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Nutritional Status at Age One Year in Patients Born with Esophageal Atresia: A Population-Based, Prospective Cohort Study

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Author contribution statement

Dr Suzanne Depoortère and Pr Frédéric Gottrand conceptualized and designed the study, collected and analyzed the data, and drafted, reviewed, and revised the manuscript.
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Dr Madeleine Aumar and Dr Audrey Nicolas critically reviewed the manuscript for important intellectual content.
Maéva Kyheng carried out the statistical analyses and revised the manuscript.
All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Keywords

undernutrition, stunting, Catch-up, Growth, prematurity, small for gestational age, Syndromic

Abstract

Word count: 253

Objective Despite recent progress in caring for patients born with esophageal atresia (EA), undernutrition and stunting remain common. Our study objective was to assess nutritional status in the first year after birth with EA and to identify factors associated with growth failure.
Study design We conducted a population-based study of all infants born in France with EA between 2010 and 2016. Through the national EA register, we collected prenatal to one-year follow-up data. We used body mass index and length-for-age ratio Z scores to define patients who were undernourished and stunted, respectively. Factors with $P < .20$ in univariate analyses were retained in a logistic regression model.
Results Among 1,154 patients born with EA, body mass index and length-for-age ratio Z scores at one year were available for about 61%. Among these, 15.2% were undernourished and 19% were stunted at the age of one year. There was no significant catch-up between ages six months and one year. Patients born preterm (41%), small for gestational age (17%), or with associated abnormalities (55%) were at higher risk of undernutrition and stunting at age one year ($P < .05$). Neither EA type nor surgical treatment was associated with growth failure.
Conclusion Undernutrition and stunting are common during the first year after birth in patients born with EA. These outcomes are significantly influenced by early factors, regardless of EA type or surgical management. Identifying high-risk patient groups with EA (i.e., those born preterm, small for gestational age, and/or with associated abnormalities) may guide early nutritional support strategies.

Contribution to the field

Despite recent progress in the care of patients born with Esophageal Atresia, wasting and stunting remain common, especially in the early years of life. Patients born with esophageal atresia are at higher risk of growth failure and do not show significant catch-up during their first year. Growth failure at one is mainly determined by neonatal factors : prematurity, intrauterine growth retardation and associated abnormalities. As our paper addresses the question of early nutrition and growth which is a critical issue in esophageal atresia using the largest population based register of this malformation, we do believe it corresponds to the target and audience of The Journal of Pediatrics.

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Ethics statements

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Nutritional Status at Age One Year in Patients Born with Esophageal Atresia: A Population-Based, Prospective Cohort Study

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Keywords : Undernutrition, stunting, catch-up, growth, prematurity, small for gestational age, syndromic

Abstract

Objective Despite recent progress in caring for patients born with esophageal atresia (EA), undernutrition and stunting remain common. Our study objective was to assess nutritional status in the first year after birth with EA and to identify factors associated with growth failure.

Study design We conducted a population-based study of all infants born in France with EA between 2010 and 2016. Through the national EA register, we collected prenatal to one-year follow-up data. We used body mass index and length-for-age ratio Z scores to define patients who were undernourished and stunted, respectively. Factors with $P < .20$ in univariate analyses were retained in a logistic regression model.

Results Among 1,154 patients born with EA, body mass index and length-for-age ratio Z scores at one year were available for about 61%. Among these, 15.2% were undernourished and 19% were stunted at the age of one year. There was no significant catch-up between ages six months and one year. Patients born preterm (41%), small for gestational age (17%), or with associated abnormalities (55%) were at higher risk of undernutrition and stunting at age one year ($P < .05$). Neither EA type nor surgical treatment was associated with growth failure.

Conclusion Undernutrition and stunting are common during the first year after birth in patients born with EA. These outcomes are significantly influenced by early factors, regardless of EA type or surgical management. Identifying high-risk patient groups with EA (i.e., those born preterm, small for gestational age, and/or with associated abnormalities) may guide early nutritional support strategies.

Short title: Nutritional Status in Patients with Esophageal Atresia

Abbreviations

BMI	Body mass index
CHARGE	Coloboma, heart defect, atresia choanae, retarded growth and development, genital hypoplasia, ear anomalies
CI	Confidence interval
EA	Esophageal atresia
GERD	Gastroesophageal reflux disease
LFA	Length-for-age
OR	Odds ratio
SD	Standard deviation
SGA	Small for gestational age
TEF	Tracheoesophageal fistula
VACTERL	Vertebral defects, anal atresia, cardiac, tracheoesophageal fistula, renal, and limb

Introduction

Esophageal atresia (EA), with or without tracheoesophageal fistula (TEF), is a rare congenital disorder that occurs in 1.9 per 10,000 births in France.[1] This condition makes oral feeding impossible and without surgical treatment, exposes the infant to inhalation of food, saliva, and gastric fluid.

