Risk Factors for Short- and Long-Term Morbidity in Children with Esophageal Atresia

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Objective To describe short- (first year of age) and long-term (after 1 year of age) outcome in patients with esophageal atresia and identify early predictive factors of morbidity in the first month of life.

Study design Charts of children with esophageal atresia born January 1990 to May 2005 were reviewed. A complicated evolution was defined as the occurrence of at least 1 complication: severe gastroesophageal reflux, esophageal stricture requiring dilatations, recurrent fistula needing surgery, need for gavage feeding for ≥3 months, severe tracheomalacia, chronic respiratory disease, and death.

Results A total of 134 patients were included. Forty-nine percent of patients had a complicated evolution before 1 year of age, and 54% had a complicated evolution after 1 year. With bivariate analysis, predictive variables of a complicated evolution were demonstrated, including twin birth, preoperative tracheal intubation, birth weight <2500 g, long gap atresia, anastomotic leak, postoperative tracheal intubation ≥5 days, and inability to be fed orally by the end of the first month. After 1 year of age, the complicated evolution was only associated with long gap atresia and inability to be fed orally in the first month. A hospital stay ≥30 days was associated with a risk of a complicated evolution at 1 year and after 1 year of age (odds ratio, 9.3 [95% CI, 4.1-20.8] and 3.5 [95% CI, 1.6-7.6], respectively).

Conclusion Early factors are predictive of morbidity in children with esophageal atresia. *(J Pediatr 2010;156:755-60)*.

See related articles, p 761 and p 852

Esophageal atresia with tracheoesophageal fistula (TEF) is a common congenital anomaly, with an incidence of 1 in 2500 to 1 in 3000.[1] Since the first successful surgery in 1941,[2] anesthetic, surgical, and neonatal care have improved tremendously, and now the long-term survival rate of these children approaches 100% in the absence of other malformations.[1,3-7] Subsequent to this increase in survival, morbidity associated with esophageal atresia/TEF repair has become an important issue in the treatment of these children.[8,9]

Clinical experience is that the outcome after esophageal atresia/TEF repair is variable; some patients have an uneventful postoperative period, and other patients experience several esophageal or respiratory complications that significantly affect their health status. The complications include gastroesophageal reflux,[9-12] esophageal strictures,[11,12] chronic dysphagia,[10,12,13] recurrent fistula,[11] pulmonary infections,[11,14] asthma,[12-14] and tracheomalacia.[12] Later, Barrett's esophagus,[8,15-17] esophageal carcinoma,[8,18-21] and scoliosis[22] have also been reported. However, although the nature of these complications is well-described, their occurrence, association, and sequence during the first years of life are less well known, although in clinical practice patients with esophageal atresia/TEF often have multisystem complications. Moreover, although several risk factors have been proposed for mortality[3,23-25] or specific complications[10,14,26,27] in this population, there are no data on risk factors for the development of global morbidity.

We hypothesized that factors present in the first month of life are predictive of respiratory and digestive complications in children who underwent surgery for esophageal atresia/TEF. The aims of this study were to describe the complications and the global outcome of these patients and to identify early predictive factors of short-term (≤1 year of age) and long-term (>1 year of age) morbidity.

Methods

We retrospectively reviewed the charts of all patients with esophageal atresia/TEF who were born January 1990 to May 2005 and were observed at St. Justine Hospital. The period from 1990 to 2005 represents a stable period in neonatal care, surgery techniques, cardiac care, and mortality.[5] Patients were excluded from the analysis when there was insufficient data in the hospital chart to determine clinical outcomes or a death in the first month of life.

