidence of respiratory complications during the first 5 years after primary surgical repair for esophageal atresia was observed.

Conclusion. Our findings indicate that the demographic composition of our study population closely aligns with the characteristics reported in literature. This comparability enhances the usefulness and generalizability of our study, as it strengthens the representativeness of our findings and allows for better extrapolation to broader populations. The use of anti-H2 blocker therapy was reported significantly higher in full term patients while the number of force feeding and stenosis was higher in the premature population. These findings suggest that a subgroup of gastrointestinal complications are related to gestational age. Further investigative studies should be conducted to explore additional factors and mechanisms underlying these complications, allowing for a more comprehensive understanding and potential interventions to mitigate the associated risks. No association between gestational age and respiratory complications during the first 5 years of life was observed. The study had several limitations including a small sample size, missing data and variability in the reporting of outcomes. Additional research studies are necessary to evaluate the impact of gestational age on postoperative complications related to the surgical treatment of esophageal atresia. These studies should aim for larger sample sizes (international collaborations), consistent outcomes and standardized definitions in order to provide more comprehensive insights.

2.3 Introduction

Esophageal atresia (EA) is a rare congenital anomaly with an incidence of 1.2 to 4.5 per 10,000 births and is often associated with severe birth defects that present challenges to patient outcomes.[26] The etiology of EA is multifactorial, involving genetic and environmental factors which further complicates clinical care, long term follow up and alignment of definitions and outcomes in clinical research.[8,9] Despite improvements in surgical care and perioperative

management, even EA patients without comorbidities experience elevated mortality rates and long-term complications impacting their health and quality of life.[10]

Prematurity, defined as birth before 37 weeks of gestation, is associated with a range of complications that contribute to increased morbidity and mortality.[41,42,43,44,45] These include amongst others apnea of prematurity, respiratory distress due to impaired lung maturity, low birthweight, necrotizing enterocolitis (NEC), sepsis and developmental delay.[41] The influence of gestational age on post-repair gastroesophageal and respiratory complications in EA patients remains unclear.[10,24,26] Exploring the impact of prematurity versus full-term birth on the prevalence of complications among patients who have undergone surgical repair for esophageal atresia holds significant importance for multiple reasons. First and foremost, comprehending the correlation between gestational age and the incidence of gastrointestinal and respiratory complications can aid clinicians in delivering optimal care to their patients. By identifying risk factors for complications, healthcare providers can tailor their treatment plans to minimize the likelihood of unfavorable outcomes and enhance long-term patient results. Secondly, this investigation can contribute to the wider domain of pediatric surgery and direct future research on the enduring consequences of congenital abnormalities.[8,19,27] Moreover, the study findings can also provide valuable insights for health policy and resource allocation determinations by highlighting the potential impact of gestational age on healthcare expenses and usage.[35,42] This study aims to investigate the impact of gestational age on respiratory and gastrointestinal complications within the first five years of life.

2.4 Methods

We conducted a retrospective chart review of a cohort of 137 patients who had undergone primary surgical repair for EA at the Montreal Children's Hospital between 2005 to 2023. Case report forms (CRFs) were completed by clinicians over a 18 year timespan. The data collected included patient

demographic characteristics (**table 1**), medical and surgical history, ongoing care and clinical outcomes (**table 2 and appendix 1**). Data was collected at birth, during primary hospital stay and through emergency and/or planned follow-up clinics. Surgical, gastro-intestinal and respiratory procedures undertaken at each follow-up were recorded. We reviewed CRF data collection forms for completeness of data registration. Available data was subsequently uploaded onto an online web-based Research Electronic Data Capture database (REDCap) created for this specific purpose. Prior to data entry in REDCap, CRFs were reviewed by two independent members of the research team for potential outliers and errors. In case of discrepancy, the principal investigator was consulted and had the final decision. In the case of blank CRF data fields, these would be registered and counted for each sub-category. Descriptive and analytical statistics of the study population were performed to estimate data integrity, obtain a better understanding of the study population, review conformity to international findings and investigate the impact of gestational age on gastrointestinal and respiratory complications as previously described (**Tables 3 and 4)**. We aimed to apply logistic regression analysis to examine the association between prematurity and full term patients on the incidence of respiratory and gastrointestinal complications while adjusting for potential confounding factors such as sex, specific lesions and/or the presence of congenital anomalies.

2.5 Statistical analysis

Descriptive analyses were performed on demographic and clinical characteristics such as sex, gestational age, birth weight, and presence of other congenital anomalies (**table 1**). Differences between preterm and full-term births were examined using independent t-tests or Mann Whitney-U test for continuous data and Chi-squared tests or Fischer exact tests for binomial data (**tables 3 and 4**). We examined the relationship between gestational age and the incidence of gastro-intestinal and respiratory complications using the chi square test and logistic regression. Clinically relevant

variables were added to the model to adjust for potential confounding. The logistic regression estimated the association between gestational age and the incidence of complications within the first five years of life. A p-value < 0.05 was considered statistically significant.

2.6 Results

From our total patient population (N=137) we found 61 patients registered with a mean GA of 37.2+/-3.2 and 63 patients with a mean birth weight of 2679 grams (SD=708). Modality of birth (vaginal vs c-section) was not a recorded outcome. The discrepancy in recorded numbers is caused by lack of data entry in CRFs throughout the recorded timeline (2005-2023). Hence, the total study population of 137 patients did not have fully recorded outcomes as demonstrated in tables (N = number of subjects with reported outcome). The anatomical variations, stratified according to the EA Gross classification, showed the following distribution (N=62): Type A=3%, Type B=1.6%, Type C=82.2%, Type D=4.8% and Type E=8%. We identified a total of 18 syndromic patients, 17 diagnosed with VACTERL (11.7%) and 1 diagnosed with CHARGE (1.6%). The categorical breakdown of congenital anomalies showed the following distribution: vertebral (23%), anorectal malformation (9.5%), cardiac (45.2%), distal esophageal fistula (95.1%), renal (27.9%), skeletal (11.1%), respiratory (8.6%), digestive (54.7%) and other (20.7%). The most frequent gastrointestinal complication observed in preterm and full term patients were use of anti-reflux medication (90.9% and 100% respectively) followed by need for dilatation (72.7% vs 50%) while need for force feeding was observed in 54.5% of preterm and 14.8% of full term patients. To investigate the impact of gestational age on respiratory and gastrointestinal outcomes we used inferential statistical tests for categorical data. An increased incidence in the reported use of anti-H2 blocker therapy was reported for the full term study population (p=0.001; OR 15.75 [2.65;93.46]) while the incidence of need for force feeding (p=0.019; OR 0.15 [0.03;0.75]) and stenosis

(p=0.046; OR [0.05, 1.03]) was significantly higher in the premature population. No other significant findings were reported for gastrointestinal complications. The incidence of respiratory complications was reported higher in the full term patient population (respiratory aggravations: 57.7% vs 33.3%; abnormal respiratory symptoms: 84.6% vs 66.7%; abnormal auscultation: 73.1% vs 46.7%) with the only exception exertional dyspnea which was higher in the preterm population (13.3% vs 7.7%). These results were statistically non-significant. Also, no significant association between gestational age and the incidence of respiratory complications during the first five years after primary surgical repair for esophageal atresia was observed.