In recent decades, thanks to medical and surgical care improvements, survival rates have increased to 95%.[1] Although more patients reach adulthood, they remain exposed to multiple complications during infancy,[2–4] including surgical (anastomosis leakage, TEF recurrence, anastomotic stricture), digestive (gastroesophageal reflux disease [GERD], esophageal dyskinesia, dumping syndrome, eosinophilic esophagitis, Barrett's esophagus), and respiratory (tracheomalacia, bronchopneumopathy), as well as complications from possible underlying conditions. These can cumulatively impair growth by reducing food intake (via dysphagia, vomiting, oral aversion, food blockages, or inhalation) and increasing energy expenditure (from dyspnea, inflammation, or frequent infections).

Previous retrospective[5–9] and monocentric[5–10] studies have shown a high risk of early-life undernutrition or stunting in patients born with EA. Identified risk factors include low birth weight,[10] low weight at discharge,[9] GERD,[7] anti-reflux surgery,[10] and needing a second surgery in the first year after birth.[11]

Preliminary analyses of the first two registry years showed that 15% of patients were underweight (Z score weight/age ≤ 2 standard deviations [SDs]) at the age of one year.[5] Herein, we evaluated nutritional status at ages six months and one year among a population-based cohort of patients born with EA. Secondary objectives were to examine growth dynamics (i.e., catch-up) from six months to one year and to identify risk factors for stunting and undernutrition at the age of one year.

Material and Methods

Data were from the French EA register, created in 2008. This population-based prospective epidemiological register[1] uses two forms to collect data on every patient born with EA in France. The first form is filled in during the initial hospitalization, the second is completed at the end of the first year of usual follow-up. Both forms were validated by a multidisciplinary committee of national experts, including epidemiologists, obstetricians, neonatologists, surgeons, and pediatricians[12] from 37 centers performing neonatal surgery in France and overseas.

Herein, we included all patients born with EA in France between January 1, 2010 and December 31, 2016. We extracted the following data: antenatal ultrasound suspicion of EA; pregnancy type (singleton, twins, multiples); gestational age at birth; sex; anthropometry at birth; type of EA according to Ladd classification[13]; associated abnormalities and types; syndromic associations[14,15]; surgery type (esophageal anastomosis with or without lengthening artifice, colic transposition or gastric transposition); anastomotic tension (subjectively reported by the surgeon at the time of surgery); age at surgery; patient condition at age one year (alive, dead, lost to follow-up); anthropometric measures at ages six months and one year; and possible complications during the first year after birth, including anastomotic stricture, need for esophageal dilatation, TEF recurrence, gastrostomy, GERD at age one year, anti-reflux surgery, aortopexy, and respiratory treatment at age one year.

Anthropometric measures were collected by doctors during dedicated consultations. Patients were measured lying down. Length was expressed in centimeters and weight in grams.

Small for gestational age (SGA) was defined as length and/or weight Z score at birth ≤ 2 SD, according to Fenton curves.[16] Delayed anastomosis was defined as anastomosis

performed more than 15 days after birth, including both patients with a long gap and those with severe comorbidities that delayed surgery (i.e., cardiac malformation and prematurity).

For each patient, we calculated body mass index (BMI) Z score and length-for-age (LFA) ratio Z score at ages six months and one year using the most recent French reference growth curves.[17] The curves updated in 2018 were based on an innovative big data method and are considered more representative of growth among contemporary French children.[17] BMI and LFA Z scores ≤ 2 SD were defined as undernutrition and stunting, respectively. We used corrected ages at six months and one year for patients born before 41 weeks of amenorrhea.[18]

Persistent GERD and the need for respiratory treatment at age one year were based on physician clinical evaluation.

We assessed the influences of neonatal characteristics, surgical type, and complications during the first year after birth. We compared type I EA with other EA types because the former is associated with a higher risk of surgical complications and comorbidities.[19–22]

The EA register was approved by the National Informatics and Privacy Committee (Commission Nationale de l'Informatique et des Libertés) and was evaluated by the National Committee of Registers. After information was given to the parents or caregivers both verbally and in writing, all data were deidentified. Using the validated questionnaires, data were collected prospectively by specialized physicians in each tertiary care center at initial neonatal hospitalization and at one-year follow-up. A clinical research assistant collected information from each center, and all forms were double-checked by two professionals to ensure quality and exhaustivity. The register was recorded in ClinicalTrials.gov (NCT02883725).

