Université de Poitiers

Faculté de Médecine et Pharmacie

ANNEE 2021

THESE

POUR LE DIPLOME D'ETAT
DE DOCTEUR EN MEDECINE
(Décret du 25 novembre 2016)

Présentée et soutenue publiquement
Le 28 mai 2021 à Poitiers
Par Madame Agate BOURG

Morbidité à moyen terme des enfants avec une atrésie de l'œsophage : étude cas-témoin long gap versus non long gap

COMPOSITION DU JURY

Président : Monsieur le Professeur Guillaume LEVARD

Membres : Monsieur le Professeur Frédéric GOTTRAND

Madame le Docteur Véronique DIAZ

Directrice de thèse : Madame le Docteur Marie AUGER HUNAULT

Université de Poitiers

Faculté de Médecine et Pharmacie

ANNEE 2021

THESE

POUR LE DIPLOME D'ETAT
DE DOCTEUR EN MEDECINE
(Décret du 25 novembre 2016)

Présentée et soutenue publiquement
Le 28 mai 2021 à Poitiers
Par Madame Agate BOURG
Née le 23/02/1993

Morbidité à moyen terme des enfants avec une atrésie de l'œsophage : étude cas-témoin long gap versus non long gap

COMPOSITION DU JURY

Président : Monsieur le Professeur Guillaume LEVARD

Membres : Monsieur le Professeur Frédéric GOTTRAND

Madame le Docteur Véronique DIAZ

Directrice de thèse : Madame le Docteur Marie AUGER HUNAULT

Année universitaire 2020 - 2021

LISTE DES ENSEIGNANTS DE MEDECINE

Professeurs des Universités-Praticiens Hospitaliers

- BOULETI Claire, cardiologie
- BOURMEYSTER Nicolas, biologie cellulaire
- BRIDOUX Frank, néphrologie
- BURUCOA Christophe, bactériologie – virologie
- CHEZE-LE REST Catherine, biophysique et médecine nucléaire
- CHRISTIAENS Luc, cardiologie
- CORBI Pierre, chirurgie thoracique et cardio-vasculaire
- DAHYOT-FIZELIER Claire, anesthésiologie – réanimation
- DEBAENE Bertrand, anesthésiologie réanimation
- DEBIAIS Françoise, rhumatologie
- DROUOT Xavier, physiologie
- DUFOUR Xavier, Oto-Rhino-Laryngologie
- FAURE Jean-Pierre, anatomie
- FRASCA Denis, anesthésiologie-réanimation
- FRITEL Xavier, gynécologie-obstétrique
- GERVAIS Elisabeth, rhumatologie
- GICQUEL Ludovic, pédopsychiatrie
- GILBERT Brigitte, génétique
- GOMBERT Jean-Marc, immunologie
- GOUJON Jean-Michel, anatomie et cytologie pathologiques
- GUILLEVIN Rémy, radiologie et imagerie médicale
- HAUET Thierry, biochimie et biologie moléculaire
- INGRAND Pierre, biostatistiques, informatique médicale
- ISAMBERT Nicolas, cancérologie
- JAAFARI Nematollah, psychiatrie d'adultes
- JABER Mohamed, cytologie et histologie
- JAYLE Christophe, chirurgie thoracique t cardio-vasculaire
- KARAYAN-TAPON Lucie, cancérologie
- KEMOUN Gilles, médecine physique et de réadaptation **(en disponibilité)**
- KRAIMPS Jean-Louis, chirurgie générale
- LECLERE Franck, chirurgie plastique, reconstructrice
- LECRON Jean-Claude, biochimie et biologie moléculaire
- LELEU Xavier, hématologie
- LEVARD Guillaume, chirurgie infantile
- LEVEQUE Nicolas, bactériologie-virologie
- LEVEZIEL Nicolas, ophtalmologie
- MACCHI Laurent, hématologie
- MCHEIK Jiad, chirurgie infantile
- MEURICE Jean-Claude, pneumologie
- MIGEOT Virginie, santé publique
- MILLOT Frédéric, pédiatrie, oncologie pédiatrique
- MIMOZ Olivier, anesthésiologie – réanimation
- NEAU Jean-Philippe, neurologie
- ORIOT Denis, pédiatrie
- PACCALIN Marc, gériatrie
- PERAULT-POCHAT Marie-Christine, pharmacologie clinique
- PERDRISOT Rémy, biophysique et médecine nucléaire
- PIERRE Fabrice, gynécologie et obstétrique
- PRIES Pierre, chirurgie orthopédique et traumatologique
- RAMMAERT-PALTRIE Blandine, maladies infectieuses
- RICHER Jean-Pierre, anatomie
- RIGOARD Philippe, neurochirurgie
- ROBERT René, réanimation
- ROBLOT France, maladies infectieuses, maladies tropicales
- ROBLOT Pascal, médecine interne
- RODIER Marie-Hélène, parasitologie et mycologie (**retraite 01/03/2021**)
- SAULNIER Pierre-Jean, thérapeutique
- SCHNEIDER Fabrice, chirurgie vasculaire
- SILVAIN Christine, hépato-gastro- entérologie
- TASU Jean-Pierre, radiologie et imagerie médicale
- THIERRY Antoine, néphrologie
- THILLE Arnaud, réanimation
- TOUGERON David, gastro-entérologie
- WAGER Michel, neurochirurgie
- XAVIER Jean, pédopsychiatrie

Maîtres de Conférences des Universités-Praticiens Hospitaliers

- ALBOUY-LLATY Marion, santé publique (**en mission 2020/21**)
- ALLAIN Géraldine, chirurgie thoracique et cardio-vasculaire
- BEBY-DEFAUX Agnès, bactériologie – virologie **(en cours d'intégration PH)**
- BEN-BRIK Eric, médecine du travail **(en détachement)**
- BILAN Frédéric, génétique
- BOISSON Matthieu, anesthésiologie-réanimation et médecine péri-opératoire (**en mission 1 an à/c nov.2020**)
- CASTEL Olivier, bactériologie - virologie – hygiène
- CAYSSIALS Emilie, hématologie
- COUDROY Rémy, réanimation
- CREMNITER Julie, bactériologie – virologie
- DIAZ Véronique, physiologie
- FROUIN Eric, anatomie et cytologie pathologiques
- GACHON Bertrand, gynécologie-obstétrique
- GARCIA Magali, bactériologie-virologie
- JAVAUGUE Vincent, néphrologie
- KERFORNE Thomas, anesthésiologie-réanimation et médecine péri-opératoire
- LAFAY-CHEBASSIER Claire, pharmacologie clinique
- LIUU Evelyne, gériatrie
- MARTIN Mickaël, médecine interne
- PALAZZO Paola, neurologie (**en dispo 1 an**)
- PERRAUD Estelle, parasitologie et mycologie
- SAPANET Michel, médecine légale
- THUILLIER Raphaël, biochimie et biologie moléculaire

Professeur des universités

- PELLERIN Luc, biochimie et biologie moléculaire

Professeur des universités de médecine générale

- BINDER Philippe

Professeurs associés de médecine générale

- BIRAULT François
- FRECHE Bernard
- MIGNOT Stéphanie
- PARTHENAY Pascal
- VALETTE Thierry
- VICTOR-CHAPLET Valérie

Maîtres de Conférences associés de médecine générale

- AUDIER Pascal
- ARCHAMBAULT Pierrick
- BRABANT Yann

Enseignants d'Anglais

- DEBAIL Didier, professeur certifié

Professeurs émérites

- ALLAL Joseph, thérapeutique (08/2020)
- BATAILLE Benoît, neurochirurgie (08/2020)
- CARRETIER Michel, chirurgie générale (08/2021)
- DORE Bertrand, urologie (08/2020)
- GIL Roger, neurologie (08/2020)
- GOMES DA CUNHA José, médecine générale (08/2021)
- GUILHOT-GAUDEFFROY François, hématologie et transfusion (08/2020)
- HERPIN Daniel, cardiologie (08/2020)
- KITZIS Alain, biologie cellulaire (16/02/2021)
- MARECHAUD Richard, médecine interne (24/11/2020)
- MAUCO Gérard, biochimie et biologie moléculaire (08/2021)
- RICCO Jean-Baptiste, chirurgie vasculaire (08/2020)
- SENON Jean-Louis, psychiatrie d'adultes (08/2020)
- TOUCHARD Guy, néphrologie (08/2021)

Professeurs et Maîtres de Conférences honoraires

- AGIUS Gérard, bactériologie-virologie
- ALCALAY Michel, rhumatologie
- ARIES Jacques, anesthésiologie-réanimation
- BABIN Michèle, anatomie et cytologie pathologiques
- BABIN Philippe, anatomie et cytologie pathologiques
- BARBIER Jacques, chirurgie générale (ex-émérite)
- BARRIERE Michel, biochimie et biologie moléculaire
- BECQ-GIRAUDON Bertrand, maladies infectieuses, maladies tropicales (ex-émérite)
- BEGON François, biophysique, médecine nucléaire
- BOINOTCatherine, hématologie – transfusion
- BONTOUX Daniel, rhumatologie (ex-émérite)
- BURIN Pierre, histologie
- CASTETS Monique, bactériologie -virologie – hygiène
- CAVELLIER Jean-François, biophysique et médecine nucléaire
- CHANSIGAUD Jean-Pierre, biologie du développement et de la reproduction
- CLARAC Jean-Pierre, chirurgie orthopédique
- DABAN Alain, cancérologie radiothérapie (ex-émérite)
- DAGREGORIO Guy, chirurgie plastique et reconstructrice
- DESMAREST Marie-Cécile, hématologie
- DEMANGE Jean, cardiologie et maladies vasculaires
- EUGENE Michel, physiologie (ex-émérite)
- FAUCHERE Jean-Louis, bactériologie-virologie (ex-émérite)
- FONTANEL Jean-Pierre, Oto-Rhino Laryngologie (ex-émérite)
- GRIGNON Bernadette, bactériologie
- GUILLARD Olivier, biochimie et biologie moléculaire
- GUILLET Gérard, dermatologie
- JACQUEMIN Jean-Louis, parasitologie et mycologie médicale
- KAMINA Pierre, anatomie (ex-émérite)
- KLOSSEK Jean-Michel, Oto-Rhino-Laryngologie
- LAPIERRE Françoise, neurochirurgie (ex-émérite)
- LARSEN Christian-Jacques, biochimie et biologie moléculaire
- LEVILLAIN Pierre, anatomie et cytologie pathologiques
- MAIN de BOISSIERE Alain, pédiatrie
- MARCELLI Daniel, pédopsychiatrie (ex-émérite)
- MARILLAUD Albert, physiologie
- MENU Paul, chirurgie thoracique et cardio-vasculaire (ex-émérite)
- MORICHAU-BEAUCHANT Michel, hépato-gastro-entérologie
- MORIN Michel, radiologie, imagerie médicale
- PAQUEREAU Joël, physiologie
- POINTREAU Philippe, biochimie
- POURRAT Olivier, médecine interne (ex-émérite)
- REISS Daniel, biochimie
- RIDEAU Yves, anatomie
- SULTAN Yvette, hématologie et transfusion
- TALLINEAU Claude, biochimie et biologie moléculaire
- TANZER Joseph, hématologie et transfusion (ex-émérite)
- TOURANI Jean-Marc, cancérologie
- VANDERMARCQ Guy, radiologie et imagerie médicale

Remerciements :

À ma directrice de thèse, Madame le Docteur Marie Auger Hunault,

D'abord ma co-interne puis ma chef, j'ai grandi durant ces quelques années à tes côtés et à travers ton exemple.
Merci Marie pour ta bonne humeur à toute épreuve, tes blagues quotidiennes et ton soutien. Merci d'avoir encadré ce projet et d'y avoir consacré tant d'énergie et de temps, tu as su me remotiver quand il le fallait et tu n'as jamais douté de moi.
Je ne serai pas là où j'en suis actuellement sans toi, et j'espère que cette collaboration durera encore quelques temps.

Au président du jury, Monsieur le Professeur Guillaume Levard,

J'ai été honorée de croiser votre route et d'apprendre la chirurgie à vos côtés durant mon internat. Vous êtes un exemple pour moi et j'espère devenir un chirurgien exemplaire, comme vous l'êtes, plus tard.
Merci de m'avoir légué une infime partie de votre savoir, j'aurais aimé que mon temps d'apprentissage à vos côtés soit encore plus long.
Vous aurez à jamais ma reconnaissance éternelle.

Au membre du jury, Monsieur le Professeur Frédéric Gottrand,

Merci d'avoir cru en moi pour porter ce travail enrichissant. Votre expertise était essentielle pour porter à bien ce projet et je suis honorée que vous ayez accepté de faire partie de mon jury.

Au membre du jury, Madame le Docteur Véronique Diaz,

Merci d'avoir répondu favorablement afin d'apporter vos compétences de pneumologue à cette étude. En espérant pouvoir continuer à collaborer avec vous pour la prise en charge multidisciplinaire des enfants à l'avenir.

Merci au CRACMO pour m'avoir accordé sa confiance pour mener à bien cette étude,

Un grand merci à tous les CHU ayant participé à l'étude, pour leur collaboration et leur réactivité :

- Le Pr GOTTRAND, le Dr SFEIR et Katialine GROFF (Lille)
- Le Pr BECMEUR et le Dr LEHN (Strasbourg)
- Le Pr PIOLAT (Grenoble)
- Le Pr BONNARD (Robert Debré APHP)
- Le Pr LEMELLE et le Dr LIENARD (Nancy)
- Le Pr SARNACKI et le Dr ROUSSEAU (Necker APHP)
- Le Dr POUZAC (Orléans)
- Le Pr LIARD (Rouen)
- Le Pr LARDY (Tours)
- Le Dr BUISSON (Amiens)
- Le Pr AUDRY et le Pr IRTAN (Armand Trousseau APHP)
- Le Pr RAVASSE et le Dr PETIT (Caen)
- Le Pr SAPIN (Dijon)
- Le Pr MARTELLI, le Pr BRANCHEREAU et le Dr FOUQUET (Kremlin Bicêtre APHP)
- Le Dr CARCAUZON (Le Mans)
- Le Dr GELAS (Lyon)
- Le Dr ALLAL (Montpellier)
- Le Pr LECLAIR (Nantes)
- Le Pr VARLET (Saint-Etienne)

À mes collègues,

Aux équipes médicales et paramédicales avec qui j'ai eu la chance de travailler depuis le début de mon internat,

Aux Docteur Giovanna Grella et Benoît Parmentier,

J'ai débuté mon internat à vos côtés et vous m'avez initié aux rouages de la chirurgie pédiatrique.
Giovanna tu es une personne en or, toujours de bonne humeur et prête à aider les autres. Cela a été un honneur de travailler avec toi et je te souhaite le meilleur pour ta vie en Italie.
Benoit je ne te remercierai jamais assez pour tout ce que tu m'as apporté chirurgicalement parlant, mais aussi du point de vue personnel. Merci pour ton soutien et ton humilité. Je te souhaite le meilleur sous le soleil breton.