TABLE 1

Total, n	137
Male, n (%)	83 (60.6%)
Mean gestational age, weeks	37.16 (SD=3.24)
Birth weight, grams	2675 (SD=708)
Type of EA, n	62
A, n (%) B, n (%) C, n (%) D, n(%) E, n (%)	2 (3%) 1 (1.6%) 51 (82.2%) 3 (4.8%) 5 (8%)
Anomalies, n (%) - Vertebral - Anorectal - Cardiac - Renal - Limb - Digestive - Respiratory tract - Other	 14 (23%) 6 (9.5%) 28 (45.2%) 17 (27.9%) 7 (11.1%) 6 (54.7%) 5 (8.6%) 12 (20.7%)
Syndrome, n (%) - VACTERL - CHARGE	18 (28.6%) 17 (27%) 1 (1.6%)

Table 1: Demographic overview of 137 esophageal atresia (EA) patients originating from Montreal Children's Hospital during the period 2005 to 2023. Incidence rates are reported in percentage as number of study subjects identified in a complete registered cohort (n=number of patients with reported outcome).

Table 2

Demographics	Sex, date of birth, place of birth, gestational age, birth weight, APGAR, date of admission to hospital, family
Prenatal	Intrauterine growth delay History of EA/TEF Multiple pregnancy In Vitro Fertilization Prenatal diagnosis
Anomalies	Skeletal, anorectal, cardiac, renal, limb, gastrointestinal, respiratory, other syndromic
Type of EA	Gross classification
Syndromes	VACTERL, CHARGE, Other
Gastrointestinal	Current medical treatment, nutrition, need for tube feeding, endoscopic evaluations, interventional procedures
Respiratory	Symptoms, aggravations, admissions, medical treatment, interventional procedures, imaging

Table 2: Categorical breakdown of variables collected. Each category represents a multitude of variables outlined in appendix 1. EA (esophageal atresia); TEF (tracheoesophageal fistula)

TABLE 3

Gastrointestinal complications	**Preterm (n=15)**	**Full term (n=29)**	**p-value Odds-Ratio (OR)**
- Current medications - Proton pump inhibitors - Cisapride - Domperidone - Anti H2	10/11 (90.9%) 10/11 (90.9%) 2/4 (50%) 6/11 (54.5%) 2/11 (18.2%)	27/27 (100%) 19/26 (73.1%) 2/4 (50%) 11/26 (42.3%) 21/27 (77.8%)	.289 .391 .597 .719 0.001** OR 15.75 [2.65, 93.46]
Need for force feeding	6/11 (54.5%)	4/27 (14.8%)	.019* OR 0.15 [0.03, 0.75]
Esophageal findings - Esophagitis - Barret's esophagus - Stenosis - Hiatal hernia - Esophageal diverticulum	 2/11 (18.2%) 0 (0%) 8/11 (72.7%) 2/11 (18.2%) 1/11 (9.1%)	 4/24 (16.7%) 1/26 (3.8%) 10/27 (37%) 0 (0%) 0 (0%)	 1.00 1.00 .046* OR [0.05, 1.03] .083 .297
Stomach/duodenum findings - Ectopic pancreas - Microgastria	 1/11 (9.1%) 0 (0%)	 4/26 (15.4%) 1/26 (3.8%)	 1.00 1.00
Histology - Peptic esophagitis - Eosinophilic esophagitis - Dilatation required	 5/11 (45.5%) 2/11 (18.2%) 8/11 (72.7%)	 7/26 (26.9%) 3/26 (11.5%) 13/26 (50%)	 .443 .623 .285
＞1 complication	10/11 (90%)	19/27 (70.4%)	.237

Table 3: Incidence of gastrointestinal complications in preterm and full term EA patients operated at the MUHC from 2005-2023. Numbers reported are based on accessibility of completed case report forms. Chi square analysis was performed to explore the difference in impact of gestational age (GA) on outcomes between preterm and full term study subjects; $p<0.05$* was considered

significant with ** representing a very high level of statistical significance. Odds Ratio (OR) <1 suggests the likelihood of an inverse relationship. In this case “anti-H2” medication therapy was significantly higher in the full term group compared to the preterm group while the “need for gavage” and “stenosis” was significantly higher in the preterm versus full term study group.

Table 4

Respiratory complications	**Preterm (n=15)**	**Full term (n=29)**	**p-value Odds Ratio (OR)**
Aggravations	5/15 (33.3%)	15/26 (57.7%)	.133
Admission - Intensive care - Hospital admission - Urgent care	 2/15 (13.3%) 2/15 (13.3%) 5/18 (27.8%)	 7/26 (26.9%) 6/26 (23.1%) 13/26 (50%)	 .297 .687 .300
Medications - Antibiotics - PO steroids - INH steroids - Ventolin	 4/15 (26.7%) 2/15 (13.3%) 2/14 (14.3%) 2/14 (14.3%)	 12/26 (46.2%) 9/26 (34.6%) 5/25 (20.0%) 7/25 (28%)	 .218 .168 1.00 .445
Diagnosis - Pneumonia - Bronchitis - Sinusitis - Asthma attack	 4/15 (26.7%) 2/15 (13.3%) 0 1/14 (7.1%)	 9/26 (34.6%) 7/25 (28%) 0 6/26 (23.1%)	 .598 .440 - .387
Abnormal respiratory symptoms - Coughing - Morning cough - Nighttime cough - Grumbling breathing - Grumbling (eating) - Wheezing - Respond to Ventolin	10/15 (66.7%) 2/14 (14.3%) 2/15 (13.3%) 1/14 (7.1%) 2/15 (13.3%) 2/15 (13.3%) 3/14 (21.4%) 1/14 (7.1%)	22/26 (84.6%) 9/25 (36.0%) 5/25 (20.0%) 9/25 (36.0%) 10/25 (40%) 4/25 (16%) 5/25 (20.0%) 4/24 (16.7%)	.181 .266 .147 .064 .152 1.00 1.00 .633
Exertional dyspnea	2/15 (13.3%)	2/26 (7.7%)	.615
Continuous dosing aerosol Corticosteroids - Without LABA - With LABA - Other inhaler	0 1/7 (14.3%) 0 0	2/26 (7.7%) 6/7 (85.7%) 1/26 (3.8%) 5/25 (20.0%)	.524 .232 1.00 .137
Abnormal auscultation	7/15 (46.7%)	19/26 (73.1%)	.091

- Rhonci - Crackles - Whistles	4/13 (30.8%) 0 0	9/21 (42.9%) 2/10 (20.0%) 4/18 (22.2%)	.719 .272 .268

Table 4: Incidence of respiratory complications in preterm and full term EA patients operated at the Montreal Children's Hospital from 2005-2023. Chi square analysis was performed to explore the difference in impact of gestational age (GA) on outcomes between preterm and full term study subjects. PO (per os); INH (inhalational); LABA (long acting beta agonists); OR (odds ratio)

2.7 Discussion

Patients with esophageal atresia form a group of medically well-defined patients who typically receive consistent surgical and medical care across most high income countries. Our study sought to explore the relationship between gestational age and predefined respiratory and gastrointestinal outcomes, addressing a gap in the existing scientific literature.[46,47] Our study sample of 137 patients who underwent primary surgical repair for EA at the MCH over 18 years revealed similarities to existing literature in terms of patient demographics, comorbidities and complications. However, the reported outcomes differ significantly across various studies, and predominantly rely on retrospective cohort studies, indicating a scarcity of scientifically rigorous data. One of the primary reasons for the lack of scientific evidence and consensus of definitions relates to the rarity and complexity of the disease presentation and treatment.[47] A low incidence of EA makes it difficult to explore prospective randomized clinical trials without a large international multicenter setup. The NECTARINE study, originating from Europe and including 77 different centers in 24 European countries, is an example of a prospective investigative study aiming to explore mortality and morbidity in a population of European neonates.[48,49] Conducted in