Statistical Analysis

Categorical variables are expressed as frequencies and percentages. Continuous variables are expressed as means (SDs), or as medians (interquartile ranges) for nonnormally distributed measures. Normality of distribution was assessed graphically and with the Shapiro–Wilk test. Differences in Z scores between six months and one year were analyzed using paired Wilcoxon signed-rank tests.

Associations between baseline characteristics and undernutrition and stunting at age one year were performed using chi-square or Fisher exact probability tests, as appropriate. To assess independent risk factors for wasting and stunting at the age of one year, baseline characteristics associated with $P < .20$ in univariate analyses were included in a backward-stepwise multivariate logistic regression model using a removal criterion of $P > .05$. Results from the final model are expressed as odds ratios (ORs) and 95% confidence intervals (CIs). To avoid case deletions due to missing data, multivariate analyses were performed after handling missing values by simple imputation using a regression switching approach (chained equations with m = 1).[23] The imputation procedure was performed under the missing at random assumption using all potential factors with a binary logistic regression model.

All statistical tests were two-tailed and $P < .05$ was considered statistically significant. Data were analyzed using SAS software package version 9.4 (SAS Institute, Cary, NC).

Results

Sample Characteristics

We included 1,154 patients (60% male). More than 40% of the sample were born prematurely and 17% were SGA. EA was associated with TEF in over 90% of cases, with other abnormalities in 55% of cases, and as part of a syndromic association (vertebral defects, anal atresia, cardiac, TEF, renal, and limb [VACTERL] or coloboma, heart defect, atresia choanae, retarded growth and development, genital hypoplasia, and ear anomalies [CHARGE]) in 30% of cases. Esophageal anastomosis was performed in almost 95% of patients and was delayed after 15 days in 12% of cases. During the first year after birth, 86 patients (7.8%) died and 39 (3.6%) were lost to follow-up. The sample characteristics are detailed in Table 1 and Figure 1.

Anthropometric Data

Birth weight was available for 99% of patients and birth length for 75%. Weight was available at both six months and one year for 75% of patients; length was available for 58% of patients at six months and 63% at one year. We were able to calculate Z scores at the age of one year for at least 60% of included patients.

Patients with missing anthropometric data at one year did not differ from those with available anthropometry regarding sex, SGA, birth term, associated abnormalities, prevalence of syndromic association, EA type, surgical treatment, or delayed anastomosis (Appendix 1).

Among patients with anthropometric data, 15.2% (n = 107/703) showed undernutrition and 19.4% (n = 138/710) showed stunting at one year. Neither BMI nor LFA Z score changed significantly between six months and one year. These data are reported in Table 2.

Risk Factors

In multivariate analyses, undernutrition and stunting were both associated with prematurity and SGA. At age one year, prematurity and SGA increased the risk of undernutrition by 2.43- and 2.02-fold, respectively, and the risk of stunting by 1.79- and 1.96-fold, respectively.

In addition, undernutrition was associated with VACTERL or CHARGE (OR = 2.05) whereas stunting was associated with the presence of at least one associated abnormality (OR = 1.68). These results are presented in Tables 3 and 4.

We did not find any significant association between surgery type and any complication during the first year after birth (not presented in Tables 3 and 4).

Discussion

Despite recent advances in caring for patients born with EA, these data indicate that they remain at higher risk of undernutrition and stunting at age one year compared with the general population. Indeed, the prevalence of undernutrition at age one year during the period most recently analyzed (15.2%) is similar to that during 2008–2009 (15%).[5] The lower rate of undernutrition, compared with stunting, at six months and one year suggests harmonious growth retardation in some patients, resulting in a normal BMI. Herein, only 9.2% of patients were born SGA, whereas 20.4% were stunted at age six months (Tables 1 and 2), suggesting that stunting at age one year was both constitutional and secondary to wasting.