TEF	Tracheoesophageal fistula

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Data were collected with standardized data abstraction forms by a single research assistant. The abstracted information included: 1) patient level variables (birth weight, type of atresia, cardiac, and other anomalies, VACTERL association (combination of 3 anomalies of vertebral, anorectal, cardiac, tracheoesophageal fistula and esophageal atresia, renal, or limb anomalies), associated syndromes, chromosomal anomalies, neonatal respiratory distress syndrome, preoperative pneumonia, and preoperative tracheal intubation; 2) surgery level variables ("long gap," excessive tension at the anastomosis as described by the surgeon, 1-step surgery, 2-step surgery). A "long gap" between the 2 ends of the esophagus in the cases of esophageal atresia was defined as a gap longer than 3 cm or greater than the height of 2 vertebral bodies[28]; 3) first month postoperative level variables (postoperative intubation ≥5 days, pneumothorax, chylothorax, anastomotic leak, empyema, early recurrent fistula, persistent inability to start oral feeding, or need of gavage feeding at the end of the first month); and 4) duration of hospital stay.

Definition of a Complicated Evolution

Because, in clinical practice, patients with esophageal atresia/TEF have multi-system complications, we broadly defined a complicated evolution as clinically significant objective events that require therapeutic intervention likely resulting in a negative impact on the child and family's quality of life. Practically, a complicated evolution was defined as the occurrence of at least 1 of these complications: severe gastroesophageal reflux (defined by presence of moderate to severe esophagitis on biopsy and/or intestinal metaplasia on esophageal biopsies and/or need of fundoplication and/or need of jejunal feeding), esophageal stricture requiring >1 dilatations, recurrent TEF requiring surgery, need of gavage feeding for ≥3 months, severe tracheomalacia (defined by the presence of cyanotic spells and bronchoscopy findings, the requirement of an aortopexy or tracheostomy, or both), severe chronic respiratory disease (respirologist diagnosis, oxygen dependence, or both), and death.

Statistical Analysis

Inter-rater reliability of the abstracted data was assessed with a random review of 60 charts. Kappa statistics and percent agreement were calculated for the categorical variables (all dichotomous) and intra-class correlation coefficients for the continuous variables. Variables with a Kappa or intra-class correlation coefficients ≤0.4 were excluded from further analysis, resulting in the removal of these variables: preoperative pneumonia, recurrent fistula in the first month, need for cardiorespiratory resuscitation, oral hypersensitivity, recurrent pneumonia, and asthma.

Statistical analysis was performed with Stata software version 9.0 (StrataCorp, Washington, DC). Appropriate descriptive statistics were used to present the distribution of clinical outcomes and predictor variables in the study population. Comparisons between groups were done with a student *t* test or Kruskal-Wallis 1-way analysis of variance by ranks for continuous variables and χ^2 test for count variables. Logistic regression models were estimated to determine predictors of a complicated evolution during the first year of life and after in children with surgery for esophageal atresia/TEF. For inclusion in the models, a minimum of 3 and 15 months of follow-up data were required for the first year and long-term models, respectively. Continuous variables were assessed with receiver operating characteristic curves to determine optimal cut-off values predictive of the outcome. A *P* value <.05 was considered to be significant. The Research and Ethics Committee at St. Justine Hospital approved the study.

Results

A total of 156 patients with esophageal atresia/TEF born between January 1990 and May 2005 were seen at St. Justine Hospital (Figure 1). In 8 charts, there were insufficient data or follow-up, and of the 148 remaining patients, 14 died in the first month of life and were therefore not eligible for analysis. Causes of mortality included chromosomal anomalies (n = 6), multiple organ failure (n = 4), hydrops fetalis (n = 1), anencephaly (n = 1), tracheal atresia (n = 1), and respiratory failure (n = 1). The median follow-up length of the study population was 64 months (range, 3-189 months); 94% of the patients were observed for >12 months (3 children died in the first year), and 81% were observed for >24 months. One hundred thirty-four patients fulfilled our inclusion criteria. Sixty-six patients were female (49%), and the mean birth weight was 2580 g ± 711 g (range, 1050-4334 g). The median gestational age was 38 weeks (range, 25-42 weeks). Eight patients (6%) were born of twin pregnancy. Forty-five patients (34%) had the VACTERL association.