Au Docteur Diana Potop et au Professeur Jiad Mcheik,

Merci Diana pour m'avoir apporté ton expertise de l'anglais médical dans l'écriture de cette thèse. Et merci pour ce que tu m'apportes au quotidien dans la pratique de la chirurgie infantile.
Merci Jiad pour votre calme et pour la transmission de votre savoir. J'ai encore beaucoup à apprendre de vous, le « magicien » de la chirurgie.

Aux chirurgiens pédiatres du CHU de Bordeaux,

Merci de m'avoir accueillie pendant un an dans votre service et de m'avoir formé. Cette année dans votre équipe a été enrichissante sur le plan professionnel et humain. En espérant pouvoir collaborer avec vous de nouveau dans le futur.

À l'équipe d'urologie du CHU de Poitiers,

En quelque sorte ma deuxième famille de la chirurgie. Pour m'avoir initiée à la chirurgie dès mon premier semestre et m'avoir accompagnée jusqu'à aujourd'hui. C'est toujours un plaisir de travailler à vos côtés.

À mes co-internes au cours de ces 8 semestres, ceux qu'on voit plus que nos familles et qui deviennent des amis.

Julie ma maman de la chirurgie, Nadia ma compatriote de la première heure, Sandrine la « presque » interne de chirurgie pédiatrique qui m'a supportée pendant un an, Alice une de mes plus belles rencontres de l'internat, mais aussi Clara, Julia, Nico et tous les autres.

A mes amis,

Au Crew,

Chloé, Mathilde, Marine, Margot, Fanny et Gaby, mes plus vieilles amies. Celles qui ont toujours été là dans les meilleurs comme dans les pires moments. Celles qui ont suivi mon aventure depuis le début et qui seront là pour encore longtemps. Merci de me faire rire, de me faire oublier le quotidien pas toujours très drôle.
Pour toutes ces années encore à venir et tous les bons moments qui nous attendent. Je mesure la chance inestimable de vous avoir rencontrées.

À la Team de l'internat de Poitiers,

Margaux, Pauline, Jeanne, Hajar, Marine, Agathe, Estelle, Nadia, Marion, Olivia, Laura. L'aventure de l'internat a commencé avec vous, en partageant les galères et les fous rires et continue chaque jour. Heureusement que vous êtes là pour partager cette vie pas toujours facile, à plusieurs on va plus loin.

À mes copains d'externat,

Léa, Thaïs, Fanny, Pauline, Alexis, Kevin et Xavier, pour toutes ces années de rigolades à apprendre la médecine. Même si nos chemins se sont séparés c'est toujours un plaisir de vous revoir.

À Charlotte,

Toi qui as su pleurer et rire avec moi depuis le début de cette folle aventure que sont les études de médecine. Pour toutes nos soirées et nos aventures, loin des yeux mais toujours près du cœur.
Tu me manques un peu plus tous les jours.

À Pauline et Constance,

Mes copines rétaises, à nos vacances ensoleillées sur une planche à voile ou sur un vélo.
Les années passent et malgré la distance vous êtes toujours là.

À ma famille,

À mes parents,

Vous avez su me donner les valeurs nécessaires pour me battre et aller au bout de mes rêves. C'est grâce à vous si j'en suis ici aujourd'hui.
Vous rendre fiers est ma plus belle récompense.

À mon frère et à ma sœur,

Tout simplement merci d'être vous, si différents de moi, et de me faire voir d'autres horizons.

À mes grands-parents Ata et Ama,

La distance n'est pas toujours facile, j'aimerais pouvoir vous voir plus souvent. Merci de m'avoir fait baigner depuis toute petite dans le goût des voyages et des histoires.
Et à Mémé et Tatie Sophie mes petits soleils.

À ma famille (nombreuse) du côté Bastie,

Qui m'a permis d'apprendre les valeurs du partage.

À ma marraine et mon parrain,

Toujours un peu près de mon cœur malgré la distance.

À Vincent,

Ma moitié, mon meilleur ami, mon âme sœur, mon compagnon du quotidien.
Merci d'être là, d'exister et surtout de me supporter. Je ne sais pas ce que je ferais sans toi.
À tous les beaux projets qui nous attendent dans cette nouvelle vie.

Table des matières

Liste des abréviations :

AO : Atrésie de l'œsophage

AOLG : Atrésie de l'œsophage long gap

AONLG : Atrésie de l'œsophage non long gap

CRACMO : Centre de référence des affections chroniques et malformatives de l'œsophage

FOT : Fistule oeso-trachéale

IRM : Imagerie à résonnance magnétique

RGO : Reflux gastro-œsophagien

SA : Semaines d'aménorrhée

Introduction

L'atrésie de l'œsophage (AO) est une anomalie malformative, congénitale, définie par une absence de continuité de l'œsophage.

Elle est présente dès la naissance et se trouve souvent associée à une connexion anormale entre l'œsophage et la trachée créant une fistule œso-trachéale.

1. Embryologie et anatomie

A. EMBRYOLOGIE

Le développement du système gastro-intestinal résulte d'une série de processus biochimiques et de plicatures de l'embryon. La formation du système digestif, et plus spécifiquement de l'œsophage, débute à partir de la quatrième semaine de développement. A ce stade, l'embryon est constitué de trois couches distinctes connectées au sac vitellin.

Au début de la quatrième semaine de développement, une plicature de l'embryon se produit de telle sorte que les bords crânien, caudal et latéraux du disque se rejoignent. Cette plicature se produit à partir de la ligne médiane, les couches fusionnent entraînant l'internalisation de la couche endodermique qui permet à l'embryon de former un tube constitué de deux couches. La couche interne est appelée endoderme et la couche externe est appelée ectoderme. Entre ces deux couches se trouve le mésoderme.

Initialement, ce tube est fermé aux deux pôles et il est le précurseur de l'intestin primitif. Cet intestin primitif se divise ensuite en trois parties : l'intestin antérieur (partie

crânienne), l'intestin moyen et l'intestin postérieur (partie caudale). L'intestin moyen se trouve entre l'intestin antérieur et l'intestin postérieur, il est en continuité avec la vésicule vitelline. La vésicule vitelline est une structure extra-embryonnaire autour de laquelle l'embryon est replié, elle constitue une réserve nutritionnelle pendant les premières semaines de développement.

L'œsophage provient donc de l'intestin antérieur, qui donnera également naissance à la trachée et aux poumons. L'endoderme de l'intestin antérieur donnera naissance à l'épithélium œsophagien et aux glandes muqueuses, le mésoderme donnera les couches musculaires striées et lisses.

La première étape de l'organogenèse œsophagienne à partir de l'intestin antérieur est la différenciation des cellules de l'intestin antérieur en trachée, poumon et œsophage.
Grâce à la signalisation biochimique particulière, l'intestin antérieur dorsal va progressivement former l'œsophage définitif, alors que la partie ventrale de celui-ci va donner naissance à la trachée et aux poumons.

Un des événements crucial de cette différenciation est la séparation de l'œsophage et de la trachée, puis la distinction des structures en continuité avec l'œsophage : le pharynx et l'estomac.
Les différentes voies moléculaires entrainant la formation des poumons, de la trachée et de l'œsophage sont imbriquées les unes avec les autres. L'expression de Sox2 dans la partie dorsale de l'endoderme permet le développement de l'œsophage, et l'expression de NKx2-1 dans la partie ventrale de l'endoderme permet le développement du système respiratoire.

Ces gènes sont exprimés et régulés spatialement, en temps adéquat, dans l'endoderme de l'intestin antérieur. Par conséquent, l'interruption de l'une de ces voies à tout moment au cours du développement, peut entraîner diverses malformations trachéo-œsophagiennes[1]. (Figure 1)

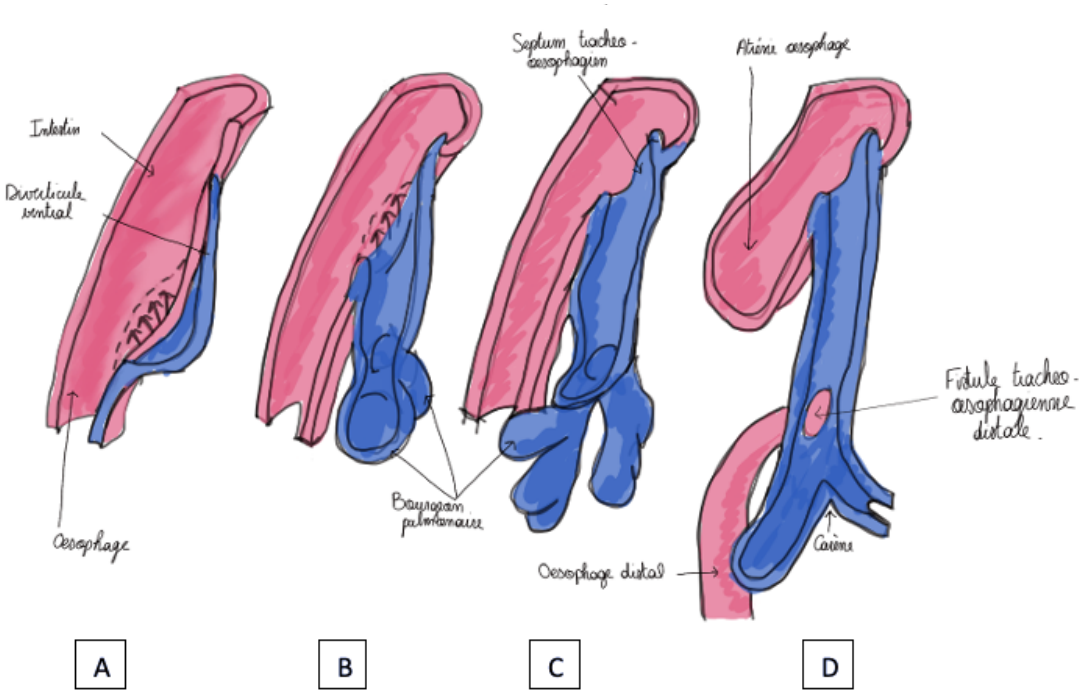


Figure 1 : Étapes successives durant le développement du septum trachéo-œsophagien.

A. Le diverticule laryngo-trachéal se forme à partir d'un débordement ventral de la partie caudale du pharynx primitif
B. Les plis trachéo-œsophagiens longitudinaux commencent à fusionner vers la ligne médiane pour former le septum trachéo-œsophagien.
C. Le septum trachéo-œsophagien est complètement formé.
D. Si le septum trachéo-œsophagien dévie vers l'arrière, une atrésie de l'œsophage avec fistule trachéo-œsophagienne se développe.

B. ANATOMIE

L'œsophage est un conduit musculo-membraneux du tube digestif, contractile, reliant le pharynx à l'estomac. Il livre le bol alimentaire à l'estomac. (Figure 2)

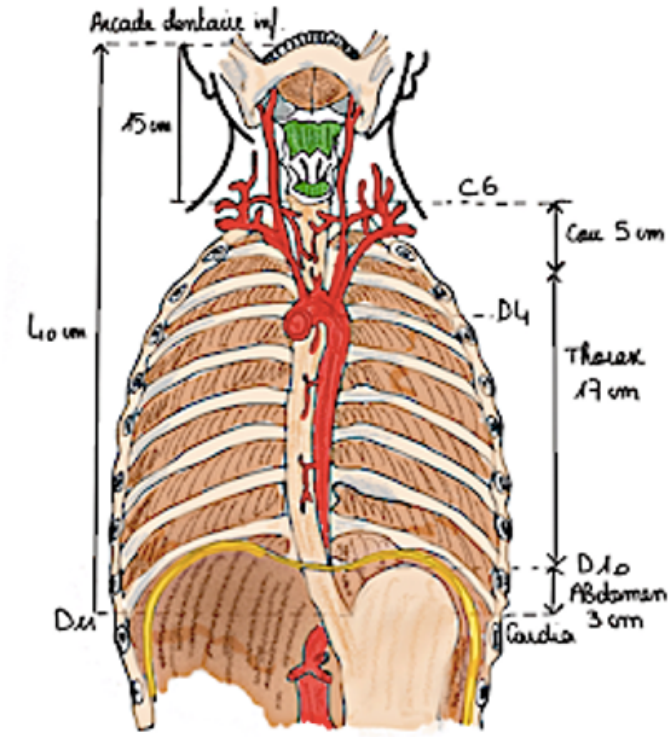


Figure 2 : Anatomie et rapports anatomiques de l'œsophage

- <u>Trajet :</u>

L'œsophage fait suite au pharynx au niveau de la bouche de l'œsophage au bord inférieur du cartilage cricoïde (hauteur C6) à 15cm environ de l'arcade dentaire inférieure.

Il descend ensuite en arrière de la trachée, médian, oblique en bas et à gauche. Il est appliqué en haut contre la colonne vertébrale puis se dirige progressivement en avant jusqu'au diaphragme, qu'il traverse au niveau du hiatus œsophagien.

Il se termine au niveau du cardia de l'estomac en regard de T12, à 2cm à gauche de la ligne médiane.

- Dimensions :

Chez un adulte, l'œsophage cervical mesure environ 6cm, l'œsophage thoracique 16cm, l'œsophage diaphragmatique 1cm et l'œsophage abdominal 1cm.

Il a un calibre de 2-3cm avec 4 réductions de calibre physiologiques : cricoïdien, aortique (crosse de l'aorte), bronchique (bronche souche gauche) et diaphragmatique.

- Structure :

La paroi de l'œsophage est souple, d'une épaisseur de 3mm. Elle comprend 3 tuniques :

◊ La tunique interne : c'est la muqueuse avec un épithélium pavimenteux stratifié.