2016-2017 this large multicenter study investigated perioperative management of more than 5600 neonates from which esophageal atresia represented a subpopulation of 134 study subjects. They reported 30-day postoperative complications as being of predominant respiratory (47%), surgical (34%) and cardiac (22%) origin. There was no correlation of complications to birth weight but interestingly they found a significant difference in the incidence of "overall postoperative complications"and "cardiac complications" when stratifying for gestational age <32 weeks versus >32 weeks.[48] Gestational age and birth weight are usually considered covariates, and these findings should as such be interpreted with caution. Also, it must be noted that the number of neonates with a gestational age <32 weeks represented only 10% (N=14) of the entire study population.[49] Despite the use of data from a large European-wide prospective multicenter cohort, this sub-study had several limitations such as a small sample size, missing data and confounding factors in a heterogeneous study population. These and similar reported findings suggest that the international EA research community needs to take additional steps to overcome limitations imposed by small sample sizes and inconsistent outcome definitions. Something which is currently being done by a research team from the UK. The OCELOT study group's initiative to develop an internationally agreed comprehensive core outcome set for patients with EA is indeed commendable. By addressing the limitations imposed by small sample sizes and inconsistent outcome definitions, this research team from the UK is taking important steps to improve the quality and standardization of EA research, which seems to be the root cause for lack of scientific evidence.

2.8 Conclusion:

This retrospective study of 137 patients undergoing primary surgical repair for esophageal atresia at the MCH between 2005-2023 demonstrates that demographic characteristics of our study population are consistent with international reported findings. Our findings suggest that gestational age does not have a significant impact on respiratory complications during the first five years of

life. Furthermore, the majority of gastrointestinal complications during this period are not influenced by gestational age. However, we observed that the full-term population had a significantly higher incidence in the use of anti-H2 blocker therapy and that the premature population had a significantly increased incidence of force feeding stenosis. Interpretation of reported outcomes should take into account lack of registered data, resulting in a small sample size (44/137 patients, 15 premature and 29 full term, with complete data set for gastrointestinal and respiratory complications). Given the limitations of our study (small sample size, missing data and poor data quality) further studies are necessary to establish a comprehensive understanding of the impact of gestational age on respiratory and gastrointestinal complications. Large international established collaborations defining and reporting clinical and patient centered outcomes are needed to improve quality in future research.

CHAPTER 3 - SUMMARY AND DISCUSSION

Esophageal atresia is a rare congenital anomaly characterized by the incomplete development of the esophagus, presenting significant challenges for affected individuals, their families, healthcare professionals, and researchers. This condition, with an estimated prevalence of 1 in 2,500 to 4,500 live births, involves the malformation of the esophageal tube, leading to a disconnection between the upper and lower segments of the esophagus. Encompassing a spectrum of five anatomical variants (A,B,C,D,E), this rare disease population presents unique challenges in terms of surgical repair, perioperative management, short- and long term clinical care and research opportunities.

In our study, long-term gastrointestinal complications related to esophageal atresia were defined based on several factors, including the use of anti-reflux medication, the requirement for force feeding, abnormal histological and endoscopic findings, as well as the need for esophageal dilations. It is important to note that these variables may be influenced by the presence of other congenital gastrointestinal complications, such as malrotation, necrotizing enterocolitis, and anastomotic leakage. However, due to the lack of available data, we were unable to evaluate the impact of these additional complications in our study. Our study encompassed a diverse range of potential endoscopic findings, including Barrett's esophagus, esophagitis, and stenosis. This was crucial because relying solely on self-reported outcomes may not always align with the objective findings observed during endoscopy. In individuals with esophageal atresia (EA), they may report symptoms such as reflux or difficulties with swallowing, even though endoscopic examination may not reveal significant abnormalities. Conversely, some individuals may not perceive symptoms, yet endoscopic evaluation shows notable pathological changes. This disparity between self-reported outcomes and endoscopic findings highlights the complex nature of EA and the various factors contributing to symptoms and complications. It underscores the significance of considering both

subjective and objective assessments to comprehensively evaluate the overall clinical status of patients. Moreover, there is a need to develop and implement improved patient-reported outcome tools to better capture the experiences and outcomes of individuals with EA

In the literature, gastroesophageal reflux disease (GERD), dysphagia and pathological endoscopic findings rank amongst the most commonly reported gastrointestinal complications.[10,37] These symptoms, experienced by individuals with esophageal atresia, are thought to partially stem from an underlying esophageal dysmotility, which is observed in all EA patients.[25] The dysmotility is believed to arise from impaired innervation of the proximal and distal segments of the esophagus, both extrinsically and intrinsically.[25] Furthermore, the dysmotility is thought to be exacerbated following surgical repair which contributes to the impaired movement and coordination of the esophageal muscles, leading to difficulties in swallowing and gastroesophageal reflux.[25] GERD has a substantial impact on patient reported outcomes and objective pathological findings such as esophagitis and Barrett's esophagus (intestinal metaplasia), which can eventually result in the need for anti-reflux surgery such as fundoplication (wrapping of the upper part of the stomach, known as the fundus, around the lower esophagus, hence creating a valve-like structure that prevents acid reflux).[10] Understanding the underlying mechanisms of patient reported gastrointestinal symptoms relating to complications such as esophagitis (inflammation caused by acidic reflux into the esophagus), eosinophilic esophagitis (EoE; immune modulated inflammation of the esophagus) esophageal dysmotility (intrinsic and extrinsic innervation of esophageal muscle layers), hiatal hernia (protrusion of part of the stomach into the chest cavity through an opening in the diaphragm) and esophageal diverticulum (pouch that forms in the esophageal wall) is crucial for developing targeted interventions to alleviate symptoms and improve long-term outcomes. However, due to small heterogeneous sample sizes, diagnostic difficulties (endoscopic procedures in the young

pediatric population require scheduling, fasting and general anesthesia) and a vast amount of potential confounding factors current knowledge is limited and often based on retrospective cohorts, case reports and animal studies.

During the first five years of life, *respiratory complications* contribute significantly to the overall incidence of complications in esophageal atresia patients.[23] In contrast to the gastrointestinal complications which rarely manifest prior to surgical intervention, the newborn EA patient can demonstrate various degrees of compromised ventilation. Passage of gastric contents via a distal TEF to the lungs, saliva spill over from the proximal esophageal pouch to the trachea or even an attempt to breastfeed in the non-diagnosed infant are the most common preoperative reasons for respiratory complications.[23] Most often this will result in acute respiratory distress, desaturation and hypoxemia due to pulmonary atelectasis or chemically induced pneumonia. A serious and concerning condition which will postpone surgical intervention, require urgent intubation and need for mechanical ventilation to assure a sufficient oxygenation. The most feared and profound respiratory condition is acute respiratory distress syndrome (ARDS) which carries a significant impact on morbidity and mortality.[23,33] Patients often require long term admission to high dependency units, continuous antibiotic treatment and long term intubation putting them at increased risk of nosocomial super infections. The NECTARINE study, a prospective European multicenter study including >5600 neonates and a subpopulation of 134 EA patients, demonstrated a 30-day incidence of “overall postoperative complications” of 47% with respiratory complications representing the majority (34%).[49] However, when comparing the overall and respiratory complications reported by NECTARINE to a recently published retrospective data analysis of American EA patients, these vary greatly with an incidence of 47% vs 22% and 34% vs 14% respectively. Our study did not provide specific data on respiratory outcomes within a 30-day

timeframe, and therefore, a direct comparison of numbers cannot be made. However, a recent publication reviewing long term respiratory complications related to EA emphasizes the importance of long term respiratory outcomes.[30] An initial high incidence of tracheomalacia up to 78% of which 26% required surgery (aortopexy; fixation or suspension of the aorta to alleviate tracheobronchial compression) was reported.[30] Lower respiratory tract infections (LRTI) and asthmatic symptoms were equally more frequent in the adolescent and adult EA population compared to controls.[30,50] Again, our study did not report on LRTI and asthma symptoms related to a control cohorte, but we did register a significant incidence of pneumonia, asthma symptoms and use of medication used to treat reactive airways.