According to Gross classification,[29] 112 (84%) of our patients had esophageal atresia type C (distal fistula), 9 (7%) had type A (isolated atresia), 8 (6%) had type E (isolated fistula), 3 (2%) had type B (proximal fistula), and 2 (1%) had type D (proximal and distal fistulas). A long gap atresia was present in 21 patients (16%). A thoracotomy was performed in all patients who underwent surgery; 112 (84%) had a primary anastomosis, of which 24 (18%) were described as being under tension by the attending surgeon. Twenty-four patients (18%) had a gastrostomy placed at the moment of the first surgery. In the early postoperative period (<1 month), a pneumothorax developed in 15 patients (11%), an anastomotic leak developed in 16 patients (12%), a chylothorax developed in 7 patients (5%), and 49 patients (37%) required gavage feeding. The median length of hospital stay was 22 days (interquartile range, 13-84); the length of hospital stay ranged from 8 to 684 days.

Evolution of the Population

The rate of complications according to the age in children with a complicated evolution is detailed in Figure 2. In the first year of life, 65 (49%) of the patients had a complicated evolution (Figure 1); of these 65 patients, 33, 14, and 18 experienced 1, 2, and ≥3 complications, respectively. Similarly, 62 of 116 patients (53%) had a complicated evolution after 1

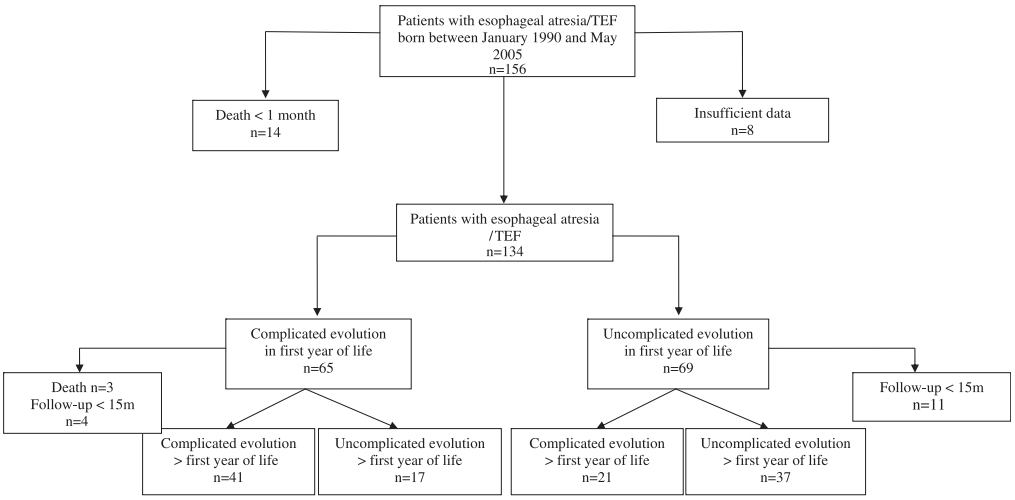

Figure 1. Distribution of the 156 children with esophageal atresia/TEF according to their evolution.

year of age; 29, 14, and 19 of these patients experienced 1, 2, and ≥3 complications, respectively. Of the 65 patients with a complicated evolution in the first year of life, 41 (63%) continued to be classified as having a complicated evolution after the first year of life, and of the 69 patients without documented serious complications in the first year of life, 21 (30%) had a complicated evolution after the first year of life.

Predictors of a Complicated Evolution after Surgery for Esophageal Atresia

Analysis of individual predictor variables and a complicated evolution in the first year and after the first year of life in children with esophageal atresia/TEF demonstrated significant predictors (Tables I and II). In the first year of life, the predictors associated with a complicated evolution were related to the patient (twin birth, birth weight <2500 g, VACTERL), the malformation (type A, long gap, and anastomotic leak), the initial respiratory condition (preoperative intubation, tracheal intubation >5 days), or the inability to be fed orally by the end of the first month (Table I). After the first year, malformation-related variables and inability to tolerate oral feeding by the end of the first month were still more frequent in children with a complicated evolution (Table II).