Previous studies have reported different rates of undernutrition (8.8–20%)[6,10] whereas few stunting data are available.[10] Our ability to compare the current findings with previous reports is limited because the latter were retrospective, based on tertiary reference centers, included small samples, and used different anthropometric markers. Lacher et al. included 111 patients over a 22-year period, reporting a weight-for-age ratio below the 3rd percentile for 20% of patients at age one year.[6] A recent Dutch study of 126 patients born with EA during 1999–2013 found that 8.8% had wasting and 7.2% were stunted at the age of one year. These lower rates can be explained by the Dutch sample's lower prevalence of prematurity (31.7% versus 40.8% herein) and syndromic associations (12.7% versus 17.8% herein).[10]

Another important finding herein is that undernutrition (16.7%) and stunting (20.4%) appear early, during the first six months after birth, though only 14% of the sample was SGA based on weight and 9% based on length. This is likely explained by these infants' associated morbidities and the complexity of their early management. No catch-up in weight or length

occurred during the second half of the first year after birth, suggesting that persistent difficulties delay catch-up growth.[6,10,24]

We found that prematurity increased the risk of undernutrition and stunting at age one year by almost twofold. Because preterm infants are at higher risk of being undernourished or stunted at age one year compared with term infants, this finding indicates that the double burden of EA and prematurity compromise nutritional status at one year, independent of SGA status or syndromic associations.[25,26]

Similarly, being born SGA was also strongly and independently associated with undernutrition and stunting at age one year, emphasizing these patients' progressive and sometimes incomplete catch-up.[27,28]

Finally, growth retardation and undernutrition were significantly and independently related to the presence of associated abnormalities, syndromic or otherwise. This suggests that associated abnormalities may play a role in stunting and wasting beyond birth anthropometrics.

These cumulative findings emphasize that undernutrition and stunting originate from early factors, determined during the fetal and neonatal period, and are independent of surgical strategy and potential complications during the first year after birth. Indeed, in contrast to previous studies, we found no significant association with GERD,[7] anti-reflux surgery, [10] or needing a second surgery in the first year after birth.[11] Nevertheless, due to the design of our registry, objective assessment of some potential risk factors, including instrumental measurement of GERD, was lacking, which limits the strength of our conclusions.

Recent guidelines recommend the optional intervention of a dietician from age six months onward.[29] In practice, nutritional care starts during the initial hospitalization, and growth is monitored by surgeons and pediatricians at months one and three. In view of our

results, which confirm previous findings on the risks of early undernutrition and stunting, systematic early intervention by a nutritional support team should be considered. Our data highlight that particular attention must be paid to high-risk patients who are born preterm, SGA, or with associated abnormalities. Nutritional care for these patients must be closely monitored, multidisciplinary, and extended into adulthood to avoid complications related to undernutrition and to ensure optimal adult size.

This study's strengths include its uniquely large sample size, which is notable for a rare disorder like EA, thanks to the national EA register. Prospective recording of a large dataset, including prenatal information, allowed us to study a large panel of possible risk factors. One study limitation was the significant proportion of missing anthropometric data at six months and one year. Despite this, the risk of bias influencing these findings appears limited given the lack of difference between patients with or without missing data (we further reduced this risk by applying a missing data imputation process). Nevertheless, this study also presents an opportunity to reiterate the importance of repeated anthropometric measurements throughout follow-up with these patients. This study carried a low risk of selection bias because it was population-based, in contrast to most previous single-center reports.

Conclusion

Despite consistent progress in their medical and surgical care, patients born with EA are at risk of undernutrition and stunting at age one year, and these impacts appear as early as six months after birth. High-risk patients include those born preterm, SGA, and/or with associated abnormalities; these patients may thus benefit the most from early nutritional support. Further studies are needed to monitor the long-term nutritional status at key childhood periods, into adulthood.

Conflict of Interest

The authors have no conflicts of interest relevant to this article to disclose.
There are no prior publications or submissions with any overlapping information, including studies and patients.

Contributors' statement

Dr Suzanne Depoortère and Pr Frédéric Gottrand conceptualized and designed the study, collected and analyzed the data, and drafted, reviewed, and revised the manuscript.

Pr Alexandre Lapillonne, Dr Rony Sfeir, Pr Arnaud Bonnard, Dr Thomas Gelas, Dr Nicoleta Panait, Dr Pierre-Yves Rabattu, Dr Audrey Guignot, Pr Thierry Lamireau, Pr Sabine Irtan, Dr Edouard Habonimana, Dr Anne Breton, Dr Virginie Fouquet, Dr Hossein Allal, Dr Frédéric Elbaz, Dr Isabelle Talon, Dr Aline Ranke, Pr Michel Abely, Dr Jean-Luc Michel, Dr Joséphine Lirussi Borgnon, Dr Philippe Buisson, Dr Françoise Schmitt, Pr Hubert Lardy, Dr Thierry Petit, Dr Yann Chaussy, Dr Corinne Borderon, Pr Guillaume Levard, Dr Clara Cremillieux, Dr Cécilia Tolg, Pr Jean Breaud, Dr Olivier Jaby, Dr Céline Grossos, Dr Philine De Vries, Dr Myriam Arnould, Dr Cécile Pelatan, Dr Stephan Geiss, Dr Christophe Laplace participated in data collection and reviewed and revised the manuscript.