After surgical correction, EA patients will have a normal anatomy including a non-communicating trachea and esophagus.[30] However, this is not always enough to avoid additional respiratory and pulmonary complications. Comorbidities related to EA equally include tracheomalacia and laryngeal cleft.[33] Tracheomalacia is characterized by a weakness or softening of the cartilage that supports the walls of the trachea and will potentially lead to various respiratory symptoms and complications, including wheezing, chronic cough, difficulty of breathing and recurrent respiratory infections.[30,33,45] Laryngeal cleft will, depending on the severity of the condition, contribute to respiratory or pulmonary complications by means of aspiration.[50] Our study revealed a low incidence of diagnosed tracheomalacia and laryngeal cleft. However, we observed a substantial occurrence of respiratory symptoms suggestive of these comorbidities suggesting a potential diagnostic underreporting. When respiratory symptoms manifest, patients will in most cases be seen by a healthcare professional. Pending the gravity of the situation, they will either be treated as outpatients or admitted to hospital with a level of care based on the severity of the situation (e.g., emergency consult, hospital admission or intensive care unit admission). Our investigation revealed

varying rates of postoperative respiratory complications among the analyzed patients, but with no significant difference between preterm and full term study subjects. Respiratory aggravations were most frequently reported. These patients demonstrated enhanced need of care. Incidence of urgent care visits were the most common outcome while hospital and intensive care unit admission was less frequently observed.

The consequences of esophageal atresia extend beyond the initial surgical repair, often requiring long-term management and multidisciplinary care.

Published in 2023, a comprehensive systematic review titled "*Variability in the Reporting of Baseline Characteristics, Treatment, and Outcomes in Esophageal Atresia Publications*"[47] sought to evaluate the extent of variability and reporting patterns in research pertaining to esophageal atresia. A total of 209 publications were included in the review, encompassing more than 730 distinct patient and treatment characteristics and outcomes. The findings underscored a substantial heterogeneity and variation in research interests and reporting practices across included publications. Of 265 identified outcomes only 2% were mentioned in over 50% of the included publications, indicating a limited focus on specific outcomes. Similarly, patient characteristics (4%) and treatment and care process characteristics (<1%) exhibited sparse attention in terms of being studied and reported in more than 50% of the publications. Moreover, the definitions and assessments of these parameters displayed inconsistent approaches throughout the included publications, posing challenges for meaningful comparison and benchmarking, even in the case of more frequently studied parameters. Several notable observations emerged from the review. Primarily, retrospective cohort studies constituted the majority of the analyzed studies, underscoring the need for increased prospective investigations to establish optimal practices in EA care. Furthermore, the majority of studies predominantly emphasized short-term outcomes

associated with primary surgical repair and its complications, with comparatively limited attention devoted to long-term outcomes. In addition, a low number of studies incorporated patient-reported outcome measures (PROMs) to assess quality of life outcomes, with considerable variation observed in the utilized instruments across the studies. The limitations of the study were focused on limiting inclusion of papers to after 2015 and the exclusion of non-English literature, possibly leading to an underestimation of outcomes due to potential geographic and local practice influences. The authors concluded that standardized measurement and reporting is essential to reduce reporting bias, enhance interpretability of results, and enable meaningful comparisons across studies and healthcare settings. These statements are equally emphasized and addressed by Paula R. Williamson et al. in their publication "*The COMET Handbook: Version 1.0*".[51] A publication which provides a comprehensive step-by-step guide to the development and implementation of core outcome sets (COS) in clinical research. The handbook addresses key considerations in COS implementation, such as outcome measurement instruments, data collection methods, and strategies for disseminating and promoting the use of COS in research. Also, it emphasizes the importance of patient involvement throughout the process, ensuring that outcomes of relevance to patients and their caregivers are included. Overall, the COMET Handbook provides a comprehensive and practical resource for the development and implementation of core outcome sets, facilitating collaboration and harmonization across research studies, and ultimately enhancing the validity and usefulness of clinical research findings. In line with "*The COMET Handbook: Version 1.0*" the OCELOT study,[51,52]conducted by TOFS (Tracheo-Oesophageal Fistula Support group), a UK initiated research project focused on understanding and improving the outcomes of individuals with EA and TEF, was initiated in 2020. The project is currently underway to define a core outcome set for esophageal atresia in the context of research and clinical trials. This initiative aims to establish a standardized set of outcomes and obtain valuable information about the

long-term outcomes, experiences, and quality of life of individuals living with EA and TEF. Outcomes and information that should be consistently measured and reported across different studies and research efforts.

These initiatives and efforts have all been initiated based on a general lack of consensus on what data to collect and which outcome variables to investigate in a rare disease population such as EA. Unfortunately we still have no uniform international guidelines for collecting data and comparing outcome variables in EA. However, this is not only a particular problem in EA. There is unfortunately an overall lack of interest in research domains pertaining to rare diseases which can be attributed to several factors. One of the main reasons is a limited awareness and knowledge about these conditions among the general population, healthcare professionals and policymakers which results in less attention, recognition and appreciation of the significance[49]. Furthermore, healthcare professionals face various challenges and constraints in their daily practice, including limited time and resources. The high clinical demands and workload placed on doctors, nurses and caregivers can make it difficult for them to allocate sufficient attention and resources. As a result, these rare conditions may not receive the same level of research as more common diseases. Another contributing factor is research funding, which is often driven by public health impact and disease prevalence. Rare diseases, by definition, have a low prevalence and may not be perceived as a priority when it comes to allocating governmental research funds. Also, policymakers and funding agencies tend to focus on diseases that affect a larger population and have a greater public health impact. Addressing these challenges requires efforts to increase awareness and knowledge about rare diseases, advocate for dedicated research funding, and foster collaboration among stakeholders to promote understanding and improve care for individuals affected by rare diseases.