The stability of the estimates around certain variables was poor because of small numbers, and therefore multiple logistic regression models were not interpretable. The length of initial hospital stay was examined as a proxy of a complicated neonatal and surgical course by using receiver operating characteristic curves (area under the curve = 0.83, 95%

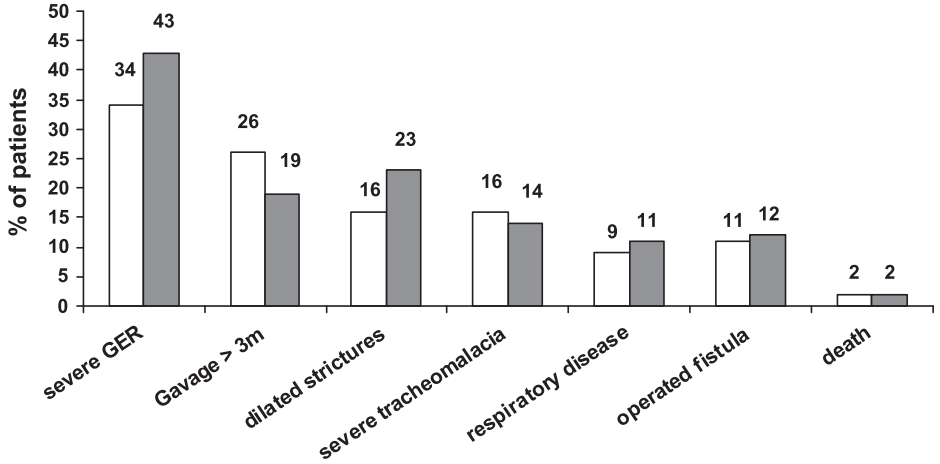

Figure 2. Complications in the 134 patients analyzed in the first year of life (□) and after the first year of life (■). GER, gastroesophageal reflux.

Table I. Distribution of predictor variables per outcome status in first year of life (n = 134)

Predictor variables (identified during the 1st month of life)	Complicated evolution† in the 1st year of life n = 65 number (%)	Non-complicated evolution in the 1st year of life n = 69 number (%)
Twin birth	8 (12)*	0 (0)
Preoperative		
Pneumonia	3 (5)	7 (10)
Neonatal RDS	3 (5)	1 (1)
Tracheal intubation	16 (25)*	2 (3)
Birth weight <2500 g	40 (62)*	17 (25)
VACTERL	28 (43)*	17 (25)
Type of atresia*		
Type A	8 (12)	1 (1)
Type B	3 (5)	0 (0)
Type C	51 (78)	61 (88)
Type D	2 (3)	0 (0)
Type E	1 (2)	7 (10)
Long gap	19 (29)*	2 (3)
2-step surgery	20 (31)*	2 (3)
Anastomotic leak	13 (20)*	3 (4)
Pneumothorax	11 (17)	4 (6)
Tracheal intubation ≥5days	23 (36)*	5 (7)
Chylothorax	6 (9)	1 (1)
Need of gavage feeding	35 (54)*	14 (20)

RDS, Respiratory distress syndrome; *VACTERL,* combination of 3 anomalies out of vertebral, anorectal, cardiac, tracheoesophageal fistula, and esophageal atresia, renal or limb anomalies.
*$P < .05$ versus patients with non-complicated evolution (2-tailed χ^2 test).
†Complicated evolution: see definition in the Methods section.

CI, 0.75-0.90; and area under the curve = 0.64, 95% CI, 0.54-0.71 for a complicated evolution during the first year and after the first year, respectively). Length of stay ≥30 days (identified from inspection of the receiver operating characteristic curves) was associated with many of the predictor variables of interest, including twin birth, preoperative respiratory problems, birth weight <2500 g, and postoperative feeding difficulties. The odds of a complicated evolution in children with an initial length of stay in hospital ≥30 days was 9.3 (95% CI, 4.1-20.8) and 3.5 (95% CI, 1.6-7.6) times greater than in children discharged before 30 days at 1 year and after 1 year of age, respectively.