◊ La tunique moyenne : c'est la sous-muqueuse, mince.

◊ La tunique externe : c'est la musculeuse, elle comporte 2 couches de fibres musculaires lisses : profonde circulaire et superficielle longitudinale.

- Rapports :

◊ Œsophage cervical : Il est contenu avec la trachée dans la gaine viscérale du cou. Il est en contact, en arrière avec la colonne vertébrale, en avant avec la face postérieure de la trachée, latéralement avec les lobes latéraux de la thyroïde, les glandes parathyroïdes, les nerfs laryngés récurrents et le paquet vasculo-nerveux du cou (carotide primitive, jugulaire interne, nerf vague et nœuds lymphatiques de la chaine jugulo-carotidienne).

◊ Œsophage thoracique :

- En arrière, se trouve le plan vertébral de T1 à T3-4, l'aorte thoracique descendante, la veine azygos et le conduit thoracique
- En avant, se situent la face postérieure de la trachée, la face dorsale du péricarde et notamment le sinus oblique du péricarde.
- A droite, l'œsophage est libre avec uniquement la plèvre médiastinale, les nœuds lymphatiques latéro-trachéaux droits, la crosse de la veine azygos et le nerf vague droit. (Voie d'abord préférentielle pour la chirurgie de l'œsophage).
- A gauche sont présents l'artère subclavière gauche, le nerf récurrent gauche ou nerf laryngé inférieur et la crosse de l'aorte.

◊ Œsophage abdominal : l'œsophage traverse le diaphragme par le hiatus œsophagien qui est un orifice musculaire, extensible et contractile, situé au niveau de T10. Cet orifice contient les deux nerfs vagues et des branches des artères et des veines cardio-tubérositaires et phréniques. Au niveau abdominal, on retrouve en avant le lobe gauche du foie et le nerf vague gauche, et en arrière le nerf vague droit.

- <u>Vascularisation :</u>

◊ Artérielle : le tiers supérieur de l'œsophage est vascularisé par les branches œsophagiennes des artères thyroïdiennes inférieures. Son tiers moyen est vascularisé par les artères bronchiques et les rameaux œsophagiens de l'aorte. La vascularisation du tiers inférieur est assurée par les artères gastrique gauche et phrénique inférieure gauche.

◊ Drainage veineux : les parties cervicale et thoracique sont drainées par les veines thyroïdiennes inférieures, azygos, hémi-azygos et hémi-azygos accessoire. La partie

abdominale de l'œsophage est drainée par la veine hémi-azygos dans la veine cave supérieure et par les veines gastriques gauches dans la veine porte. Il existe donc à ce niveau une anastomose porto-systémique.

◊ Drainage lymphatique :

- Concernant le tiers supérieur, les lymphatiques se déversent dans les ganglions lymphatiques cervicaux profonds.
- Au niveau du tiers moyen, ils se déversent dans les ganglions médiastinaux supérieurs et postérieurs.
- Au niveau du tiers inférieur, ils suivent l'artère gastrique gauche pour aboutir aux ganglions gastriques et aux ganglions du tronc cœliaque. Les connexions entre ces trois aires de drainage sont nombreuses.

- Innervation :

L'innervation sympathique provient du ganglion cervico-thoracique et du plexus solaire, entrainant une accélération du péristaltisme lors de l'alimentation.

L'innervation parasympathique provient du nerf X et ralentit le péristaltisme.

2. L'atrésie de l'œsophage (AO)

A. DEFINITION AO ET INCIDENCE

L'AO est une malformation congénitale de la partie supérieure du tube digestif. Son étiologie, avec ou sans fistule oeso-trachéale (FOT) associée, est un échec de la séparation ou un développement incomplet de l'intestin antérieur primitif[2]. De nombreux gènes sont impliqués dans cette anomalie (Shh, SOX2, CHD7, MYCN, FANCB) mais l'origine exacte n'est pas connue, certainement plurifactorielle.

Sa prévalence dans le monde varie entre 1 pour 2500 et 1 pour 4500 naissances[3]. En France l'incidence est de 1,8 pour 10 000 naissances avec un sex ratio de 1,3 (H/F)[4]. L'incidence de l'AO/FOT augmenterait avec l'âge de la mère[5].

De plus, dans la littérature, dans 50% des cas, les patients avec une AO/FOT ont des anomalies congénitales associées, notamment les malformations composant le syndrome de VACTERL (anomalies vertébrales, atrésie anale, anomalie cardiaque, fistule oeso-trachéale, anomalie rénale et malformations des extrémités) ou le syndrome de CHARGE (colobome, anomalie cardiaque, atrésie des choanes, retard de croissance, anomalies génitales et anomalie des oreilles)[3].

B. CLASSIFICATION AO

L'AO et les FOT (associées dans plus de 90% des cas) sont classées en 5 catégories selon la configuration anatomique. Il s'agit de la classification de Ladd[6,7]. (Figure 3)

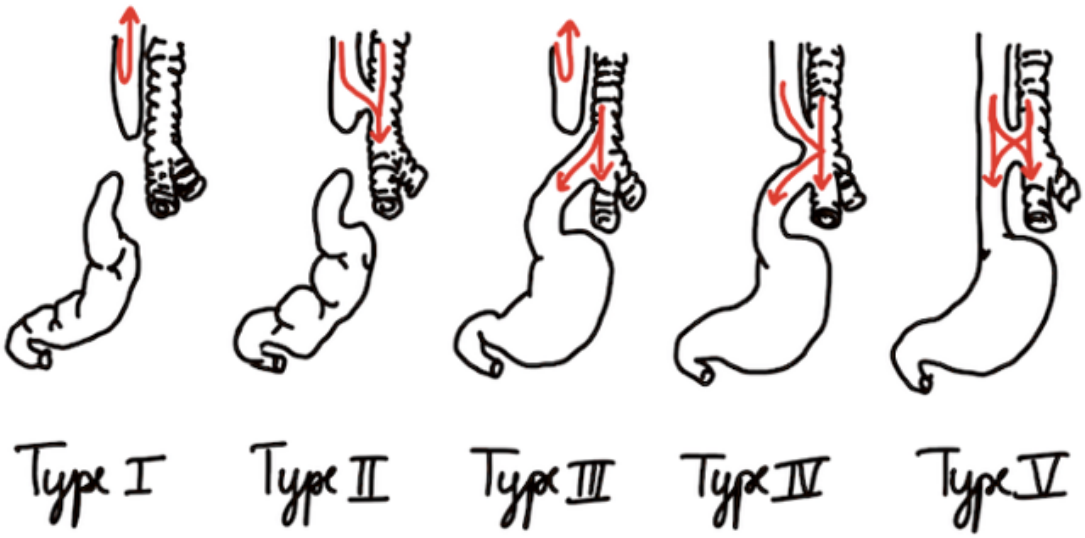


Figure 3 : Classifications des atrésies de l'œsophage

Type I : Atrésie isolée sans fistule (7-10%)
Type II : Atrésie avec fistule trachéo-œsophagienne dans le segment supérieur (1%)
Type III : Atrésie avec fistule trachéo-œsophagienne dans le segment inférieur (80-85%)
Type IV : Variante du type III (4%)
Type V : Deux ou plusieurs fistules (2-3%)

La forme la plus rencontrée est le type 3. En France, 87% des enfants présentant une AO sont classés type 3[4].

C. DIAGNOSTIC ANTENATAL ET POST-NATAL

Un tiers des fœtus avec une AO/FOT sont diagnostiqués avant la naissance[8], mais ce diagnostic reste rare dans les formes avec une fistule au niveau du cul-de-sac inférieur de l'œsophage.

En période prénatale, les patients avec une atrésie de l'œsophage peuvent présenter un polyhydramnios (principalement lors du 3e trimestre), un petit estomac, ou encore un « upper sign pouch » après 32 semaines d'aménorrhée (SA) (mais très rare)[8,9]. L'« upper sign pouch » correspond à la visualisation du cul-de-sac supérieur lors de l'imagerie prénatale. En cas de diagnostic suspecté, une IRM fœtale est parfois réalisée[10].

A la naissance, les symptômes les plus fréquents sont une hypersalivation, un étouffement lors de la prise alimentaire, des fausses routes, une inhalation et l'impossibilité de descendre une sonde nasogastrique dans l'estomac. Si une FOT est associée, une distension gazeuse de l'estomac peut également être observée[11].

3. Techniques chirurgicales AOLG et AO

A. VOIE D'ABORD CLASSIQUE

La première chirurgie de l'œsophage a été réalisée en 1941 par Haight[12]. La voie d'abord standard pour la chirurgie de l'œsophage est une thoracotomie latéro-dorsale droite. La thoracotomie gauche peut exceptionnellement être utilisée en fonction des malformations associées (ex : un arc aortique droit).

L'enfant est installé en décubitus latéral gauche avec le bras droit en abduction et l'épaule à 90°.

L'incision est réalisée environ 1cm en dessous de la pointe de la scapula, de la ligne médio-axillaire à l'angle de la scapula.

Le muscle grand dorsal est mobilisé en coupant ses attaches au fascia antérieur, puis le bord du muscle dentelé antérieur est mobilisé de son origine à la pointe de la scapula le long de la 6^{e} côte et refoulé vers le haut.

Les muscles intercostaux sont ensuite séparés le long du bord supérieur de la 5^{e} côte ce qui laisse entrevoir le feuillet pariétal de la plèvre.

La chirurgie est réalisée en intra-pleural ou en extra-pleural, en effectuant un décollement de la plèvre en arrière jusqu'à atteindre la région de l'œsophage. Sur le trajet, la veine azygos devra être, soit refoulée, soit ligaturée. Il s'agit ensuite d'identifier le nerf vague droit qui court le long du bord latéral de l'œsophage proximal.

La thoracotomie droite est la voie d'abord avec le moins de structure anatomique à risque sur son trajet pour atteindre l'œsophage.

De plus en plus fréquemment, la thoracoscopie droite peut être utilisée si le poids et l'état respiratoire de l'enfant le permettent[13].

B. TECHNIQUES CHIRURGICALES DES ATRESIES DE L'ŒSOPHAGE LONG GAP

Les voies d'abords décrites ci-dessus sont utilisées si l'anastomose oeso-œsophagienne est réalisable en un seul temps. En cas d'atrésie de l'œsophage long gap (AOLG), plusieurs autres techniques chirurgicales sont possibles.

Nous prendrons comme définition d'une AOLG, dans cette étude, une AO où l'écart inter-fragmentaire est trop important pour pouvoir réaliser une anastomose dans les 28 premiers jours de vie.

Parmi les différentes techniques chirurgicales utilisées pour la réparation des AOLG il est à noter :

- la préservation de l'œsophage natif avec une élongation par traction mécanique selon la technique de Foker[14].

- le remplacement œsophagien par une interposition de colon [15,16], de jéjunum[17] ou par une transposition gastrique[18], sans qu'aucune technique n'ait encore vraiment fait preuve de sa supériorité par rapport aux autres[19].

4. Complications à court et moyen terme des AO

De nos jours, grâce aux progrès des techniques chirurgicales et de la néonatalogie, la survie des enfants atteint d'atrésie de l'œsophage est aux alentours de 85-90%. Le pronostic vital de ces enfants dépend majoritairement des anomalies cardiaques et chromosomiques associées. [20] La mortalité précoce est le plus souvent due aux anomalies cardiaques alors que la mortalité retardée est plutôt due à des complications respiratoires.

L'enjeu majeur de cette pathologie actuellement est donc de comprendre et de réduire au maximum les comorbidités associées à cette pathologie à moyen et à long terme.

A. COMORBIDITES DIGESTIVES

Le développement embryologique commun des voies digestives et respiratoires explique une grande partie des comorbidités présentes chez les enfants atteint d'une AO.

Dans un premier temps, nous allons nous intéresser aux comorbidités digestives. L'AO touche donc un œsophage anormal dans sa structure anatomique mais aussi dans sa motilité. Il est donc facile de comprendre que cet œsophage est plus susceptible de présenter un reflux gastro-œsophagien (RGO) devant un défaut de fermeture du sphincter inférieur de l'œsophage. La dissection du cul-de-sac inférieur de l'œsophage accentue ce reflux. A moyen terme, ce RGO s'exprime par une œsophagite, des dysphagies avec des blocages alimentaires aux solides et parfois aux liquides, des troubles de l'oralité. Tous ces éléments ont pour conséquence des troubles nutritionnels[21].

Devant ce RGO, une intervention chirurgicale pour réalisation d'une valve anti-reflux est parfois pratiquée. La mise en place d'une gastrostomie devant des troubles de l'alimentation important peut être envisagée.

A plus long terme, ces enfants ont un risque augmenté d'apparition d'œsophage de Barrett, qui constituerait un risque accru de développer un cancer œsophagien à l'âge adulte, même si cette notion reste controversée[22].

Cet œsophage opéré est aussi source de complications du point de vue chirurgical sur l'anastomose. En effet, dans la littérature, on note une prévalence importante de fistules anastomotiques en post-opératoire précoce et de sténoses anastomotiques à plus long terme. Ces sténoses anastomotiques nécessitent parfois de nombreuses dilatations sous endoscopie et parfois une reprise chirurgicale si la sténose est trop serrée et empêche l'alimentation [23].

B. COMORBIDITES RESPIRATOIRES

L'embryologie de cette malformation explique les morbidités respiratoires et pulmonaires. La présence dès la naissance d'une fistule entre l'œsophage et la trachée a un impact négatif sur la croissance et le bon développement des poumons des patients. L'évaluation à long terme, sur le plan respiratoire, des enfants atteint d'une AO est devenue primordiale. En effet, on rapporte très souvent des tests fonctionnels respiratoires pathologiques, avec des troubles obstructifs[24]. Ces troubles respiratoires commencent dès le plus jeune âge et ont tendance à s'aggraver[25]. La principale composante de l'altération de la fonction pulmonaire est l'obstruction des voies aériennes[26].

Chez ces enfants la présence d'asthme du nourrisson ou d'infections pulmonaires à répétition est fréquente[27]. Le suivi par une équipe de pneumo pédiatrie apparaît donc indispensable.