Our study was based on a retrospective data analysis of 137 esophageal atresia patients surgically and medically treated at the MCH from 2005 to 2023. The study, aiming to provide insight into the postoperative respiratory and gastrointestinal complications during the first five years of life, highlights the challenges encountered by conducting a retrospective study in a rare disease population as previously discussed. The large timespan of 18 years, a small sample size of 137 study subjects, a substantial amount of missing data and a lack of definition of outcome variables consistent with international literature were noted as the primary reasons for lack of robust statistical outcomes, once again demonstrating the need for international consensus and collaboration.[53]

The limitations of our study relates to sample size, missing data, confounding factors and data quality. *Data quality* issues, such as interpretation of hand-written notes or factual errors in data entry, could affect the accuracy and outcome of the statistical analysis. To mitigate this challenge, we aimed to perform data cleaning and stepwise review of data of multiple team members to ensure the accuracy and consistency of the data. The *sample size* of study subjects and concomitant respiratory and gastrointestinal events is limited resulting in reduced power of the statistical analysis hence limiting the generalizability of the findings. To mitigate this challenge, we attempted to explore the possibility of combining our data with other studies. However, due to a substantial variation in reporting outcomes and definitions this was not feasible. Addressing the issue of *missing data* is of paramount importance in data analysis due to its potential impact on the accuracy and reliability of the results. This becomes particularly critical when dealing with a small study population such as in this current study. While sensitivity analysis and multiple imputation methods are effective means of handling missing data, they may not always be feasible or necessary in such cases when considering factors such as complexity and resource requirements. Sensitivity analysis and multiple imputation methods can be computationally intensive and require

advanced statistical expertise. In small studies with limited resources, conducting these analyses may be impractical due to time, cost, or expertise constraints. Also, sensitivity analysis and multiple imputation methods are based on assumptions about the nature and mechanism of missing data, such as missing completely at random or missing at random. In small study populations, these assumptions may be more likely to be violated, making the application of these methods less reliable. We considered the use of complete case analysis and pairwise deletion. Both complete case analysis and pairwise deletion provide straightforward methods for addressing missing data. However, these approaches involve a trade-off, as they may result in reduced sample sizes and introduce bias to the analysis if the missing data do not conform to the assumption of missing completely at random. In the end we were not able to apply this method due to a low number of study subjects. *Confounding factors*, such as the presence of other congenital anomalies, could affect the relationship between gestational age and the outcomes of interest. To mitigate this challenge, we aimed to adjust for potential confounding factors in the statistical analysis using multiple logistic regression models. By including these factors, the regression analysis would estimate the independent effect of the exposure on the outcome while adjusting for the potential confounding effects of the included variables. Due to a low number of study subjects and outcomes we were not able to perform logistic regression analysis.

To address these limitations and further advance the understanding of this rare condition, our study team has initiated the establishment of a pan-Canadian esophageal atresia network. This collaborative network brings together surgeons, anesthetists, intensive care physicians and other relevant stakeholders from across Canada. By pooling resources, expertise and data, this network aims to enhance sample sizes, improve data quality, and establish standardized definitions for outcome variables, thereby fostering more robust statistical analyses and generating more reliable research outcomes.These efforts are essential for advancing our understanding of EA, improving

patient care, and ultimately enhancing outcomes for individuals affected by this condition. By working together and harnessing the power of collective expertise and resources, we can overcome the hurdles in EA research and make significant strides towards better diagnosis, treatment, and long-term management of the condition.

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APPENDIX 1

Confidential

1.0 Initial History

Study Subject ID / Study Subject ID:	_____
[v_no]	
Birth details	
Sexe Sex:	○ F ○ M
Date de naissance Date of Birth:	_____ (jj-MM-AAAA / DD-MM-YYYY)
Heure Hour:	_____ (HH:MM)
Lieu de naissance Place of birth:	○ Hôpital / Hospital ○ Autres / Other
Si autre lieu de naissance, spécifier If other place of birth, specify:	_____ (Décrivez / Describe)
Âge gestationnel Gestational Age	_____ (Week)
GA < 37	_____
Poids de naissance Birth weight	_____ (grams (g))
Retard de Croissance Intra-utérin (RCIU) Intrauterine Growth Delay	○ Oui / Yes ○ Non / No
APGAR 1 min	○ 1 ○ 2 ○ 3 ○ 4 ○ 5 ○ 6 ○ 7 ○ 8 ○ 9 ○ 10 ○ Inconnue /Unknown

APGAR 5 mins	○ 1 ○ 2 ○ 3 ○ 4 ○ 5 ○ 6 ○ 7 ○ 8 ○ 9 ○ 10 ○ Inconnue /Unknown
Apgar 10 min	○ 1 ○ 2 ○ 3 ○ 4 ○ 5 ○ 6 ○ 7 ○ 8 ○ 9 ○ 10 ○ Inconnue /Unknown

Admission Details

Date d'admission a l'hopital Date of hospital admission	_____ (JJ-MM-AAAA / DD-MM-YYYY)
Transfert après naissance pour chirurgie Transfer after birth for surgery	○ Oui / Yes ○ Non / No
Si oui, date If yes, date:	_____ (JJ-MM-AAAA / DD-MM-YYYY)
Délai tranfert Transfer delay:	○ < 24 h ○ 24-48 h ○ > 48 h ○ Inconnue/Unknown

Familiaux / Family history

ATCD familiaux atresie oesophage Family history of EATEF	○ Oui / Yes ○ Non / No
Si oui (ATCD familiaux Atoe) , specifier If yes (Family history of EATEF), specify:	☐ Sœur / Sister ☐ Frère / Brother ☐ Mère / Mother ☐ Père / Father ☐ Oncle / Uncle ☐ Tante / Aunt ☐ GPM / Maternal Grandfather ☐ GMM / Maternal Grandmother ☐ GPP / Paternal Grandfather ☐ GMP / Paternal Grandmother ☐ Autre/Other

Autre / Other:	_____ (Décrivez / Describe)
Atopie familiaux Family history of EA	◯ Oui / Yes ◯ Non / No
Si oui (Atopie familiaux) , specifier If yes (Family history of EA), specify:	☐ Sœur / Sister ☐ Frère / Brother ☐ Mère / Mother ☐ Père / Father ☐ Autre/Other
Autre / Other:	_____ (Décrivez / Describe)
Grossesse multiple / Multiple pregnancy	◯ Oui / Yes ◯ Non / No
Si oui, specifier If yes, specify	◯ Jumeaux / Twins ◯ Triplets / Triplets ◯ Autres / Other
Si autres, spécifier # If other, specify #	_____ (Input as number of children [4-10 children] as an integer)
Fecondation in-vitro? IVF?	◯ Oui / Yes ◯ Non / No
Dx	
Type d'atrésie Type of Esophageal Atresia	☐ A (isolée/isolated) ☐ B (F proximale / F proximal) ☐ C (F distale / F distal) ☐ D (F distale + prox / F distal + prox) ☐ E (F en H)
Dx prenatal Diagnosed prenatally	◯ Oui / Yes ◯ Non / No ◯ Suspecté / Suspected
Intubation pré-anesthésique Pre-anesthetic intubation	◯ Oui / Yes ◯ Non / No

Intubation pré-anesthésique/Pre-anesthetic intubation

	Oui / Yes	Non / No
Pneumonie pre-op Pre-op pneumonia	○	○
Maladie des membranes hyalines pre-op Pre-op hyaline membrane disease	○	○
Autres pathologies Other pathologies	○	○
Intubation elective Elective intubation	○	○