Dr Madeleine Aumar and Dr Audrey Nicolas critically reviewed the manuscript for important intellectual content.

Maéva Kyheng carried out the statistical analyses and revised the manuscript.

All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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References

1. Sfeir R, Rousseau V, Bonnard A, et al. Risk Factors of Early Mortality and Morbidity in Esophageal Atresia with Distal Tracheoesophageal Fistula: A Population-Based Cohort Study. *J Pediatr*. 2021;234:99-105.e1. doi:10.1016/j.jpeds.2021.02.064
2. Krishnan U, Mousa H, Dall'Oglio L, et al. ESPGHAN-NASPGHAN Guidelines for the Evaluation and Treatment of Gastrointestinal and Nutritional Complications in Children With Esophageal Atresia-Tracheoesophageal Fistula: *J Pediatr Gastroenterol Nutr*. 2016;63(5):550-570. doi:10.1097/MPG.0000000000001401
3. Gottrand M, Michaud L, Sfeir R, Gottrand F. Motility, digestive and nutritional problems in Esophageal Atresia. *Paediatr Respir Rev*. 2016;19:28-33. doi:10.1016/j.prrv.2015.11.005
4. Schier F, Korn S, Michel E. Experiences of a parent support group with the long-term consequences of esophageal atresia. *J Pediatr Surg*. 2001;36(4):605-610. doi:10.1053/jpsu.2001.22299
5. Schneider A, Blanc S, Bonnard A, et al. Results from the French National Esophageal Atresia register: one-year outcome. *Orphanet J Rare Dis*. 2014;9:206. doi:10.1186/s13023-014-0206-5
6. Lacher M, Froehlich S, von Schweinitz D, Dietz HG. Early and long term outcome in children with esophageal atresia treated over the last 22 years. *Klin Padiatr*. 2010;222(5):296-301. doi:10.1055/s-0030-1249610
7. Legrand C, Michaud L, Salleron J, et al. Long-term outcome of children with oesophageal atresia type III. *Arch Dis Child*. 2012;97(9):808-811. doi:10.1136/archdischild-2012-301730
8. Seo J, Kim DY, Kim AR, et al. An 18-year experience of tracheoesophageal fistula and esophageal atresia. *Korean J Pediatr*. 2010;53(6):705-710. doi:10.3345/kjp.2010.53.6.705
9. Harrington AW, Riebold J, Hernandez K, et al. Feeding and Growth Outcomes in Infants with Type C Esophageal Atresia Who Undergo Early Primary Repair. *J Pediatr*. Published online October 21, 2021:S0022-3476(21)00978-1. doi:10.1016/j.jpeds.2021.10.012
10. Vergouwe FWT, Spoel M, van Beelen NWG, et al. Longitudinal evaluation of growth in oesophageal atresia patients up to 12 years. *Arch Dis Child Fetal Neonatal Ed*. 2017;102(5):F417-F422. doi:10.1136/archdischild-2016-311598
11. Menzies J, Hughes J, Leach S, Belessis Y, Krishnan U. Prevalence of Malnutrition and Feeding Difficulties in Children With Esophageal Atresia. *J Pediatr Gastroenterol Nutr*. 2017;64(4):e100-e105. doi:10.1097/MPG.0000000000001436
12. Sfeir R, Michaud L, Sharma D, Richard F, Gottrand F. National Esophageal Atresia Register. *Eur J Pediatr Surg Off J Austrian Assoc Pediatr Surg Al Z Kinderchir*. 2015;25(6):497-499. doi:10.1055/s-0035-1569466
13. Ladd WE, Swenson O. Esophageal Atresia and Tracheo-esophageal Fistula. *Ann Surg*. 1947;125(1):23-40.
14. Hudson A, Trider CL, Blake K. CHARGE Syndrome. *Pediatr Rev*. 2017;38(1):56-59. doi:10.1542/pir.2016-0050
15. Solomon BD. VACTERL/VATER Association. *Orphanet J Rare Dis*. 2011;6:56. doi:10.1186/1750-1172-6-56
16. Fenton TR, Kim JH. A systematic review and meta-analysis to revise the Fenton