C. COMORBIDITES ORTHOPEDIQUES

La chirurgie de l'AO, malgré le développement de la thoracoscopie, se réalise encore majoritairement par un abord direct via une thoracotomie droite. La réalisation d'une thoracotomie chez un nouveau-né n'est pas anodine[28]. D'après certains travaux précédemment réalisés, il est reconnu que les enfants opérés d'une AO par thoracotomie sont plus susceptibles de présenter à l'adolescence des scolioses mineures ou majeures, ou une asymétrie de la scapula[29].

Ces déformations, en plus de nécessiter un suivi orthopédique particulier, ont potentiellement un impact sur la qualité respiratoire et pourraient aggraver le pronostic fonctionnel respiratoire de ces enfants.

Problématique

1. Travaux préliminaires

Dans une thèse publiée en 2011, intitulée *« Évolution des atrésies de l'œsophage « à large défect » opérées en France entre 2008 et 2011 : évaluation des pratiques et du suivi »,* le docteur Benoit Parmentier avait relevé tous les enfants nés avec une AOLG entre 2008 et 2010 en France afin d'étudier les différentes techniques chirurgicales utilisées pour la réparation de l'œsophage ainsi que le devenir à court terme de ces enfants.

Il en était sorti une série nationale multicentrique d'AOLG sur une période de 3 ans. Cette étude concluait que les stratégies d'anastomoses différées visant à préserver l'œsophage natif étaient principalement utilisées. Le taux de complication global chez ces enfants était de 90% entraînant une hospitalisation prolongée et de nombreuses réhospitalisations dans l'enfance.

Annexe 1

Dans une thèse publiée en 2018, intitulée « *Suivi à moyen terme d'une cohorte nationale d'atrésie de l'œsophage long gap : analyse de l'oralité et de la morbidité* », le docteur Julie Thomas, gastro pédiatre, reprenait la cohorte du Dr Parmentier pour étudier les comorbidités à moyen terme de ces enfants.

Il en ressortait que la dénutrition chez ces enfants n'était pas imputable aux caractéristiques de naissance, que la morbidité digestive était au premier plan chez ces enfants (RGO, blocages alimentaires et dysoralité) et qu'il existait plus de dysoralité en cas de préservation de l'œsophage natif.

Annexe 2

2. Objectifs

Pour poursuivre le travail réalisé dans ces deux thèses, et afin de réaliser une étude comparative, nous avons repris la cohorte des enfants atteints d'une AOLG et l'avons appariée à des patients du registre national avec une AO, ayant bénéficié d'une anastomose dans les premiers jours de vie.

L'objectif principal de cette étude est donc de réaliser une étude comparative des comorbidités à 6 ans des enfants avec une AOLG à celles d'enfants ayant pu avoir une anastomose digestive dans les 7 premiers jours de vie.

Article

Midterm comorbidity of esophageal atresia : long-gap versus non-long-gap case-control study

BOURG A[1], GOTTRAND F[2], PARMENTIER B[1], THOMAS J[1], BECMEUR F[3], LEHN A[3], PIOLAT C[4], BONNARD A[5], SFEIR R[6], LEMELLE JL[7], LIENARD J[7], SARNACKI S[8], ROUSSEAU V[8], POUZAC M[9], LIARD A[10], BUISSON P[11], RAVASSE P[12], PETIT T[12], SAPIN E[13], BRANCHEREAU S[14], FOUQUET V[14], MARTELLI H[14], CARCAUZON V[15], KALFA N[16], ALLAL H[16], LECLAIR MD[17], DE NAPOLI S[17], LARDY H[18], AUDRY G[19], IRTAN S[19], VARLET F[20], GELAS T[21], MCHEIK J[1], LEVARD G[1], POTOP D[1], AUGER-HUNAULT M[1]

1- Pediatric Surgery unit, University Hospital Center of Poitiers, 86000 Poitiers, France
2- Gastroenteroly unit, University Hospital of Lille Jeanne de Flandre, 59000 Lille, France
3- Pediatric surgery unit, University Hospital of Strasbourg, 67200 Strasbourg, France
4- Pediatric surgery unit, University Hospital of Grenoble, 38700 Grenoble, France
5- Pediatric surgery unit, Robert Debré Hospital APHP, 75019 Paris, France
6- Pediatric surgery unit, University Hospital of Lille Jeanne de Flandre, 59000 Lille, France
7- Pediatric surgery unit, University Hospital of Nancy, 54035 Nancy, France
8- Pediatric surgery unit, Necker Hospital APHP, 75015 Paris, France
9- Pediatric surgery unit, Hospital of Orléans, 45100 Orléans, France
10- Pediatric surgery unit, University Hospital of Rouen, 76000 Rouen, France
11- Pediatric surgery unit, University Hospital of Amiens-Picardie, 80054 Amiens, France
12- Pediatric surgery unit, University Hospital of Caen Normandie, 14000 Caen, France
13- Pediatric surgery unit, University Hospital of Dijon F.Mitterand, 21000 Dijon, France
14- Pediatric surgery unit, Bicetre Hospital APHP, 94270 Le Kremlin-Bicêtre, France
15- Pediatric surgery unit, Hospital of Le Mans, 72000 Le Mans, France
16- Pediatric surgery unit, University Hospital of Montpellier, 34295 Montpellier, France
17- Pediatric surgery unit, University Hospital of Nantes Hotel Dieu, 44093 Nantes, France
18- Pediatric surgery unit, University Hospital of Tours, 37000 Tours, France
19- Pediatric surgery unit, Armand Trousseau Hospital APHP, 75012 Paris, France
20- Pediatric surgery unit, University Hospital of Saint-Etienne, 42270 Saint-Priest-en-Jarez
21- Pediatric surgery unit, University Hospital of Lyon HCL Women Mother Children Hospital, 69500 Bron, France

Corresponding author:
Agate BOURG
CHU de Poitiers, 2 rue de la Miletrie 86021 Poitiers
Tel: +33 5 49 44 42 44
Fax: +33 5 49 44 30 35
Email: agate.bourg@gmail.com

Abstract:

Introduction: Esophageal atresia (EA) is a rare congenital malformation. The initial surgery depends on the length of the gap. Nowadays, the survival rate of operated children is higher but medium and long-term morbidity is still important. The aim of this study was to compare morbidity at 6 years between long gap esophageal atresia (LGEA) and non-long gap esophageal atresia (NLGEA).

Materials and Methods: We performed a multicentric retrospective study of patients with EA between 2008 and 2010 with a follow-up until the age of 6. For each LGEA, 2 NLGEA were included. The digestive, respiratory and orthopedic morbidity at 6 years were collected from all the medical records in association with CRACMO (Centre de Référence des Affections Chroniques et Malformatives de l'Oesophage).

Results: Thirty-one patients with LGEA and sixty-two with NLGEA were included. There were more esophagitis cases in LGEA group than in NLGEA one (45% vs 15%, p=0.005). More anti-reflux surgeries were performed in LGEA group (65% for LGEA vs 19% for NLGEA, p<0.001). LGEA group had more digestive symptoms like bolus impaction in the esophagus or dysphagia (68% vs 33%, p=0.003) and more complications such as anastomotic stricture (71% vs 38%, p=0.006). There was no significant difference between the two groups regarding respiratory symptoms. NLGEA group had more tracheomalacia than LGEA group (33% vs 6,6%, p=0.006). NLGEA group had more spine deformation than LGEA group (23% vs 3,2%, p=0.026).

Discussion: The 6-year morbidity was higher for LGEA group especially the digestive comorbidity. In the long-term, the follow-up should be scrutinized closer for these children.

Key words: Esophageal atresia, Long-gap esophageal atresia, Complications, Midterm outcome.

INTRODUCTION:

Esophageal atresia (EA) is a congenital malformation with an incidence in France of 2.8 to 4.0 per 10000 births [1]. Since the first successful surgery in 1941, anesthetic, surgical and neonatal care have improved remarkably. Now the long-term survival rate of these children reaches almost 100% in the absence of other malformations [2].

A 2010 study (Annexe 1) has highlighted that immediate post-natal care often depends on the length of the esophageal defect. Children with LGEA had more reported sequelae such as anastomotic dehiscence, severe gastro esophageal reflux, which needed fundoplications and dilatations for strictures.

Despite the improvements made in neonatal care, mid-term co-morbidities are still observed. A study from 2018 (Annexe 2) focuses on digestive and respiratory co-morbidities and their consequences on the quality of life [3,4,5,6].

The aim of this study was to compare LGEA and NLGEA groups regarding digestive, respiratory and orthopedic comorbidities encountered after 6 years of follow-up.

MATERIALS AND METHODS:

After an institutional review board approval (by the scientific committee of the CRACMO (*Centre de référence des Affections Chroniques et Malformatives de l'Oesophage*), a multicentric retrospective case-report study was performed including all patients that had EA surgery.

During a 2-year period from 1st of January 2008 to 31st of December 2010, all patients with LGEA operated in France were included.
All medical data were collected and centralized in a national association: CRACMO. Data collected were comorbidity present at birth, at 1 year and at 6 years respectively.

In this panel were included all patients born between 2008 and 2010 who underwent esopagheal surgery for EA after the age of 28 days because of the importance of the gap length.
Patients who had a delayed surgery for other reasons than the length of the gap were excluded. Patients lost to follow-up were also excluded.
For each LGEA case, 2 NLGEA control patients operated before 7 days of life in the same hospital were included. For each case, the control patients that were selected had to be born right before and right after the LGEA patient. If the medical records of these patients were missing, then the second patients born right before and right after the LGEA case were included.

Two sources were used to collect the medical data from: the medical records from each center and the PNDS (Protocole National de Diagnostic et de Soins) collected in Lille, the national referent center of CRACMO. All data at birth, at 1 year and at 6 years were collected by CRACMO.
Judgement criteria were digestive comorbidity, respiratory comorbidity and orthopedic comorbidity at 6 years. We generally defined a complicated evolution as all situations that required one or more therapeutic interventions and that could impact the child's wellbeing and its quality of life. We defined digestive comorbidity by the presence of gastro-esophageal reflux disease (GERD), esophagitis confirmed by fibroscopy and biopsy, GERD surgery, anastomotic stricture, number of dilatations, dysphagia or bolus impaction, anastomotic leak and gastro-esophageal follow-up. Respiratory comorbidity was defined by cough, dyspnea,

asthma, tracheomalacia, and the need for pneumologic follow-up. Finally, we defined orthopedic comorbidity at 6 years by deformation of the spine and orthopedic follow-up.
Subject description was realized using count (proportion) for binary variables and mean (standard deviation) for continuous variables.

Comparison between long gap esophageal atresia and non-long gap esophageal atresia groups was assessed using t-test (displaying mean difference, confidence interval and p-value) and Fisher's exact test (displaying Odd Ratio, its confidence interval and p-value).
Missing values were ignored in statistical tests and reported in corresponding tables.
All analyses were processed with R software version 4.0.1 with a significance threshold of 0,05.

RESULTS:

Study population is detailed in *Flow chart.*

In the control group, 2 patients died (1 at the age of 4 months, due to cardiac arrest after hypokalemia and one at the age of 5 months who had CHARGE syndrome, due to septic shock after digestive perforation).

Details regarding children at birth are summarized in *Table 1*.

Post-operative conditions for children are summarized in *Table 2*.

Some patients had one or more complicated evolutions after surgery. Complications were digestive in 10 cases for NLGEA and in 24 cases for LGEA (2 duodenal stenosis, 18 anastomotic leaks, 23 anastomotic strictures, 1 digestive perforation, 2 bowel obstructions and 1 eventration). There were 9 respiratory complications in NLGEA group and 7 in LGEA group (2 atelectasis, 10 pneumothorax, 5 pneumopathies and 2 recurrent eso-tracheal fistulas). We identified 4 NLGEA patients and 3 LGEA patients that had septic related complications (4 central catheter infections, 1 pyelonephritis, 1 mother-fetal infection and 2 mediastinitis). Also there were 8 NLGEA and 6 LGEA patients that had other type of unfavorable outcome (3 acute renal failures, 4 bradycardias, 3 surgeries for arterial canal, 1 chylothorax, 1 intra-ventricular hemorrhage, 1 Claude Bernard Horner syndrome and 2 deep vein catheter thrombosis).

Complications during the first year of life were mostly digestive (one or more for the same patient) : 15 cases for NLGEA group (2 dysphagias, 3 GERD, 10 anastomotic strictures and 3 other digestive problems) and 17 cases for LGEA group (3 GERD, 12 anastomotic strictures, 9 anastomotic leaks, 1 recurrent eso-tracheal fistula). Unfavorable respiratory outcomes concerned 11 cases in the NLGEA group (8 bronchiolitis and 3 pneumopathies) and 6 cases in LGEA group (6 bronchiolitis and 1 pneumopathy). Other complications were 1 cardiac failure in NLGEA group and 1 pulmonary hypertension in LGEA group.

The results of digestive morbidity are presented in *Table 3*.

Statistics about respiratory morbidity are described in *Table 4*.

Details about orthopedic deformation and follow-up are described in *Table 5*.

DISCUSSION:

This is the first French nationwide study to compare comorbidity between LGEA and NLGEA at midterm. The length of the gap influences significatively the digestive, respiratory and orthopedic morbidity at 6 years.

The survival rate of children with esophageal atresia has increased in the last 40 years, but complications that require therapeutic intervention occur in more than half the patients during the first year of life and later.

The length of initial hospital stay can be used as a proxy of neonatal disease severity. In our study the length of hospital stay is significatively higher in the LGEA group.

Also in the LGEA group the incidence of prematurity is higher. The hydramnios due to the absence of fistula could explain these results.

In our study, there are more anastomotic strictures in LGEA group. The inevitable and possible damage of the esophagus during the surgical procedure may rationalize this higher incidence[7]. Actually, dissection and mobilization of the esophageal segments and the esophageal lengthening may lead to local ischemia, post-operative scarring of the esophagus and injury of the vagal nerves. Several hospitalizations for anastomotic stricture dilatation under general anesthesia are reported in the LGEA group [8]. The quality of life of these children is known to be affected by these comorbidities[9]. Persistent esophageal strictures occurred mainly in association with symptomatic GERD.