Si oui, pneumonie pré-op, précisez ou
If yes, pre-op pneumonie, specify where

☐ Poumon gauche / Left lung
☐ Poumon droit / Right lung

Si oui, autre pathologies, précisez
If yes, other pathologies, specify

_____
(Décrivez / Describe)

1.1 Initial History - Associated Anomalies

Study Subject ID / Study Subject ID:	_____
[v_no]	
Skeletal Anomalies of Vertebrae and ribs	
Vertébrales Vertebrae	○ Oui / Yes ○ Non / No
Nb de vertèbres Number of vertebrae	_____ (Number of missing vertebrae [0-33])
Nb anormal de côtes Number of abnormal ribs	_____ (Number of missing ribs [0-24])
Nb de vertèbres papillons Number of butterfly vertebrae	_____ (number of butterfly vertebrae [0-33])
Hémivertèbres thoraciques Thoracic hemivertebrae	○ Oui / Yes ○ Non / No
Anomalie sacrum Sacral abnomalies	○ Oui / Yes ○ Non / No
Autres, specifiez Other, specify	○ Oui / Yes ○ Non / No
Autres, specifiez Other, specify	_____ (Décrivez / Describe)
Anorectal Malformations	
Anorectales Anorectal	○ Oui / Yes ○ Non / No
Si oui If yes	○ Basse / Low ○ Haute / High ○ Cloaque / Cloacal ○ Intermédiaire / Intermediate

Neonatal Cardiac Abnormalities	
Anomalie Cardiaque Cardiac malformation	○ Oui / Yes ○ Non / No
Hémodynamique significative Significant Hemodynamic	○ Oui / Yes ○ Non / No (If cardiology abnormality, was there a significant change in hemodynamics?)
Nécessitant une chirurgie Surgery required	○ Oui / Yes ○ Non / No (If hemodynamics were impacted by the cardiac malformation, was surgery required?)
Si oui If yes	☐ CIA / ASD ☐ CIV / VSD ☐ Canal artériel persistant / Persistent ductus arteriosus ☐ Tétralogie de Fallot / Tetralogy of Fallot ☐ Transpo Gros Vaisseaux / Transposition of the great vessels ☐ Tronc Artériel commun / Truncus arteriosus ☐ CAV / AV Canal ☐ FOP / PFO ☐ Coarctation de l'aorte / Coarctation of the aorta ☐ Arc aortique drt/Right aortic arch ☐ Sous-clavière aberrante / ARSA ☐ Retour veineux anormal / Anomalous Pulmonary vein return ☐ Anomalie valvulaire / Valve anomaly ☐ Dextrocardie / Dextrocardia ☐ Autres / Other
Si autre, specifier If other, specify	_____ (Décrivez / Describe)

Renal Abnormalities	
Rénales Renal system	○ Oui / Yes ○ Non / No
Si oui If yes	☐ Rein unique / Single kidney ☐ Rein en fer à cheval / Horseshoe kidney;Renal Fusion ☐ Anomalie pyélocalcielles / Pyelocalcial abnomalies ☐ Hydronéphrose / Hydronephrosis ☐ Reins dysplasiques / Dysplastic kidney ☐ Rein ectopique / Ectopic kidney ☐ Agénésie rénale bilatérale / Bilateral renal agenesis ☐ Autres / Other
Si autres, specifier If other, specify	_____

Limb Abnormalities	
Membres Extremities	○ Oui / Yes ○ Non / No
Si oui If yes	☐ Agénésie / Agensis ☐ Hypoplasie / Hypoplasia
Si oui, agénésie/hypoplasie If yes, agensis/hypoplasia	☐ Radius / Radius ☐ Pouce / Thumb ☐ Doigts / Fingers ☐ Membres inférieurs / Inferior ☐ Autres / Other
Si autres, specifiez If other, specify	_____

Gastrointestinal Abnormalities	
Digestives Digestive	○ Oui / Yes ○ Non / No
Si oui If yes	☐ Sténose congénitale oesophage / Congenital esophagael stenosis ☐ Atrésie/web duodénale / Web/duodenal atresia ☐ Pancréas annulaire / Annular pancreas ☐ Atrésie grêle / Small Atresia ☐ Malrotation / Malrotation ☐ Hirschsprung /Hirschsprung ☐ Autres / Other
Si autres, specifiez If other, specify	_____

Respiratory Malformation	
Voies Respiratoires Respiratory tract Malformation	○ Oui / Yes ○ Non / No
si oui / if yes	☐ Agénésie pulmonaire / Pulmonary agenesis ☐ Hypoplasie pulmonaire / Pulmonary hypoplasia ☐ Atrésie trachéale / Tracheal atresia ☐ Sténose trachéale / Tracheal stenosis ☐ Atrésie/sténose choanes / Choanal atresia/stenosis ☐ Sténose sous-glottique / Subglottic stenosis ☐ Fente laryngée / Laryngeal cleft ☐ Trachéomalacie / Tracheomalacia ☐ Autres / Other
Laryngeal cleft Grade	○ I ○ II ○ III ○ IV
Tracheomalacia Grade	○ I ○ II ○ IV

Si autre, specifiez If other, specify	_____ (Décrivez / Describe)

Other Abnormalities

Autre malformation Other abnormalities	○ Oui / Yes ○ Non / No
Si oui, specifiez If yes, specify	☐ Oreilles / Ears ☐ Opthalmologique / Opthalmological ☐ Neurologique / Neurological ☐ Cutanée / Dermatalogical ☐ Génitale/Gynécologique / Genital/Gynecologic ☐ Autres / Other
Si autres, speci / If other abnormalities, please specify	_____

Congenital Abnormalities

Syndrome	○ Oui / Yes ○ Non / No ○ Unknown / Inconnue
Si oui If yes	☐ VACTERL (≥ 3 anomalies) / VACTERL (≥ 3 anomalies) ☐ Trisomie 21 / Trisomy 21 ☐ Trisomie 18 / Trisomy 18 ☐ Syndrome de CHARGE / CHARGE syndrome ☐ Autres / Other
si autres, specifiez if other, specify	_____ (Décrivez / Describe)

3.0 Gastroenterological Treatments

Study Subject ID / Study Subject ID:	_____
[v_no]	
Symptoms	○ Oui / Yes ○ Non / No
Preciser	_____
Traitements actuels Current treatments	○ Oui / Yes ○ Non / No
IPP Proton pump inhibitors	○ Oui / Yes ○ Non / No
Date de debut Start of date	_____ (JJ-MM-AAAA / DD-MM-YYYY)
Date de'arret End date	_____ (JJ-MM-AAAA / DD-MM-YYYY)
Spécifiez IPP Specify PPI	☐ Oméprazole ☐ Lanzoprazole ☐ Pantoprazole ☐ Esoméprazole
Complete items below for Oméprazole	
Dose	_____ (mg)
Dose poids Dose weight	_____ (mg/kg)
Frequence Frequency	○ DIE ○ BID ○ TID ○ QID
Complete items below for Lanzoprazole	
Dose	_____ (mg)

Dose poids Dose weight	_____ (mg/kg)
Frequence Frequency	○ DIE ○ BID ○ TID ○ QID
Complete items below for Pantoprazole	
Dose	_____ (mg)
Dose poids Dose weight	_____ (mg/kg)
Frequency Frequency	○ DIE ○ BID ○ TID ○ QID
Complete items below for Esoméprazole	
	_____ (mg)
Dose poids Dose weight	_____ (mg/kg)
Frequence Frequency	○ DIE ○ BID ○ TID ○ QID
	○ Oui / Yes ○ Non / No
Date du debut Start date	_____ (JJ-MM-AAAA / DD-MM-YYYY)
Dose	_____ (mg)
Weight-based dose	_____ (mg/kg)