Discussion

Survival of children with esophageal atresia/TEF has improved dramatically in the last 40 years.[4,7,12] Subsequently, the focus has shifted to the short- and long-term morbidity

Table II. Distribution of predictor variables per outcome status after the first year of life (n = 116)

Predictor variables (identified during the 1st month of life)	Complicated evolution† after the 1st year of life n = 62 number (%)	Non-complicated evolution after the 1st year of life n = 54 number (%)
Twin birth	6 (10)	2 (4)
Preoperative		
Pneumonia	4 (6)	3 (6)
Neonatal RDS	3 (5)	1 (2)
Tracheal intubation	13 (21)	4 (7)
Birth weight <2500 g	29 (47)	24 (44)
VACTERL	24 (39)	16 (30)
Type of atresia*		
Type A	6 (10)	3 (6)
Type B	3 (5)	0 (0)
Type C	53 (85)	45 (83)
Type D	0 (0)	1 (2)
Type E	0 (0)	5 (9)
Long gap	18 (29)*	3 (6)
2-step surgery	17 (27)*	3 (6)
Anastomotic leak	11 (18)	5 (9)
Pneumothorax	6 (10)	8 (15)
Tracheal intubation ≥5days	15 (24)	10 (19)
Chylothorax	4 (6)	2 (4)
Need of gavage feeding	29 (47)*	11 (20)
Complex evolution in 1st year of life	41 (66)*	17 (31)

*$P < .05$ versus patients with non-complicated evolution (2-tailed χ^2 test).
†Complicated evolution: see definition in the Methods section.

associated with these congenital anomalies.[9] In our cohort of children with esophageal atresia/TEF, complications that require therapeutic interventions occur in more than half the patients both in the first year of life and after the first year. More important, significant problems developed at an older age in some of the children who did not have complications identified during the first year of life. In our cohort, variables associated with a complicated clinical evolution in the first year of life included patient variables (twin birth, birth weight <2500 g), type of malformation (type A and long gap), initial respiratory complications (preoperative intubation, tracheal intubation >5 days), and the inability to feed orally by the end of the first month. After the first year, malformation-related variables and inability to tolerate oral by the end of the first month were still more frequent in children with a complicated evolution. Because easily usable in clinical practice, the length of initial hospital stay was used as a proxy of neonatal disease severity and showed that a length of stay longer than 30 days is highly associated with a poor outcome during and after the first year of life.

This study is the first to show predictive factors of morbidity in a cohort of children with esophageal atresia/TEF. Previous studies have reported various classifications of patients for prediction of mortality[3,23-25] or have described in details the esophageal atresia/TEF-related digestive, respiratory and orthopedic complications (for a review see[9]). Determination of risk factors of a complicated evolution following esophageal atresia/TEF repair could positively impact the long-term prognosis of these children by identifying those who may benefit from a more intensive follow-up program. Theoretically, this would allow earlier management of medical and surgical complications thus decreasing the long-term morbidity reported in these children. Such individualized patient adapted care may also reassure the parents and decrease the impact of the malformation on family life.[30]

In the present series, the survival rate, the causes of mortality and the incidence of complications are in keeping with previous reports from other institutions suggesting that our data may apply to other centers.[5,9] However, the validity of the predictive factors requires confirmation in other centers since some variables may be center-dependent. For example, in our center, most patients are intubated <48 hours postoperatively, which makes an intubation >5 days an indicator of severe respiratory disease or other problem. This may not be representative of the postoperative practices in other centers.[31,32] Another limitation of this study is that there were small numbers of patients in certain subgroups, which limited our analysis to models with single predictor variables. Subsequently, the role of confounding was not evaluated, and therefore it is possible that some of the predictive variables reported in this study may not be significant in an adequately powered multivariate analysis. In light of this limitation, a proxy related to multiple predictor variables of interest and duration of hospital stay was used in the final analysis. Despite these limitations, we believe that the variables reported here will be helpful clinically in the selection of patients who need a more careful follow-up.

In children who undergo surgery for an esophageal atresia/TEF, clinically significant morbidity occurs in >50% before and after 1 year of age. We have identified, in the first month of life, early predictive factors of short- and long-term global morbidity. We propose that these factors may be used to identify patients who will benefit from a more intensive medical follow-up program. ■

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