Prevalence of GERD in EA population is significant[10]. Since few years, the CRACMO issued consensus-based guidelines for EA population[2]. It recommends regular monitoring including esophageal fibroscopy during the childhood in order to screen the evolution of this GERD. Repercussion of GERD is clinical discomfort with retro-sternal burns. Esophageal mucosa anomalies are a long-term unfavorable outcome of GERD[11]. However, complications such as Barret's esophagus highlight the need for continued long term follow-up for these children[12]. It could be interesting to study long-term prevalence of esophageal cancer in this population.

In these patients, esophagitis lesions due to GERD can trigger feeding disorders in a nutritionally precarious population[13]. According to the literature our study confirms that children with LGEA, due to later reconstructive surgery, depend on parenteral nutrition or gastrostomy[14]. Feeding disorder is defined as a broad range of eating problems that may or may not be accompanied by swallowing difficulties for food, liquids or both. Oral motor and sensorial functions normally develop within the first 12 to 24 months of age. We easily

understand that if introduction of an oral diet is delayed, the acquisition of feeding swallowing abilities is impaired[15,16,17,18]. We noticed that a gastrostomy still present at 6 years old is highly more common in the LGEA group. In case of long-term oral abstinence, the gastrostomy is generally considered a good option, as this facilitates easy and efficient intake of calories and nutrients, not interfering with the opportunity to develop normal oral sensitivity, feeding and swallowing abilities [19].

Children with EA are also subject to respiratory comorbidities in medium and long term [20,21]. Respiratory morbidity following EA is not to be neglected and the complication rate is similar to that observed in children with congenital diaphragmatic hernia [22]. However, we didn't find any significant difference between our two groups, except for tracheomalacia and the respiratory follow-up. Regarding the tracheomalacia, the first human data described a deficiency in cartilage in 75% of examined tracheas[23]. These trachea abnormalities not only concern only the site of the fistula, but persistent or worsening respiratory symptoms associated with persistent tracheomalacia may be potentially aggravated by a tracheal diverticulum at the fistula repair site. This can explain the higher rate of tracheomalacia in the NLGEA group.

Moreover, children may also suffer from associated abnormalities and prematurity, conditions which further interfere with the general health status. Respiratory pathologies are known to be more frequent in premature children due to the poor development of their lungs[24]. They could influence the medium-term results of respiratory comorbidity in NLGEA patients.

Prevalence of scoliosis in patients after EA repair ranges from 6 to 50%[25]. Thoracotomies are a risk factor for scoliosis development during puberty[26]. Shoulder asymmetry and ribs block at the site of thoracotomy can explain the occurrence of scoliosis. However, we have to keep in mind the coexistence of congenital vertebral malformations in VACTERL syndrome.

In our study, the incidence of scoliosis in NLGEA group was significantly higher. This can be explained by early surgery performed in this group.

Nowadays thoracoscopic surgery is being developed for EA surgical treatment[27]. This technique is less invasive and could greatly reduce the rate of orthopedic malformation caused by surgery in the long term [28].

One limitation of our study is the small number of patients and the loss of follow-up in NLGEA group which restricted our analysis. Therefore, our study doesn't take into consideration prematurity regarding the long-term outcomes. It could be interesting to carry out a comparative study of co-morbidities analyzing the prematurity aspect of these children and the length of hospitalization[29].

The management of a newborn with EA continues to be challenging. Our study highlights the heterogeneity of the pathology. Regarding the long-term sequalae, we differentiate two really different diseases. The LGEA an NLGEA feature should be a decisive criteria for the follow-up. LGEA group may benefit from a more intensive follow-up program[30,31].

REFERENCES

1. Sfeir, R. *et al.* Esophageal atresia: Data from a national cohort. *J. Pediatr. Surg.* 48, (2013).
2. Dingemann, C. *et al.* ERNICA Consensus Conference on the Management of Patients with Long-Gap Esophageal Atresia: Perioperative, Surgical, and Long-Term Management. *Eur. J. Pediatr. Surg.* (2020)
3. O'Donnell, J. E. M. *et al.* Clinician Knowledge of Societal Guidelines on Management of Gastrointestinal Complications in Esophageal Atresia. *J. Pediatr. Gastroenterol. Nutr.* 72, (2021).
4. Jové Blanco, A. *et al.* Comorbidities and course of lung function in patients with congenital esophageal atresia. *Arch. Argent. Pediatr.* 118, (2020).
5. Mikkelsen, A. *et al.* Traumatic stress, mental health and quality of life in adolescents with esophageal atresia. *J. Pediatr. Surg.* (2020)
6. Comella, A. *et al.* Esophageal morbidity in patients following repair of esophageal atresia: A systematic review. *J. Pediatr. Surg.* (2020)
7. Chiang, C.-M. *et al.* Risk factors and management for anastomotic stricture after surgical reconstruction of esophageal atresia. *J. Formos. Med. Assoc. Taiwan Yi Zhi* (2020)
8. Serhal, L. *et al.* Anastomotic stricture after surgical repair of esophageal atresia: frequency, risk factors, and efficacy of esophageal bougie dilatations. *J. Pediatr. Surg.* 45, (2010).
9. Gallo, G. *et al.* Quality of life after esophageal replacement in children. *J. Pediatr. Surg.* (2020)
10. Koivusalo, A., Pakarinen, M. P. & Rintala, R. J. The cumulative incidence of significant gastrooesophageal reflux in patients with oesophageal atresia with a distal fistula—a systematic clinical, pH-metric, and endoscopic follow-up study. *J. Pediatr. Surg.* 42, (2007).
11. Deurloo, J. A. *et al.* Esophagitis and Barrett esophagus after correction of esophageal atresia. *J. Pediatr. Surg.* 40, (2005).

12. Petit, L.-M. *et al.* Prevalence and Predictive Factors of Histopathological Complications in Children with Esophageal Atresia. *Eur. J. Pediatr. Surg.* 29, (2019).
13. Birketvedt, K. *et al.* Nutritional Status in Adolescents with Esophageal Atresia. *J. Pediatr.* 218, (2020).
14. Lu, Y.-H. *et al.* Risk factors for digestive morbidities after esophageal atresia repair. *Eur. J. Pediatr.* (2020)
15. Khan, K. M. *et al.* Achievement of feeding milestones after primary repair of long-gap esophageal atresia. *Early Hum. Dev.* 85, (2009).
16. R. Baird, D. Levesque, R. Birnbaum, M. Ramsay, A pilot investigation of feeding problems in children with esophageal atresia, Diseases of the Esophagus, 28; (2015)
17. 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.* 64, (2017).
18. Ozsin-Ozler, C., Turgut, M. D., Uzamis-Tekcicek, M. & Soyer, T. Oral Health Status among Children with Repaired Esophageal Atresia. *Eur. J. Pediatr. Surg.* (2020)
19. Mason, S. J., Harris, G. & Blissett, J. Tube Feeding in Infancy: Implications for the Developmentof Normal Eating and Drinking Skills. *Dysphagia* 20, (2005).
20. Beucher, J. *et al.* Long-term evaluation of respiratory status after esophageal atresia repair. *Pediatr. Pulmonol.* 48, (2013).
21. Dittrich, R., Stock, P., Rothe, K. & Degenhardt, P. Pulmonary outcome of esophageal atresia patients and its potential causes in early childhood. *J. Pediatr. Surg.* 52, (2017).
22. Gischler, S. J. *et al.* A prospective comparative evaluation of persistent respiratory morbidity in esophageal atresia and congenital diaphragmatic hernia survivors. *J. Pediatr. Surg.* 44, (2009).
23. Wailoo, M. P. & Emery, J. L. The trachea in children with tracheo-oesophageal fistula. *Histopathology* 3, (1979).

24. Donoso, F., Hedenström, H., Malinovschi, A. & Lilja, H. E. Pulmonary function in children and adolescents after esophageal atresia repair. *Pediatr. Pulmonol.* 55, 206–213 (2020).
25. Gilsanz, V., Boechat, I., Birnberg, F. & King, J. Scoliosis after thoracotomy for esophageal atresia. *Am. J. Roentgenol.* 141, (1983).
26. Soliman, H. A. *et al.* Prevalence and natural history of scoliosis and associated congenital vertebral anomalies in patients operated for esophageal atresia with or without tracheoesophageal fistula. *J. Pediatr. Surg.* 54, (2019).
27. Bastard, F. *et al.* Thoracic skeletal anomalies following surgical treatment of esophageal atresia. Lessons from a national cohort. *J. Pediatr. Surg.* 53, (2018).
28. Mishra, P. R., Tinawi, G. K. & Stringer, M. D. Scoliosis after thoracotomy repair of esophageal atresia: a systematic review. *Pediatr. Surg. Int.* 36, (2020).
29. Ritz, L. A. *et al.* Outcome of Patients With Esophageal Atresia and Very Low Birth Weight (≤ 1,500 g). *Front. Pediatr.* 8, (2020).
30. Sri Paran, T., Decaluwe, D., Corbally, M. & Puri, P. Long-term results of delayed primary anastomosis for pure oesophageal atresia: a 27-year follow up. *Pediatr. Surg. Int.* 23, (2007).
31. Taylor, A. C. F. *et al.* Gastroesophageal Reflux and Related Pathology in Adults Who Were Born With Esophageal Atresia: A Long-Term Follow-up Study. *Clin. Gastroenterol. Hepatol.* 5, (2007).

ACKNOWLEDGEMENTS

The authors are grateful to Diana Potop for reviewing the English text.

AUTHOR CONTRIBUTIONS

CRACMO for data, Agate Bourg, Marie Auger Hunault, Frederic Gottrand and all participative centers for data collection and management, Agate Bourg for data analysis, Agate Bourg et Marie Auger Hunault for manuscript writing, Frederic Gottrand for project development.

COMPLIANCE WITH ETHICAL STANDARDS

All the authors declare that they have no conflict of interest.

LEGENDS

Flow chart: Inclusion of cases and control patients

Table 1: Demographics data and clinical conditions at birth

Table 2: Clinical post-operative conditions

Table 3: Digestive morbidity at 6 years

Table 4: Respiratory morbidity at 6 years

Table 5: Orthopedic follow-up

TABLES AND FIGURES

Flow chart: inclusion of cases and controls

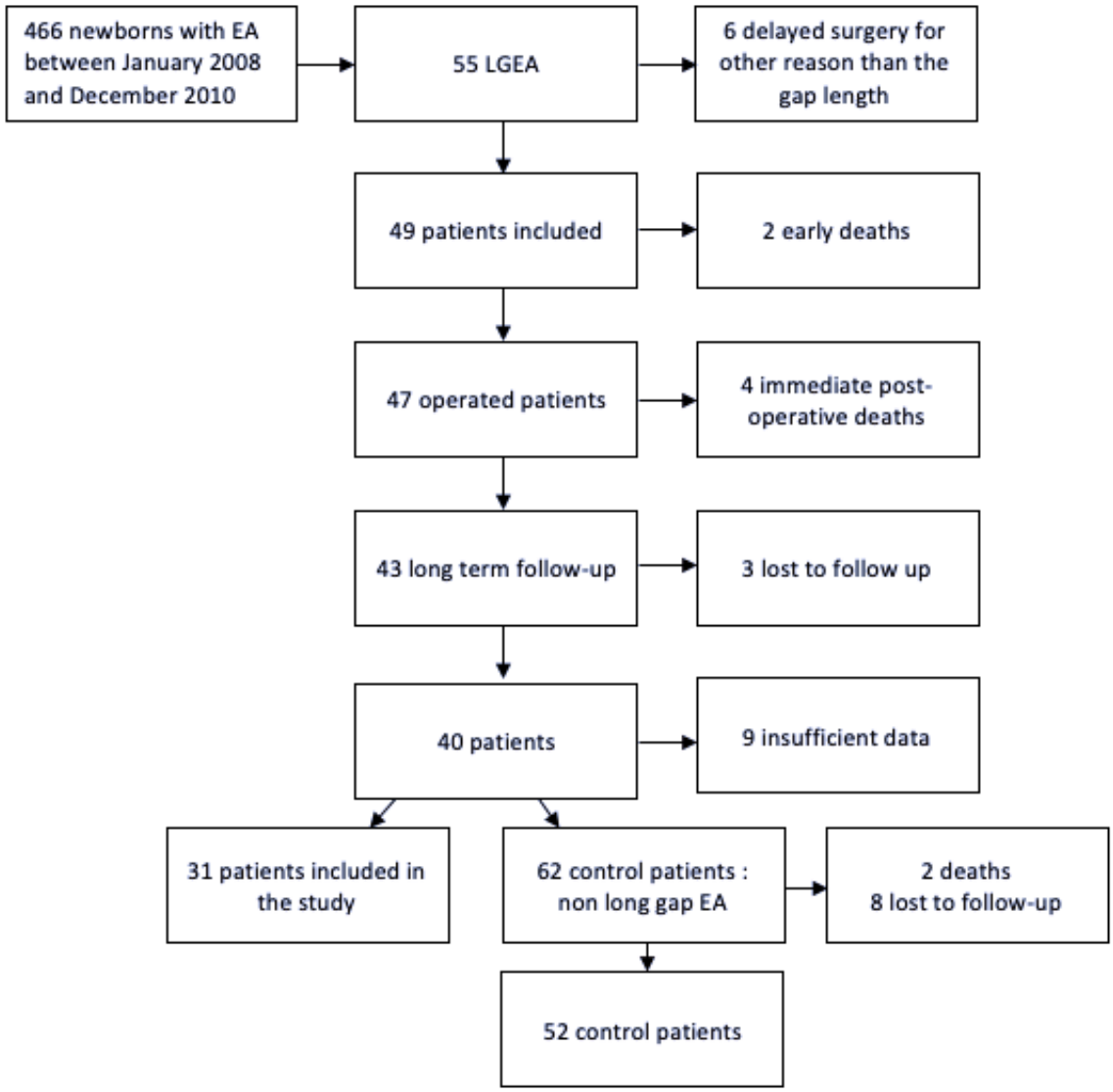


Table 1: Demographics data and clinical conditions at birth

Characteristic	NLGEA, N = 62[1]	LGEA, N = 31[1]	Size effect[2]	P value
Sex			OR=1.7 [0.65 ; 4.6]	p=0.3
Male	42 (68%)	17 (55%)		
Female	20 (32%)	14 (45%)		
Antenatal diagnosis	13 (21%)	25 (81%)	OR=15 [4.8 ; 55]	**p<0.001**
Associated malformations	35 (56%)	16 (52%)	OR=0.82 [0.32 ; 2.1]	p=0.7
-Neurologic	3 (4.9%)	1 (3.2%)	OR=0.65 [0.01 ; 8.5]	p>0.9
Missing value(s)	1	0		
-Renal	10 (16%)	3 (9.7%)	OR=0.56 [0.09 ; 2.4]	p=0.5
-Cardio-vascular	22 (35%)	7 (23%)	OR=0.53 [0.17 ; 1.5]	p=0.2
-Limb	7 (11%)	1 (3.2%)	OR=0.26 [0.01 ; 2.2]	p=0.3
-Ano-rectal	6 (9.7%)	1 (3.2%)	OR=0.31 [0.01 ; 2.8]	p=0.4
-Genito-urinary	7 (11%)	0 (0%)	OR=0.00 [0.00 ; 1.3]	p=0.091
-Costo-vertebral	10 (16%)	5 (16%)	OR=1.0 [0.24 ; 3.6]	p>0.9
-Others	13 (21%)	5 (16%)	OR=0.73 [0.18 ; 2.5]	p=0.8
VACTERL	12 (19%)	4 (13%)	OR=0.62 [0.13 ; 2.3]	p=0.6
CHARGE	2 (3.2%)	0 (0%)	OR=0.00 [0.00 ; 11]	p=0.6
Mother's age (years)	30.1 (5.3)	30.0 (4.5)	μ=-0.08 [-2.3 ; 2.1]	p>0.9
Missing value(s)	8	3		
Birth term (gestational age)	37.39 (2.96)	35.63 (3.24)	μ=-1.8 [-3.1 ; -0.37]	**p=0.014**
Missing value(s)	1	0		
Birth weight (grams)	2,533 (714)	2,205 (516)	μ=-327 [-585 ; -69]	**p=0.014**
Birth size (centimeters)	46.4 (4.2)	44.6 (4.4)	μ=-1.8 [-3.9 ; 0.30]	p=0.091
Missing value(s)	8	5		