growth chart for preterm infants. *BMC Pediatr*. 2013;13:59. doi:10.1186/1471-2431-13-59
17. De nouvelles courbes de croissance de référence françaises. Salle de presse | Inserm. Published March 6, 2018. Accessed May 16, 2019. https://presse.inserm.fr/de-nouvelles-courbes-de-croissance-de-reference-francaises/30775/
18. Dietitians of Canada, Canadian Paediatric Society, College of Family Physicians of Canada, Community Health Nurses of Canada, Secker D. Promoting optimal monitoring of child growth in Canada: using the new WHO growth charts. *Can J Diet Pract Res Publ Dietit Can Rev Can Prat Rech En Diet Une Publ Diet Can*. 2010;71(1):e1-3. doi:10.3148/71.1.2010.54
19. Campos J, Tan Tanny SP, Kuyruk S, et al. The burden of esophageal dilatations following repair of esophageal atresia. *J Pediatr Surg*. 2020;55(11):2329-2334. doi:10.1016/j.jpedsurg.2020.02.018
20. Lu YH, Yen TA, Chen CY, et al. Risk factors for digestive morbidities after esophageal atresia repair. *Eur J Pediatr*. 2021;180(1):187-194. doi:10.1007/s00431-020-03733-1
21. Koivusalo AI, Sistonen SJ, Lindahl HG, Rintala RJ, Pakarinen MP. Long-term outcomes of oesophageal atresia without or with proximal tracheooesophageal fistula - Gross types A and B. *J Pediatr Surg*. 2017;52(10):1571-1575. doi:10.1016/j.jpedsurg.2017.04.021
22. Stadil T, Koivusalo A, Svensson JF, et al. Surgical treatment and major complications Within the first year of life in newborns with long-gap esophageal atresia gross type A and B - a systematic review. *J Pediatr Surg*. 2019;54(11):2242-2249. doi:10.1016/j.jpedsurg.2019.06.017
23. Buuren S van, Groothuis-Oudshoorn CGM. mice: Multivariate Imputation by Chained Equations in R. *J Stat Softw*. 2011;45(3). Accessed November 15, 2021. https://research.utwente.nl/en/publications/mice-multivariate-imputation-by-chained-equations-in-r
24. Little DC, Rescorla FJ, Grosfeld JL, West KW, Scherer LR, Engum SA. Long-term analysis of children with esophageal atresia and tracheoesophageal fistula. *J Pediatr Surg*. 2003;38(6):852-856.
25. Cooke RJ, Ainsworth SB, Fenton AC. Postnatal growth retardation: a universal problem in preterm infants. *Arch Dis Child Fetal Neonatal Ed*. 2004;89(5):F428-430. doi:10.1136/adc.2001.004044
26. Lapillonne A, Razafimahefa H, Rigourd V, Granier M, intervenants au séminaire Nutrition du prématuré du GEN-IdF. [Nutrition of the preterm infant]. *Arch Pediatr Organe Off Soc Francaise Pediatr*. 2011;18(3):313-323. doi:10.1016/j.arcped.2010.12.006
27. Arai S, Sato Y, Muramatsu H, et al. Risk factors for absence of catch-up growth in small for gestational age very low-birthweight infants. *Pediatr Int*. 0(0). doi:10.1111/ped.13939
28. Hokken-Koelega ACS, Ridder MAJD, Lemmen RJ, Hartog HD, Keizer-Schrama SMPFDM, Drop SLS. Children Born Small for Gestational Age: Do They Catch Up? *Pediatr Res*. 1995;38(2):267-271. doi:10.1203/00006450-199508000-00022
29. Protocole national de diagnostic et de soins (PNDS) : atrésie de l'œsophage. *Perfect En Pédiatrie*. 2019;2(2):98-115. doi:10.1016/j.perped.2019.04.002