Frequence Frequency	○ DIE ○ BID ○ TID ○ QID
Domperidone Domperidone	○ Oui / Yes ○ Non / No
Date du debut Start date	_____ (jj-MM-AAAA / DD-MM-YYYY)
Dose	_____ (mg)
Weight-based dose	_____ (mg/kg)
Frequence Frequency	○ DIE ○ BID ○ TID ○ QID
Cisapride Cisapride	○ Oui / Yes ○ Non / No
Date du debut start date	_____ (jj-MM-AAAA / DD-MM-YYYY)
Dose	_____ (mg)
Weight-based dose	_____ (mg/kg)
Frequence Frequency	○ DIE ○ BID ○ TID ○ QID
Eyrthromycine Erythromycine	○ Oui / Yes ○ Non / No
Date du debute Start date	_____ (jj-MM-AAAA / DD-MM-YYYY)
Dose	_____ (mg)

Weight-based dose	_____ (mg/kg)
Frequence Frequency	○ DIE ○ BID ○ TID ○ QID
Autres Other	_____ (Nom de drug / Drug name)
Date du debute Start date	_____ (jj-MM-AAAA / DD-MM-YYYY)
Dose	_____ (mg)
Weight-based dose	_____ (mg/kg)
Frequence Frequency	○ DIE ○ BID ○ TID ○ QID
Commentaires	_____

3.1 Nutrition

Study Subject ID / Study Subject ID: _____

[v_no]

	Oui / Yes	Non / No
Alimentation orale a 100% 100% oral feed	○	○
Introduction des purees Introduction of purees	○	○
Introduction des solides Introduction of solids	○	○
Suppl. alimentaires Nutrient supplements	○	○

Date du debut
Start date _____ (JJ-MM-AAAA / DD-MM-YYYY)

Besoin de gavage a domicille
Need for tube feeding
○ Oui / Yes
○ Non / No

Si oui, type de gavage
If yes, type of tube feeding
☐ Naso-quastrique / Naso-gastric
☐ Naso-jejunal / Naso-jejunal
☐ Gastrostomie / Gastrostomy
☐ Jejunostomie / Jejunostomy
☐ Gastro-jejunostomie / gastro-jejunostomy

Apport calorique
Caloric intake
○ Exclusif / Exclusive
○ Complementaire / Complementary

Date du debut du gavage
Date force feeding _____ (JJ-MM-AAAA / DD-MM-YYYY)

Date de fin du gavage
End date of forced feeding _____ (JJ-MM-AAAA / DD-MM-YYYY)

HAIV
Intravenous hyperalimentation (IVH)
○ Oui / Yes
○ Non / No

Date debut de l'HAIV
Start date of the IVH _____ (JJ-MM-AAAA / DD-MM-YYYY)

Date de fin de l'haiv
Date IVH ended _____ (JJ-MM-AAAA / DD-MM-YYYY)

3.2 Endoscopic Evaluation

Study Subject ID / Study Subject ID:	_____
[v_no]	
Evaluation endoscropique Endoscopic evaluation	○ Oui / Yes ○ Non / No
Si oui, date If yes, date	_____ (JJ-MM-AAAA / DD-MM-YYYY)
Endoscopies multiples Multiple endoscoies	○ Oui / Yes ○ Non / No
Si oui, date If yes, dates	_____ (format dd-Mmm-yyyy (Month in english starting with capital letter). Comma between each date (ex dd-Mmm-yyyy, dd-Mmm-yyyy, ect))
Oesophage Esophagitis	○ Oui / Yes ○ Non / No
Si oui, grade If yes, grade	○ 1 ○ 2 ○ 3 ○ 4
Barrett "endoscopique" Barrett "endosope"	○ Oui / Yes ○ Non / No
Si oui, classification If yes, classification	○ C ○ M
Stenose Stenosis	○ Oui / Yes ○ Non / No
Si oui, location If yes, location	○ Anastomotique ○ Congenitale
Distance stenose/arcade dentaire Stenosis/dental arch distance	_____ (cm)
Hernie hiatale Hiatal hernia	○ Oui / Yes ○ Non / No
Si oui, nombre de cm If yes, number of cm	_____
Diverticule oesophagien Esophageal diverticulum	○ Oui / Yes ○ Non / No

Autre(s) anomalie(s) Other abnormalities	○ Oui / Yes ○ Non / No
Si oui, precisez if yes, specify	_____
Estomac/duodenum Stomach/duodenum	○ Oui / Yes ○ Non / No

	Oui / Yes	Non / No
Ulceres Ulcers	○	○
Pancreas ectopique Ectopic pancreas	○	○
Microgastrie Microgastric	○	○
Autre(s) anomalie(s) Other abnormalities	○	○

Si oui, precisez if yes specify	_____
Evaluation Histologique OEsophage Histological Evaluation of Esophagus	○ Oui / Yes ○ Non / No

	Oui / Yes	Non / No
Oesophagite peptique Peptic esophagitis	○	○
Oesophagite eosinophilique (ie eosinos/ch) Eosinophilic esophagitis (ie > 15 eosinos/ch)	○	○
Barrett histologique: metaplasie intestinale Barrett histology: intestinal metaplasia	○	○
Barrett histologique: metaplasie gastrique Barrett histologique: gastrique metaplasie	○	○
Cancer: Adenocarcinome Cancer: Adenocarcinoma	○	○
Cancer: Epidermoide Cancer: Epidermoid	○	○

3.3 Gastroenterological Procedures

Study Subject ID / Study Subject ID:	_____
[v_no]	
Procedures endoscopiques Endoscopic procedures	○ Oui / Yes ○ Non / No
Dilatation Dilation	○ Oui / Yes ○ Non / No
Nbre Number	_____
Dates Dates	_____
Dates	_____
Ballons Ballons	○ Oui / Yes ○ Non / No
Nbre Number	_____
dates dates	_____
Dates	_____
Bougies Bougie	○ Oui / Yes ○ Non / No
Nbre Number	_____
Dates Dates	_____
Dates Dates	_____
Dilatation retrograde Retrograde dilation	○ Oui / Yes ○ Non / No
Nbre Number	_____
Dates Dates	_____

Dates Dates	_____
Mitomycine mitomycin	○ Oui / Yes ○ Non / No
Nbre Number	_____
Dates dates	_____
Dates dates	_____
Steriodes Steriodes	○ Oui / Yes ○ Non / No
Nbre Number	_____
Dates Dates	_____
Dates Dates	_____
Desimpaction Desimpaction	○ Oui / Yes ○ Non / No
Nbre Number	_____
Dates Dates	_____
Dates Dates	_____
Perforation/Dechirure Perforation/Tear	○ Oui / Yes ○ Non / No
Nbre Number	_____
Dates	_____
Dates	_____

3.4 Additional Gastroenterological Evaluations

Study Subject ID / Study Subject ID:	_____
[v_no]	
Etude de la vidange gastrique Evaluate of gastric emptying	○ Oui / Yes ○ Non / No
Si yes If yes	○ Normal ○ Anamalie
Date Date	_____ (jj-MM-AAAA / DD-MM-YYYY)
Evaluation radiologique Radiological evaluation	○ Oui / Yes ○ Non / No
Si oui, date If yes, date	_____ (jj-MM-AAAA / DD-MM-YYYY)
Stenose Stenosis	○ Oui / Yes ○ Non / No
Fistula Fistula	○ Oui / Yes ○ Non / No
Autre abnormalities Other abnormalities	○ Oui / Yes ○ Non / No
Si oui, precisez If yes, specify	_____
Dilatation radiologique Radiological dilation	○ Oui / Yes ○ Non / No
Date Date	_____ (jj-MM-AAAA / DD-MM-YYYY)
Evaluation manometrique Manometric evaluation	○ Oui / Yes ○ Non / No
Si oui, date If yes, date	_____ (jj-MM-AAAA / DD-MM-YYYY)
HRM High resolution manometry	○ Oui / Yes ○ Non / No