Characteristic	NLGEA, N = 62[1]	LGEA, N = 31[1]	Size effect[2]	P value

[1]n (%); Mean (SD)

[2]OR: Odd Ratio; μ: mean difference

Compared to NLGEA-treated subjects, those treated with LGEA were more likely to have an antenatal diagnosis (OR=15 [4.8; 55], p<0.001) and had significantly lower mean term (μ=-1.8 [-3.1; -0.37], p=0.014) and birth weight (μ=-327 [-585; -69], p=0.014).

Table 2: Clinical post-operative conditions

Characteristics	NLGEA, N = 62[1]	LGEA, N = 31[1]	Size effect[2]	P value
Endotracheal ventilation (days)	4.4 (8.3)	6.5 (12.2)	μ=2.0 [-2.9 ; 6.9]	p=0.4
Missing value(s)	2	0		
Non-invasive ventilation (days)	1.15 (3.48)	1.97 (4.38)	μ=0.82 [-1.1 ; 2.7]	p=0.4
Missing value(s)	2	2		
Parenteral nutrition (days)	6 (15)	27 (30)	μ=21 [7.4 ; 34]	**p=0.004**
Missing value(s)	8	7		
Complicated evolution after surgery	30 (48%)	24 (77%)	OR=3.6 [1.3 ; 11]	**p=0.008**
Hospital stay (days)	34 (23)	144 (53)	μ=110 [90 ; 131]	**p<0.001**
Missing value(s)	2	1		
Complicated evolution before 1 year old	19 (31%)	20 (65%)	OR=4.0 [1.5 ; 11]	**p=0.003**
Number of hospitalizations during first year of life	0.92 (0.98)	1.19 (1.14)	μ=0.28 [-0.21 ; 0.76]	p=0.3
Missing value(s)	2	0		
Surgical follow-up	50 (83%)	25 (81%)	OR=0.84 [0.24 ; 3.1]	p=0.8
Missing value(s)	2	0		

[1]Mean (SD); n (%)

[2]OR: Odd Ratio; μ: mean difference

Compared to subjects treated as NLGEA, those treated as LGEA had a longer parenteral duration (μ=21 [7.4; 34], p=0.004) and a longer time before returning home (μ=110 [90; 131], p<0). 001), were significantly more likely to have complications overall (OR=3.6 [1.3; 11], p=0.008) and before the age of 1 year (OR=4.0 [1.5; 11], p=0.003).

Table 3: Digestive morbidity at 6 years

Characteristic	NLGEA, N = 62[1]	LGEA, N = 31[1]	Size effect[2]	P value
GERD	19 (37%)	17 (55%)	OR=2,1 [0.78 ; 5.8]	p=0.12
Missing value(s)	10	0		
Oesophagitis	8 (15%)	14 (45%)	OR=4.4 [1.4 ; 15]	**p=0.005**
Missing value(s)	10	0		
Anti-reflux surgery	10 (19%)	20 (65%)	OR=7.4 [2.5 ; 24]	**p<0.001**
Missing value(s)	10	0		
Anastomotic stricture	20 (38%)	22 (71%)	OR=3.8 [1.4 ; 12]	**p=0.006**
Missing value(s)	10	0		
Dilatations (number)	0.77	3.03	μ=2.3 [1.0 ; 3.5]	**p<0.001**
Missing value(s)	10	0		
Bolus impaction/Dysphagia	17 (33%)	21 (68%)	OR=4.2 [1.5 ; 13]	**p=0.003**
Missing value(s)	10	0		
Previous gastrostomy	6 (12%)	31 (100%)	OR= -	**p<0.001**
Missing value(s)	10	0		
Gastrostomy in place at 6 years old	1 (1,9%)	5 (16%)	OR=9,5 [1,0 ; 471]	**p=0.025**
Missing value(s)	10	0		
Gastroenterology follow-up	25 (48%)	29 (94%)	OR=15 [3.3 ; 145]	**p<0.001**
Missing value(s)	10	0		

[1]n (%); Mean (SD)

[2]OR: Odd Ratio; μ: mean difference

The OR for gastrostomy is not calculable as all subjects in the long gap esophageal atresia group had one. This would be equivalent to dividing it by 0. However, it is known that this difference is significant, although not measurable by a OR.

Table 4: Respiratory morbidity at 6 years

Characteristic	AOLNG, N = 62[1]	AOLG, N = 31[1]	Size effect[2]	P value
Respiratory symptoms	25 (48%)	10 (32%)	OR=0.52 [0.18 ; 1.4]	p=0.2
Missing value(s)	10	0		
Tracheomalacia	17 (33%)	2 (6.5%)	OR=0.14 [0.02 ; 0.69]	**p=0.006**
Missing value(s)	10	0		
Cough	31 (60%)	19 (61%)	OR=1.1 [0.39 ; 3.0]	p>0.9
Missing value(s)	10	0		
Dyspnea	42 (81%)	22 (71%)	OR=0.59 [0.18 ; 1.9]	p=0.4
Missing value(s)	10	0		
Asthma	14 (27%)	13 (43%)	OR=2.1 [0.72 ; 5.9]	p=0.15
Missing value(s)	10	1		
Pneumologic follow-up	27 (52%)	24 (77%)	OR=3.1 [1.1 ; 10]	**p=0.035**
Missing value(s)	10	0		

[1]n (%)

[2]OR: Odd Ratio; μ: mean difference

Table 5: Orthopedic follow-up

Characteristic	AOLNG, N = 62[1]	AOLG, N = 31[1]	Size effect[2]	P value
Deformation of the spine	12 (23%)	1 (3.2%)	OR=0.11 [0.00 ; 0.84]	**p=0.026**
Missing value(s)	10	0		
Orthopedic follow-up	17 (33%)	2 (6.5%)	OR=0.14 [0.02 ; 0.69]	**p=0.006**
Missing value(s)	10	0		

[1]n (%)

[2]OR: Odd Ratio; μ: mean difference

Conclusion

L'AO est une pathologie rare en France et dans le monde. Sa prise en charge est actuellement de plus en plus encadrée permettant une survie importante de ces enfants à la naissance.

De nombreuses comorbidités sont cependant liées à la réparation chirurgicale de cet œsophage et aux malformations associées, parmi lesquelles en premier lieu, les pathologies pulmonaires, digestives et orthopédiques.

L'hétérogénéité des manifestations cliniques de nos patients selon leur groupe d'appartenance est manifeste lors de la prise en charge à la naissance. Cette hétérogénéité se maintient lors du suivi à long terme avec des comorbidités significativement plus présentes chez les AOLG.

Certains résultats dans cette thèse ont plus particulièrement attiré notre attention. L'apparition de scoliose, par exemple, est plus présente chez les enfants opérés d'atrésie non long gap. Nous avançons l'hypothèse chez eux d'une thoracotomie réalisée plus précocement, dans les premiers jours de vie, influençant peut-être plus le développement de la cage thoracique et du rachis.

De même, on rapporte ici que malgré la volonté répandue des chirurgiens de préserver l'œsophage natif dans les atrésies de l'œsophage long gap, on trouve (significativement) moins de dysoralité à long terme chez les enfants dont l'œsophage a été remplacé. Cette donnée est peut-être expliquée par la petite taille de notre échantillon, mais nous pousse à la réflexion.

Enfin, nous pensons que cette étude doit mener à une surveillance différente durant l'enfance des patients atteints d'AO, selon qu'il s'agit d'une AOLG ou d'une AONLG au vu de

l'évolution significativement différente d'un point de vue de l'oralité ou du suivi pneumo-pédiatrique dans nos deux groupes d'étude.

Références bibliographiques

1. Clark, D. C. Esophageal Atresia and Tracheoesophageal Fistula. *Am. Fam. Physician* **59**, (1999).
2. Scott, D. A. Esophageal Atresia / Tracheoesophageal Fistula Overview. *GeneReviews* (1993).
3. Cassina, M. *et al.* Prevalence, characteristics, and survival of children with esophageal atresia: A 32-year population-based study including 1,417,724 consecutive newborns. *Birt. Defects Res. A. Clin. Mol. Teratol.* **106**, (2016).
4. Sfeir, R. *et al.* Esophageal atresia: Data from a national cohort. *J. Pediatr. Surg.* **48**, (2013).
5. Lupo, P. J. *et al.* Population-based birth defects data in the United States, 2010–2014: A focus on gastrointestinal defects. *Birth Defects Res.* **109**, (2017).
6. Ladd, W. E. & Swenson, O. Esophageal Atresia and Tracheo-esophageal Fistula. *Ann. Surg.* **125**, (1947).
7. Ladd, W.E, The Surgical Treatment of Esophageal Atresia and Tracheoesophageal Fistulas *New England Journal of Medicine,* **230** (1944)
8. Pretorius, D. H., Drose, J. A., Dennis, M. A., Manchester, D. K. & Manco-Johnson, M. L. Tracheoesophageal fistula in utero. Twenty-two cases. *J. Ultrasound Med.* **6**, (1987).
9. Shulman, A. *et al.* Prenatal identification of esophageal atresia: the role of ultrasonography for evaluation of functional anatomy. *Prenat. Diagn.* **22**, (2002).
10. Hochart, V. *et al.* The contribution of fetal MR imaging to the assessment of oesophageal atresia. *Eur. Radiol.* **25**, (2015).
11. Karnak, İ., Şenocak, M. E., Hiçsönmez, A. & Büyükpamukçu, N. The diagnosis and treatment of H-type tracheoesophageal fistula. *J. Pediatr. Surg.* **32**, (1997).
12. Haight, C. Congenital atresia of the esophagus with tracheoesophageal fistula : Reconstruction of esophageal continuity by primary anastomosis. *Ann. Surg.* **120**, (1944).

13. Patkowski D., Rysiakiewicz K. *et al* Thoracoscopic Repair of Tracheoesophageal Fistula and Esophageal Atresia *Jour. Laparoendoscopic & Advanced Surgical Techniques* (2009)
14. Mochizuki, K., Obatake, M., Taura, Y. et al. A modified Foker's technique for long gap esophageal atresia. *Pediatr Surg Int* **28**, (2012)
15. Burgos, L. *et al.* Colonic interposition for esophageal replacement in children remains a good choice: 33-year median follow-up of 65 patients. *J. Pediatr. Surg.* **45**, (2010).
16. Hamza, A. F. Colonic replacement in cases of esophageal atresia. *Semin. Pediatr. Surg.* **18**, (2009).
17. Bax, K. M. A. Jejunum for bridging long-gap esophageal atresia. *Semin. Pediatr. Surg.* **18**, (2009).
18. Spitz, L., Kiely, E. & Pierro, A. Gastric transposition in children—a 21-year experience. *J. Pediatr. Surg.* **39**, (2004).
19. Gallo, G., Zwaveling, S., Groen, H., Zee, D. V. der & Hulscher, J. Long-Gap Esophageal Atresia: a Meta-Analysis of Jejunal Interposition, Colon Interposition, and Gastric Pull-Up. *Eur. J. Pediatr. Surg.* **22**, (2012).
20. Choudhury, S. R. *et al.* Survival of patients with esophageal atresia: Influence of birth weight, cardiac anomaly, and late respiratory complications. *J. Pediatr. Surg.* **34**, (1999).
21. Connor, M. J., Springford, L. R., Kapetanakis, V. V. & Giuliani, S. Esophageal atresia and transitional care—step 1: a systematic review and meta-analysis of the literature to define the prevalence of chronic long-term problems. *Am. J. Surg.* **209**, (2015).
22. Jayasekera, C. S., Desmond, P. V., Holmes, J. A., Kitson, M. & Taylor, A. C. F. Cluster of 4 cases of esophageal squamous cell cancer developing in adults with surgically corrected esophageal atresia—time for screening to start. *J. Pediatr. Surg.* **47**, (2012).
23. Engum, S. A., Grosfeld, J. L., West, K. W., Rescorla, F. J. & Scherer, L. R. T. Analysis of Morbidity and Mortality in 227 Cases of Esophageal Atresia and/or Tracheoesophageal Fistula Over Two Decades. *Arch. Surg.* **130**, (1995).