Tables

Table 1. Sample Characteristics

			MD [a]
Male	n (%)	685 (59.4%)	0
Pregnancy	n (%)		0
○ Singleton		1099 (95.2%)	
○ Twins		53 (4.6%)	
○ Triplets		2 (0.2%)	
Prenatal diagnosis of EA	n (%)	287 (24.9%)	0
Weight at birth	n (%)	1147 (99%)	7
	mean ± SD	2,498 ± 713.1	
Length at birth	n (%)	865 (75%)	289
	mean ± SD	46.7 ± 4.2	
SGA [b] (weight or length)		118 (17%)	461
SGA for weight	n (%)	159 (14.1%)	26
SGA for length		78 (9.2%)	304
Birth term (weeks of amenorrhea)	n (%)		23
○ ≥ 37		670 (59.2%)	
○ 32–36		364 (32.2%)	
○ < 32		97 (8.6%)	
Total with associated abnormality	n (%)	628 (54.4%)	0
○ Neurologic	n (%)	86 (7.5%)	0
○ Renal	n (%)	113 (9.8%)	0
○ Cardiac	n (%)	326 (28.2%)	0
○ Limbs	n (%)	103 (8.9%)	0
○ Anorectal	n (%)	109 (9.4%)	0
○ Genital	n (%)	71 (6.2%)	0
○ Costovertebral	n (%)	199 (17.2%)	0
VACTERL [c] or CHARGE [d] association	n (%)	205 (17.8%)	0
Other syndromic association	n (%)	150 (13%)	0
EA[e] type	n (%)		18
○ Type I		89 (7.8%)	
○ Type II		17 (1.5%)	
○ Type III		1002 (88.2%)	
○ Type IV		11 (1%)	
○ Type V		17 (1.5%)	
Surgical treatment			*38*
1) Esophageal anastomosis	n (%)	**1090 (97.7%)**	
→ *Age at anastomosis (days)*	mean ± SD	14.5 ± 52	*19*
a. Standard anastomosis	n (%)	1056 (94.6%)	
b. Anastomosis with lengthening artifice	n (%)	34 (3%)	
2) Colic transposition	n (%)	**16 (1.4%)**	
→ *Age at colic transposition (days)*	mean ± SD	172.3 ± 113.8	*0*
3) Gastric transposition	n (%)	**10 (0.9%)**	
→ *Age at gastric transposition (days)*	mean +/ SD	157.2 ± 69.7	*0*
Anastomotic tension	n (%)	323 (30.7%)	103
Timing of esophageal anastomosis	n (%)		19
○ Primary (≤ 15 days)		944 (88.1%)	
○ Delayed (> 15 days)		127 (11.9%)	

Surgical approach	n (%)		
○ Thoracotomy		960 (84.3%)	15
○ Thoracoscopy		143 (12.9%)	45
○ Cervicotomy		7 (0.6%)	27
Outcome at one year of age	n (%)		64
○ Alive		965 (88%)	
○ Dead		86 (7.8%)	
○ Lost to follow-up		39 (3.6%)	

[a] Missing data, [b] Small for Gestational Age, [c] Vertebral defects, Anal atresia, Cardiac, Tracheoesophageal fistula, Renal and Limb, [d] Coloboma, Heart defect, Atresia choanae, Retarded growth and development, Genital hypoplasia, Ear anomalies, [e] Esophageal atresia

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Table 2. Anthropometrics at Ages Six Months and One Year

	Six months	One year
BMI [a] Z score n (%) Mean ± SD [b] Median (Q1 [c] ; Q3 [d])	 657 (56.9%) −0.7 ± 2.3 −0.7 (−1.7 ; 0.3)	 703 (60.9%) −0.7 ± 2.3 −0.6 (−1.6 ; 0.2)
LFA [e] Z score n (%) Mean ± SD [b] Median (Q1 [c] ; Q3 [d])	 662 (57.4%) −1 ± 1.9 −0.9 (−1.8 ; 0.1)	 710 (61.5%) −0.9 ± 1.7 −0.8 (−1.8 ; 0)
Undernutrition BMI [a] Z score < −2 SD [b] n/N (%) 95% CI	 110/657 (**16.7%**) [13.97 ; 19.82]	 107/703 (**15.2%**) [12.57 ; 17.88]
Stunting LFA [e] Z score < −2 SD [b] n/N (%) 95% CI	 135/662 (**20.4%**) [17.39 ; 23.67]	 138/710 (**19.4%**) [16.53 ; 22.35]
BMI [a] Z score delta between six months and one year n Mean Median IQR [f] *P*	 538 −0.01 ± 1.93 0.02 −0.64 ; 0.71 0.45	
LFA [e] Z score delta between six months and one year n Mean Median IQR [f] *P*	 546 0.22 ± 1.67 0.01 −0.51 ; 0.70 0.11	

[a] Body Mass Index, [b] Standard Deviation, [c] First Quartile, [d] Third Quartile, [e] Length-for-age, [f] Interquartile Range