Catheters perfuses Infusion catheter	○ Oui / Yes ○ Non / No
Evaluation pH metrie/imedancemetrie pH metry/impedence metry evaluation	○ Oui / Yes ○ Non / No
Evaluation pH metrie/imedancemetrie pHmetry/impedence metry evaluation	☐ pHmetrie ☐ pHmetrie/Impedancemetrie ☐ Examens multiples
Date	_____
Si oui, dates If yes, dates	_____ (Input date as dd-Mmm-yyyy. Only entry the additional dates in this field.)
Medications (durant etude) Medication (during study)	○ Oui / Yes ○ Non / No (medications taken during the study)
Si oui, preciser type et dose If yes, specify type and dose	_____
Si oui, preciser dose If yes, specify dose	_____
Si oui, preciser unite de measure If yes, specify unit measurement	_____ (enter in lowercase [aa])
Positionnement de la sonde Position of probe	☐ Radiologique ☐ Manometrique ☐ Formule ☐ Inconnu
Duree totale(ph< 4) Total duration (pH< 4)	_____ (%)
Examen Physique	_____
Impressions et plans	_____

4.0 Respiratory Symptoms and Treatments

Study Subject ID / Study Subject ID:	_____
[v_no]	
Aggravations respiratories aigues (ARA) x DV Acute respitatory aggrevation	○ Oui / Yes ○ Non / No
Combien de fois How many times	_____
ARA ayant necessite soins intensifs Acute respiratory aggrevation requiring intensive care	○ Oui / Yes ○ Non / No
Combien de ARA How many acute respiratory aggrevations	_____
ARA ayant necessite hospotalisation sans USI Acute respitatory aggrevation requiring hospitalization but not intensive care	○ Oui / Yes ○ Non / No
Combien de ARA how many acute respiratory aggrevations required hospitalization but not intensive care	_____
ARA ayant necessite ixsite a l'urgence acute respitory aggrevations that required urgance/emergency care	○ Oui / Yes ○ Non / No
Combien de ARA how many acute respitatory aggrevations required urgance/emergency care	_____
ARA ayant necessite antibiotiques ambulatoire ARA requiring antibiotics	○ Oui / Yes ○ Non / No
Combien de ARA Number of ARA the require antibiotics	_____
ARA necessite steriordes PO ambulatoire Acute respiratory aggrevations requiring steriods by mouth	○ Oui / Yes ○ Non / No
Combein de ARA How man acute respiratory aggrevations requiring steroids by mount	_____
ARA ayant necessite steriodes inh ambulatoire Acute respitory aggrevations that require steriods by inhalation	○ Oui / Yes ○ Non / No

Combien de ARA How many acute respiratory aggrevations that require steroirds by inhalation	_____
ARA ayant necessite ventolin IHN ambulatoire Acute respiratory aggrevation requiring ventolin	◯ Oui / Yes ◯ Non / No
Combien de ARA How many acute respiratory aggrevation requiring ventolin	_____
ARA ayant necessite absenteisme scolaire Acute respiratory aggrevation that requires school absence	◯ Oui / Yes ◯ Non / No
ARA ayant necessite absenteisme scolaire Acute respiratory aggrevation that requires school absence	_____
ARA avec diagnostic de pneumonie Acute respiratory aggrevations with a pneumonia diagnosis	◯ Oui / Yes ◯ Non / No
combien de ARA How many acute respiratory aggrevations with a pneumoni diagnosis	_____
ARA avec diagnostic de bronchite Acute respiratory aggrevations with a bronchitis diagnosis	◯ Oui / Yes ◯ Non / No
Combien de ARA How many acute respiratory aggrevations with bronchitis diagnosis	_____
ARA avec diagnostic de sinusite Acute respiratory aggrevation with a sinusitis diagnosis	◯ Oui / Yes ◯ Non / No
Combien de ARA How many acute respiratory aggrevations with sinusitis diagnosis	_____
ARA avec de diagnostic de crise d'asthme Acute respiratory aggrevation with asthma attack	◯ Oui / Yes ◯ Non / No
Combien de ARA	_____
Sympyomes respiratoires a bas bruit x DR	◯ Oui / Yes ◯ Non / No

	Oui / Yes	Non / No
SRBB avec toux 30/30 ou presque	○	○
SRBB avec toux 30/30 ou presque lors des boires	○	○
SRBB avec toux 30/30 ou presque au level AM	○	○
SRBB avec toux 30/30 ou presque à l'effort :	○	○
SRBB avec toux 30/30 ou presque au coucher	○	○
SRBB avec respiration ronchonnante	○	○
SRBB avec RR augmentee lors repas ou boires	○	○
SRBB avec wheezing occasionnel (WO)	○	○
SRBB avec wheezing occasionnel respondant au ventolin	○	○

Dyspnea d'effort	○ Oui / Yes ○ Non / No
Usage d'aerosols doseurs en continus x DV	○ Oui / Yes ○ Non / No
Usage de corticosteroides inhales sans LABA	○ Oui / Yes ○ Non / No
Si oui, nom	_____
Posologie	_____
Usage de corticosteriodes inhales avec LABA	○ Oui / Yes ○ Non / No
Si oui, nom	_____
Posologie	_____
Usage d'autre Rx inhale continu	○ Oui / Yes ○ Non / No
Si oui, nom	_____
Posologie	_____

4.1 Respiratory Function

Study Subject ID / Study Subject ID:	_____
[v_no]	
Rythme respiratoire	_____
SpO2 (AA)	_____ (Value of SpO2)
Auscultation pulmonaire anormale	○ Oui / Yes ○ Non / No
Auscultation pulmonaire avec ronchi	○ Oui / Yes ○ Non / No
Si oui, preciser	_____
Auscultation pulmonaire avec crepitants	○ Oui / Yes ○ Non / No
Si oui, preciser	_____
Auscultation pulmonaire avec sybillances	○ Oui / Yes ○ Non / No
Si oui, preciser	_____
Thorax	○ Symetrique ○ Asymetrique
Hippocratisme digit (clubbing)	○ Oui / Yes ○ Non / No
Spirometrie chez enfants ages de 6 ans et plus	○ Oui / Yes ○ Non / No
Capacity vital (CVF)	_____
VEMS	_____
VEMS/CVF	_____

DEMM	_____
DEP	_____
Radiographie pulmonaire faite lors de visit	○ Oui / Yes ○ Non / No
Radiographie pulmonaire anormale	○ Oui / Yes ○ Non / No
Si oui, preciser	_____
Radiographie pulmonaire x DV	○ Oui / Yes ○ Non / No
Si oui, preciser la date	_____ (JJ-MM-AAAA / DD-MM-YYYY)
Radiographie pulmonaire x DV anormale	○ Oui / Yes ○ Non / No
Si oui, preciser	_____
CT scan thorax x DV	○ Oui / Yes ○ Non / No
Si oui, preciser date	_____ (JJ-MM-AAAA / DD-MM-YYYY)
CT scan thorax x DV anormal	○ Oui / Yes ○ Non / No
Si oui, preciser	_____