24. Beucher, J. *et al.* Long-term evaluation of respiratory status after esophageal atresia repair. *Pediatr. Pulmonol.* **48**, (2013).
25. Jové Blanco, A. *et al.* Comorbidities and course of lung function in patients with congenital esophageal atresia. *Arch. Argent. Pediatr.* **118**, (2020).
26. Donoso, F., Hedenström, H., Malinovschi, A. & Lilja, H. E. Pulmonary function in children and adolescents after esophageal atresia repair. *Pediatr. Pulmonol.* **55**, (2020).
27. Gatzinsky, V., Jönsson, L., Ekerljung, L., Friberg, L.-G. & Wennergren, G. Long-term respiratory symptoms following oesophageal atresia. *Acta Paediatr.* **100**, (2011).
28. Bastard, F. Les anomalies squelettiques thoraciques après cure d'atrésie de l'oesophage. *Registre national*. **44** (2016).
29. Mishra, P. R., Tinawi, G. K. & Stringer, M. D. Scoliosis after thoracotomy repair of esophageal atresia: a systematic review. *Pediatr. Surg. Int.* **36**, (2020).

Annexe 1

Series of long gap esophageal atresia operated in France between 2008 and 2010: analysis of practices and outcomes

BOURG A[1], AUGER-HUNAULT M[1], POTOP D[1], SFEIR R[2], DAGRY B[3], MBOYO A[3], LAUFENBURGER A[4], BOUBNOVA J[5], PETIT T[6], SAPIN E[7], JOYEUX L[7], PIOLAT C[8], JACQUIER C[8], ALLAL H[9], LEMELLE JL[10], LAM THANH J[10], LECLAIR MD[11], DE NAPOLI S[11], RICARD J[12], POLI-MEROL ML[13], ELBAZ F[14], LARDY H[15], BECMEUR F[16], SCHNEIDER A[16], MURE PY[17], PEYCELON M[18], CAPITO C[19], AIGRAIN Y[19], BONNARD A[20], VARLET F[21], SAUVAT C[22], MICHEL JL[22], KOTOBI H[23], GATIBELZA ME[1], LEVARD G[1], HARPER L[24], AUDRY G[18], AUBERT F[18], GOTTRAND F[25], PARMENTIER B[1]

1- Pediatric surgery unit, University Hospital Center of Poitiers, 86000 Poitiers, France
2- Pediatric surgery unit, University Hospital of Lille Jeanne de Flandre, 59000 Lille, France
3- Pediatric surgery unit, Hospital of Le Mans, 72000 Le Mans, France
4- Pediatric surgery unit, Hospital of Orléans, 45100 Orléans, France
5- Pediatric surgery unit, Bicetre Hospital APHP, 94270 Le Kremlin-Bicêtre, France
6- Pediatric surgery unit, University Hospital of Caen Normandie, 14000 Caen, France
7- Pediatric surgery unit, University Hospital of Dijon F.Mitterand, 21000 Dijon, France
8- Pediatric surgery unit, University Hospital of Grenoble, 38700 Grenoble, France
9- Pediatric surgery unit, University Hospital of Montpellier, 34295 Montpellier, France
10- Pediatric surgery unit, University Hospital of Nancy, 54035 Nancy, France
11- Pediatric surgery unit, University Hospital of Nantes Hotel Dieu, 44093 Nantes, France
12- Pediatric surgery unit, University Hospital of Amiens-Picardie, 80054 Amiens, France
13- Pediatric surgery unit, University Hospital of Reims, 51100 Reims, France
14- Pediatric surgery unit, University Hospital of Rouen, 76000 Rouen, France
15- Pediatric surgery unit, University Hospital of Tours, 37000 Tours, France
16- Pediatric surgery unit, University Hospital of Strasbourg, 67200 Strasbourg, France
17- Pediatric surgery unit, University Hospital of Lyon HCL Women Mother Children Hospital, 69500 Bron, France
18- Pediatric surgery unit, Armand Trousseau Hospital APHP, 75012 Paris, France
19- Pediatric surgery unit, Necker Hospital APHP, 75015 Paris, France
20- Pediatric surgery unit, Robert Debré Hospital APHP, 75019 Paris, France
21- Pediatric surgery unit, University Hospital of Saint-Etienne, 42270 Saint-Priest-en-Jarez
22- Pediatric surgery unit, University Hospital of La Réunion, La Réunion
23- Pediatric surgery unit, Robert Ballanger Hospital, 93602 Aulnay-Sous-Bois
24- Pediatric surgery unit, University hospital of Bordeaux, 33000 Bordeaux
25- Gastroenteroly unit, University Hospital of Lille Jeanne de Flandre, 59000 Lille, France

Corresponding author:

Agate BOURG
CHU de Poitiers, 2 rue de la Miletrie 86021 Poitiers
Tel : +33 5 49 44 42 44
Fax : +33 5 49 44 30 35
Email : agate.bourg@gmail.com

Abstract:

Aim: Esophageal atresia (EA) is the most common esophageal congenital malformation in France. Two different forms exist: “immediate anastomosis” form and long gap esophageal atresia (LGEA). The aim of this study was to describe and evaluate the current management and mid-term outcomes of patients with LGEA in France.

Methods: We prospectively analyzed the medical charts of all cases with LGEA identified in the French EA Registry born between 2008, January 1st and 2010, December 31st. We defined LGEA as all infants born with EA for whom primary anastomosis could not be achieved before 1 month of life because of the length of the gap.

Results: Forty-nine children were included. Gestational age (GA) ranged between 26,8 and 41 weeks (median = 36 weeks) and birthweight ranged between 550 and 3740 grams (median = 2060g). A surgical gastrostomy was performed during initial management in all cases. Additional surgery included: closure of a distal (n=7) or proximal (n=1) tracheo-esophageal fistula, esophagostomy (n=4) or Foker's technique (n=2). Twenty children had complications and two of them died. EA repair was performed either by delayed anastomosis (n=33, 70%) or esophageal replacement (n=14, 30%) at a median age of 87 days (19-454) and a median weight of 4250 g (2400-8300). The esophageal replacement techniques used were gastric transposition (n=4), gastric transposition combined with a Collis gastroplasty (n=4), gastric tube (n=3), esophago-coloplasty (n=2) and Collis-Nissen procedure (n=1). Ninety complications were reported in thirty-eight patients (81%) including 22 anastomotic leaks and 28 anastomotic strictures. At the end of follow-up (median: 1151,5 days, range: 19-1968) the mortality rate was 12%. Exclusive oral feeding was achieved in 88% of survivors and considered as « normal » in 71%. Persistent gastro-esophageal reflux was reported in eight cases despite 26 anti-reflux procedures. Five children required surgical revision of the anastomosis for refractory stricture (n=4) or persistent fistula (n=1).

Conclusion: Most surgeons in France favored delayed anastomosis for LGEA. Over time, mortality rate of infants with LGEA has decreased significantly leading to a survival rate of 88%. Despite these improvements, children have significant respiratory and digestive morbidity, highlighting the need for multidisciplinary management.

Introduction:

Esophageal atresia (EA) is the most frequent congenital esophageal malformation with an incidence of 1.8/10000 newborn in France[1]. In clinical practice, there are two different forms of management and prognosis: “immediate anastomosis” EA and long gap esophageal atresia (LGEA).

LGEA represents 10% of all cases of EA and remains a therapeutic challenge for pediatric surgeons. These children generally undergo a neonatal gastrostomy and, when it exists, an eso-tracheal fistula closure[2,3]. Salivary stasis in upper pouch may be managed by esophagostomy or aspiration until esophageal replacement or esophageal anastomosis is performed[4,5]. Insufficient esophageal length requires a delayed repair that contributes to postponed oral feeding, increasing the risk of oral disorders and aspiration[4].

Different surgical techniques may be used for esophageal repair: esophageal replacement (gastric tube[6], eso-coloplasty[7], jejunoplasty[8] or gastric transposition[9]) and delayed anastomosis of native esophagus. There is no consensus on the ideal surgical management.

Survival rates of children with LGEA are lower than children with the immediate anastomosis form[10]. Mortality rate for LGEA can reach up to 35% during infancy, partly because of associated malformations (70% of cases)[11]. In survivors, long-term sequelae may be digestive (gastro-esophageal reflux disease (GERD), anastomotic strictures, dysphagia and dysmotility, delayed growth, nutritional dependence) respiratory (asthma, tracheomalacia, pulmonary infections), cancerous (endobrachyesophagous) or impacted quality of life (schooling, sport practices…)[10,12]. Currently, literature provides only few data on outcomes of these patients. A multicentric study with a sufficient number of homogeneous patients is mandatory to correctly evaluate the prognosis of these children, identify complications and help their management improval[13].

The aim of this study is to analyze a cohort of long gap esophageal atresia patients, determine current practices and evaluate their outcome.

Study design:

After an institutional review board approval, a national multicentric prospective cohort study was performed including all patients born or managed in France for LGEA between 2008 January 1st and 2010 December 31st. LGEA was defined as delayed esophageal repair (after 1 month of life) due to the importance of gap-length. We identified in the French EA registry from CRACMO (Centre de Reference des Affections Chroniques et Malformatives de l'Oesophage) every case of delayed esophageal anastomosis within all cases of EA managed during the study period. We excluded every case in which the anastomosis had been delayed for any other reason than a long gap between pouches.

CRACMO registry collects clinical data of every case of EA until one year of life. Medical charts of all eligible patients identified through the registry were reviewed.

Collected data included: demographic data, pregnancy, family, neonatal period and esophageal malformation characteristics, initial intervention data and post-operative course, corrective intervention data and post-operative course, clinical characteristics at first discharge, one year follow-up and until the most recent visit was identified.

We defined two groups depending on the surgical management of LGEA. "Native esophagus conservation" and "esophagus replacement" groups were compared using Fisher's exact test for qualitative data and Mann-Whitney's test for quantitative data, $p < 0,05$ value was statistically significant.

Study was approved by CRACMO ethics committee. CRACMO national register was authorized by the national committee of informatic and liberties (CNIL).

Results:

Over the study period, a total of 466 patients with EA were identified in the French EA registry of which 55 had an anastomosis after 1 month of life. Six cases were excluded after reviewing the medical charts. Anastomosis in those cases had been delayed because of a low birth weight in 2 cases, a poor respiratory tolerance in 2 cases, a right aortic arch in 1 case and a polymalformative syndrome with care limitation in 1 case.
A flow-chart of patient characteristics and management is shown in *Figure 1*.

Forty-nine cases from 22 different hospitals were included, representing 11% of all EA over study period. Their demographic characteristics are described in *Table 1*.

Neonatal work-up showed a single co-existent anomaly in 26 cases (52%) and several co-existent anomalies in 14 cases (28,5%).
Co-existent anomalies were neurologic (n=3, 6%), renal (n=7, 14%), cardiovascular (n=12, 24%), ano-rectal (n=4, 8%), genito-urinary (n=5, 10%), limbs (n=4, 8%), costo-vertebral (n=10, 20%) and others (n=7, 14%).
A karyotype was performed in 38 cases (77,6%) and none of them were abnormal.

LGEA diagnosis was made on preoperative X-ray in 31 cases (lack of gastric aeration in 29 cases and subjective assessment of the length of the gap in 2 cases) and intraoperatively in 18 cases (fluoroscopic assessment of the gap through gastrostomy in 9 cases, failure of primary repair after closure of TEF in 7 cases and 2 Foker's procedures).

Initial surgery was performed at a median age of 2 days (1-20). Two newborns were operated later (19 and 20 days of life) because of prematurity and low birth weight.
A surgical gastrostomy was performed initially in all cases. An additional procedure was performed in 14 cases: proximal (n=1) or distal (n = 7) fistula closure, Foker's procedure (n=2) and esophagostomy (n=4).
Two patients died after initial surgery: 1 case of ulcero-necrotizing enterocolitis and 1 case of respiratory decompensation.

Characteristics of patients between “native esophagus conservation” and “esophagus replacement” groups are summarized in *Tables 2*.
In “esophagus replacement” group there were: 4 cases of gastric transposition, 4 cases of gastric transposition associated to Collis, 3 cases of gastric tube, 2 cases of Coloplasty and 1 case of Collis Nissen.
There is no significant difference between the two groups except for weight at birth.

Table 3 mentions corrective surgery. Weight at corrective surgery was significantly higher in the “esophagus replacement” group. Anastomotic tension was subjectively assessed by the operating surgeon. When an elongation technique was used, either Monero or Livatidis procedures were performed in all cases (n=3).

Data about post-operative outcomes are listed in *Table 4*.
We classified complications in four main groups:

-Related to surgery: anastomotic fistula (n=22; 49%), anastomotic stricture requiring at least one dilatation (n=28; 62%), adhesion-related small bowel obstruction (n=1), bilateral recurrent laryngeal nerve paralysis (n=1), peritonitis secondary to perforation caused by jejunostomy (n=1), gastric volvulus (n=1), chylothorax (n=1), Claude Bernard Horner syndrome (n=1) and pneumoperitoneum (n=1).

-Iatrogenic: central venous catheter infection (n=6), deep vein thrombosis (n=1), cardiac arrest caused by accidental extubation (n=1) and pneumothorax following anastomotic stricture dilatation (n=1).

-Respiratory: pneumonia (n=6), bronchiolitis (n=2), tracheomalacia (n=2), respiratory distress due to a high cervical fistula which was not initially diagnosed (n=2), pulmonary hypertension (n=1) and acute respiratory distress syndrome (n=1).

-Infections: pyelonephritis (n=5), gastroenteritis (n=1).

Two patients died after corrective surgery: 1 early necrosis of colic transplant and 1 septic shock due to chronical mediastinitis.

Forty-five patients were still alive at the age of one.
Thirty-eight patients required readmission (84%); 3 patients were still not discharged before the age of one.
Figure 2 shows the different reasons for readmission.

Post-operative complications requiring readmission, gastro-enterologic, respiratory complications and causes of readmission related to associated

malformations are summarized in *Figure 3.* Revision of the anastomosis due to refractory stricture was performed in 4 cases, all of them being in the conservative group.

All data about patients at one year are presented in *Table 5*.

Discussion:

EA is the most frequent congenital esophageal malformation, its incidence in France being 1.8/10000 newborn[1]. Associated malformations are present in 50% of cases, including VACTERL sequence in 13% and cardiac malformation in 1 out of 3 cases[13]. In classic EA, neonatal surgery is performed to close trachea-esophageal fistula and restore continuity[2]. The main post-operative complications are anastomotic leaks (8 to 25%)[13,14] and anastomotic strictures (37%)[15]. Risk factors for strictures are anastomotic tension[15] and GERD[16].