Table 3. Predictive Factors for Undernutrition at Age One Year

	UNIVARIATE ANALYSIS			MULTIVARIATE ANALYSIS		
	UNDERNUTRITION BMI [a] Z Score < −2 SD [b]		*P*	Odds Ratio	95% CI [c]	*P*
	No (n = 596)	Yes (n = 107)				
Sex: Male	250 (41.9%)	37 (34.6%)	0.15			
Pregnancy: Multiple (versus singleton)	21 (3.5%)	2 (1.9%)	0.56			
Prenatal diagnosis	138 (23.2%)	35 (32.7%)	0.04			
SGA [d]	97 (20.5%)	24 (28.2%)	0.11	2.02	(1.26 ; 3.25)	0.003
Prematurity: birth < 37 weeks of amenorrhea	218 (36.6%)	61 (57%)	< 0.001	2.43	(1.59 ; 3.74)	< 0.001
At least one abnormality	309 (51.9%)	64 (59.8%)	0.13			
○ Neurologic	41 (6.9%)	8 (7.5%)	0.82			
○ Renal	60 (10.1%)	12 (11.2%)	0.72			
○ Cardiac	143 (24.0%)	29 (27.1%)	0.49			
○ Limbs	42 (7.0%)	13 (12.1%)	0.07			
○ Anorectal	50 (8.4%)	18 (16.8%)	0.007			
○ Genital	30 (5.0%)	12 (11.2%)	0.013			
○ Costovertebral	100 (16.8%)	26 (24.3%)	0.06			
VACTERL [e] or CHARGE [f] association	95 (15.9%)	31 (29.0%)	0.001	2.05	(1.26 ; 3.32)	0.004
Other syndromic association	65 (10.9%)	16 (15.0%)	0.23			
EA [g] type: Type I (versus Types II, III, IV and V)	47 (8.0%)	10 (9.3%)	0.63			
Esophageal anastomosis (versus colic and gastric transposition)	573 (96.1%)	105 (98.1%)	0.41			
Primary anastomosis (versus delayed anastomosis)	537 (90.1%)	90 (84.1%)	0.07			
Thoracotomy (versus thoracoscopy and cervicotomy)	503 (85.4%)	95 (89.6%)	0.25			

[a] Body Mass Index, [b] Standard Deviation, [c] Confidence Interval, [d] Small for Gestational Age, [e] Vertebral defects, Anal atresia, Cardiac, Tracheoesophageal fistula, Renal and Limb, [f] Coloboma, Heart defect, Atresia choanae, Retarded growth and development, Genital hypoplasia, Ear anomalies, [g] Esophageal atresia

Table 4. Predictive Factors for Stunting at Age One Year

	UNIVARIATE ANALYSIS			MULTIVARIATE ANALYSIS		
	STUNTING LFA [a] Z score < −2 SD [b]		*P*	Odds Ratio	95% CI [c]	*P*
	No (n = 572)	Yes (n = 138)				
Sex: Male	239 (41.8%)	51 (37%)	0.30			
Pregnancy: Multiple (versus singleton)	19 (3.3%)	4 (2.9%)	1.00			
Prenatal diagnosis	144 (25.2%)	32 (23.4%)	0.65			
SGA [d]	87 (19.1%)	36 (33%)	0.002	1.96	(1.28 ; 3.00)	0.002
Prematurity: birth < 37 weeks of amenorrhea	212 (37.1%)	69 (50%)	0.005	1.79	(1.22 ; 2.62)	0.003
At least one abnormality	288 (50.3%)	88 (64.2%)	0.003	1.68	(1.13 ; 2.48)	0.01
○ Neurologic	41 (7.2%)	8 (5.8%)	0.57			
○ Renal	61 (10.7%)	13 (9.4%)	0.67			
○ Cardiac	130 (22.7%)	42 (30.4%)	0.06			
○ Limbs	41 (7.2%)	14 (10.1%)	0.24			
○ Anorectal	52 (9.1%)	16 (11.6%)	0.37			
○ Genital	31 (5.4%)	11 (8%)	0.25			
○ Costovertebral	95 (16.6%)	32 (23.2%)	0.07			
VACTERL [e] or CHARGE [f] association	94 (16.4%)	32 (23.2%)	0.06			
Other syndromic association	59 (10.3%)	25 (18.1%)	0.01			
EA [g] type: Type I (versus Types II, III, IV and V)	46 (8.1%)	11 (8.0%)	0.96			
Esophageal anastomosis (versus colic and gastric transposition)	552 (96.5%)	133 (96.4%)	1.00			
Primary anastomosis (versus delayed anastomosis)	518 (90.6%)	116 (84.1%)	0.03			
Thoracotomy (versus thoracoscopy and cervicotomy)	488 (86.2%)	117 (86%)	0.95			

[a] Length-for-age, [b] Standard Deviation, [c] Confidence Interval, [d] Small for Gestational Age, [e] Vertebral defects, Anal atresia, Cardiac, Tracheoesophageal fistula, Renal and Limb, [f] Coloboma, Heart defect, Atresia choanae, Retarded growth and development, Genital hypoplasia, Ear anomalies, [g] Esophageal atresia

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Figure 1.TIF