Progress in neonatal resuscitation these last decades has greatly improved prognosis[17], with mortality ranging between 0% and 2,5%[13,17].

Mean outcomes are influenced by respiratory sequelae (50% of cases after 36 years follow-up)[18] and GERD (up to 44% of children at 5 years old)[19]. Long-term complications warrant extended follow-up[12].

Most of the published studies present a single technique performed by an experimented surgeon[4,20]. These studies lack of reproducibility for all the pediatric surgeon population. To the best of our knowledge, this is the first multicentric study which aims to prospectively analyze the management of LGEA population immediately after birth and during the first year of life.

There is no consensus regarding the definition of LGEA[21,22,11]. It reflects a lack of adherence to international guidelines promoting a systematic measurement of the gap[23], without any consensus on the best way to achieve it. Therefore, we chose a pragmatic LGEA definition for this study. It is possible that some cases of type I and II EA could have benefited from immediate anastomosis if the gap had been measured. During the study period, 2 type I EA have been managed with immediate anastomosis and were not included. The use of our pragmatic definition helped us to select EA cases with or without TEF with an incidence of LGEA of 10,5% (49/466). In this study, the definition of LGEA reaches the same number of type III and IV EA as type I and II. Different practices for gap measurement were found: measurement of the defect

during initial surgery using X-ray (with or without opacification) or measurement of the vertebral distance. It shows that data about gap length were poor and not comparable.

Substantial variation in the management of infants with EA is reported in literature. Most of authors believe that native esophagus should be preferred and argue for delayed anastomosis[24,25] sometimes requiring elongation techniques[26,5,27,28]. For others, preserving the native esophagus leads to severe complications[29] and they advocate esophageal replacement using gastric transposition[9], coloplasty[7], gastric tube[6,30], jejunoplasty[8] or a Collis procedure[31]. Most studies concern short periods of time and few patients[11,24,32,33,34].

Anastomotic stricture was the most frequent complication (62% of children) requiring dilatations. In literature, the rate of stricture varies between 33% and 76%[24,33,34]. The main risk factor for stricture is believed to be the anastomotic tension during surgery. Therefore, it is a bit surprising to observe in this study comparable rates of anastomotic strictures between both groups, knowing that esophageal replacement is theoretically a less tension provider. Nevertheless, refractory strictures were only observed in conservative group and more particularly in cases of Foker's esophageal elongation technique.

The key finding in this study appears to be a better evaluation of morbidity and mortality for a better parent counseling during the prenatal period. Complication rate is high in this series (90%), partly because we chose to report all kind of complication and not only surgical related complications. Thus, initial surgery was complicated in 41% of cases. Post-operative complication rate was 81% with a majority of anastomotic leaks and strictures. The surgical management is one of the main factors leading to anastomotic tension and GERD, making LGEA a worse prognostic group, which leads to higher anastomotic leak or stricture rates and finally long-term GERD and esophagus dysmotilty.

In this study, one out of two children had an anastomotic leak, whereas in literature this rate is variable[11,32,34]. This difference is probably related to lack of consensus concerning the definition of an anastomotic leak. However, the majority of cases didn't require additional surgery as reported in literature[35].

Mortality rate was 12%, this high rate being related to prognostic factors such as absence of oral feeding at 1 month of life and length of the gap. Even if the follow-up is 1 year, the study highlights the significant differences between the LGEA and the non-long-gap esophageal atresia, with lower mortality and morbidity rates[36].

The study is limited by the size of the cohort, due to the rarity of the pathology (1,5 patient per center per year in our study). One aim of this study was to compare different surgical procedures, but their diversity didn't allow us to statistically compare morbidity and mortality. "Native esophagus conservation" group and "esophagus replacement" group were not statistically comparable for birth weight and weight at surgery. However, there are different studies in literature that compare these two groups, but none of them show a significant difference between different surgical techniques[37,38,39,20,40,24,41,30,42,43,31]. Because of the bias of our study, we were not able to decide between conservation and esophageal replacement. Refractory stenoses are more frequent in the conservative group.

Moreover, the definition of LGEA is arguable and variable according to each medical center. But this classification is necessary because there is no precise measurement of the gap. We strongly believe improvements should be made in measuring the gap.

Conclusion:

The majority of french pediatric surgeons choose a conservative management for LGEA. This technique seems to be reliable with a high rate of success, but also with significant peri-operative morbidity.

Most authors agree that the surgical technique should be based on the surgeon's preference. Complication rate was high as 90% requiring long hospitalizations and many readmissions.

It might be interesting to evaluate morbidity of patients in this cohort in the medium term, around the age of 6-8 years. In this way, it could be possible to improve the overall care of these patients throughout their lives.

Bibliography :

1. Sfeir, R. *et al.* Esophageal atresia: Data from a national cohort. *J. Pediatr. Surg.* **48** (2013)
2. Alberti, D., Boroni, G., Corasaniti, L. & Torri, F. Esophageal atresia: pre and post-operative management. *J. Matern. Fetal Neonatal Med.* **24** (2011)
3. Holland, A. J. A. & Fitzgerald, D. A. Oesophageal atresia and tracheo-oesophageal fistula: current management strategies and complications. *Paediatr. Respir. Rev.* **11** (2010)
4. Foker, J. E., Kendall, T. C., Catton, K. & Khan, K. M. A flexible approach to achieve a true primary repair for all infants with esophageal atresia. *Semin. Pediatr. Surg.* **14** (2005)
5. Tamburri, N., Laje, P., Boglione, M. & Martinez-Ferro, M. Extrathoracic esophageal elongation (Kimura's technique): a feasible option for the treatment of patients with complex esophageal atresia. *J. Pediatr. Surg.* **44** (2009)
6. Gupta, L., Bhatnagar, V., Gupta, A. K. & Kumar, R. Long-Term Follow-up of Patients with Esophageal Replacement by Reversed Gastric Tube. *Eur. J. Pediatr. Surg.* **21** (2011)
7. Hamza, A. F. Colonic replacement in cases of esophageal atresia. *Semin. Pediatr. Surg.* **18** (2009)
8. Bax, K. M. A. Jejunum for bridging long-gap esophageal atresia. *Semin. Pediatr. Surg.* **18** (2009)
9. Spitz, L., Kiely, E. & Pierro, A. Gastric transposition in children—a 21-year experience. *J. Pediatr. Surg.* **39** (2004)
10. Rintala, R. J., Sistonen, S. & Pakarinen, M. P. Outcome of esophageal atresia beyond childhood. *Semin. Pediatr. Surg.* **18** (2009)
11. Al-Shanafey, S. & Harvey, J. Long gap esophageal atresia: an Australian experience. *J. Pediatr. Surg.* **43** (2008)
12. Ludman, L. & Spitz, L. Quality of life after gastric transposition for oesophageal atresia. *J. Pediatr. Surg.* **38** (2003)

13. Burge, D. M. *et al.* Contemporary management and outcomes for infants born with oesophageal atresia. *BJS Br. J. Surg.* **100** (2013)
14. Atzori, P. *et al.* Preoperative tracheobronchoscopy in newborns with esophageal atresia: does it matter? *J. Pediatr. Surg.* **41** (2006)
15. Serhal, L. *et al.* Anastomotic stricture after surgical repair of esophageal atresia: frequency, risk factors, and efficacy of esophageal bougie dilatations. *J. Pediatr. Surg.* **45** (2010)
16. de Lagausie, P. GER in Oesophageal Atresia: Surgical Options. *J. Pediatr. Gastroenterol. Nutr.* **52** (2011)
17. Orford, J., Cass, D. T. & Glasson, M. J. Advances in the treatment of oesophageal atresia over three decades: the 1970s and the 1990s. *Pediatr. Surg. Int.* **20** (2004)
18. Sistonen, S. *et al.* Repaired oesophageal atresia: respiratory morbidity and pulmonary function in adults. *Eur. Respir. J.* **36** (2010)
19. Koivusalo, A., Pakarinen, M. P. & Rintala, R. J. The cumulative incidence of significant gastrooesophageal reflux in patients with oesophageal atresia with a distal fistula—a systematic clinical, pH-metric, and endoscopic follow-up study. *J. Pediatr. Surg.* **42** (2007)
20. Foker, J. E., Kendall Krosch, T. C., Catton, K., Munro, F. & Khan, K. M. Long-gap esophageal atresia treated by growth induction: the biological potential and early follow-up results. *Semin. Pediatr. Surg.* **18** (2009)
21. Ron, O., De Coppi, P. & Pierro, A. The surgical approach to esophageal atresia repair and the management of long-gap atresia: results of a survey. *Semin. Pediatr. Surg.* **18** (2009)
22. Gross, E. R. *et al.* The role of fiberoptic endoscopy in the evaluation and management of long gap isolated esophageal atresia. *Pediatr. Surg. Int.* **26** (2010)
23. van der Zee, D. C. *et al.* Position Paper of INoEA Working Group on Long-Gap Esophageal Atresia: For Better Care. *Front. Pediatr.* **5** (2017)

24. Sri Paran, T., Decaluwe, D., Corbally, M. & Puri, P. Long-term results of delayed primary anastomosis for pure oesophageal atresia: a 27-year follow up. *Pediatr. Surg. Int.* **23**, (2007)
25. Bagolan, P. *et al.* Long gap esophageal atresia and esophageal replacement: moving toward a separation? *J. Pediatr. Surg.* **39** (2004)
26. Khan, K. M., Sabati, A. A., Kendall, T. & Foker, J. E. The Effect of Traction on Esophageal Structure in Children with Long-Gap Esophageal Atresia. *Dig. Dis. Sci.* **51** (2006)
27. Zaritzky, M., Ben, R., Zylberg, G. I. & Yampolsky, B. Magnetic compression anastomosis as a nonsurgical treatment for esophageal atresia. *Pediatr. Radiol.* **39** (2009)
28. Stringel, G., Lawrence, C. & McBride, W. Repair of long gap esophageal atresia without anastomosis. *J. Pediatr. Surg.* **45** (2010)
29. Cowles, R. A. & Coran, A. G. Gastric Transposition in Infants and Children. in *Esophageal and Gastric Disorders in Infancy and Childhood* (2017)
30. Borgnon, J. *et al.* Esophageal replacement in children by an isoperistaltic gastric tube: a 12-year experience. *Pediatr. Surg. Int.* **20** (2004)
31. Nakahara, Y. *et al.* Modified Collis-Nissen procedure for long gap pure esophageal atresia. *J. Pediatr. Surg.* **47** (2012)
32. Séguier-Lipszyc, E. *et al.* The management of long gap esophageal atresia. *J. Pediatr. Surg.* **40** (2005)
33. Burjonrappa, S., Thiboutot, E., Castilloux, J. & St-Vil, D. Type A esophageal atresia: a critical review of management strategies at a single center. *J. Pediatr. Surg.* **45** (2010)
34. Hunter, C. J., Petrosyan, M., Connelly, M. E., Ford, H. R. & Nguyen, N. X. Repair of long-gap esophageal atresia: gastric conduits may improve outcome—a 20-year single center experience. *Pediatr. Surg. Int.* **25** (2009)
35. Zhao, R., Li, K., Shen, C. & Zheng, S. The outcome of conservative treatment for anastomotic leakage after surgical repair of esophageal atresia. *J. Pediatr. Surg.* **46** (2011)

36. Castilloux, J., Noble, A. J. & Faure, C. Risk Factors for Short- and Long-Term Morbidity in Children with Esophageal Atresia. *J. Pediatr.* **156** (2010)
37. Gupta, D. K. *et al.* Esophageal replacement in the neonatal period in infants with esophageal atresia and tracheoesophageal fistula. *J. Pediatr. Surg.* **42** (2007)
38. Holland, A. J. A. *et al.* Surgical outcomes of esophageal atresia without fistula for 24 years at a single institution. *J. Pediatr. Surg.* **44** (2009)
39. Tannuri, U., Tannuri, A. C. A., Gonçalves, M. E. P. & Cardoso, S. R. Total gastric transposition is better than partial gastric tube esophagoplasty for esophageal replacement in children. *Dis. Esophagus* **21** (2008)
40. Tannuri, U., Maksoud-Filho, J. G., Tannuri, A. C. A., Andrade, W. & Maksoud, J. G. Which is better for esophageal substitution in children, esophagocoloplasty or gastric transposition? A 27-year experience of a single center. *J. Pediatr. Surg.* **42** (2007)
41. Friedmacher, F. & Puri, P. Delayed primary anastomosis for management of long-gap esophageal atresia: a meta-analysis of complications and long-term outcome. *Pediatr. Surg. Int.* **28** (2012)
42. Schneider, A., Ferreira, C. G., Kauffmann, I., Lacreuse, I. & Becmeur, F. Modified Spitz Procedure Using a Collis Gastroplasty for the Repair of Long-Gap Esophageal Atresia. *Eur. J. Pediatr. Surg.* **21** (2011)
43. Cauchi, J. A., Buick, R. G., Gornall, P., Simms, M. H. & Parikh, D. H. Oesophageal substitution with free and pedicled jejunum: short- and long-term outcomes. *Pediatr. Surg. Int.* **23** (2007)

ACKNOWLEDGEMENTS

The authors are grateful to Diana Potop and Luke Harper for reviewing the English text.

AUTHOR CONTRIBUTIONS

CRACMO for data, Benoit Parmentier, Frederic Gottrand, Georges Audry, Frederic Aubert and all participative centers for data collection and management, Benoit Parmentier for data analysis, Benoit Parmentier, Agate Bourg et Marie Auger Hunault for manuscript writing, Frederic Gottrand for project development.

COMPLIANCE WITH ETHICAL STANDARDS

All the authors declare that they have no conflict of interest.

LEGENDS

Figure 1: Flow chart
Table 1: Demographic characteristics
Table 2: Characteristics of “native esophagus conservation” and “esophagus replacement” groups.
Table 3: Corrective surgery
Table 4: Post-operative information for “esophagus replacement” and “native esophagus conservation” groups.
Figure 2: Cause of readmission before one year
Figure 3: Post-operative, gastro-enterologic, nutritional and respiratory complications and hospitalizations relative to associated malformations
Table 5: Outcomes at one year of “esophagus replacement” and “native esophagus conservation” groups.

Figure 1: Flow chart

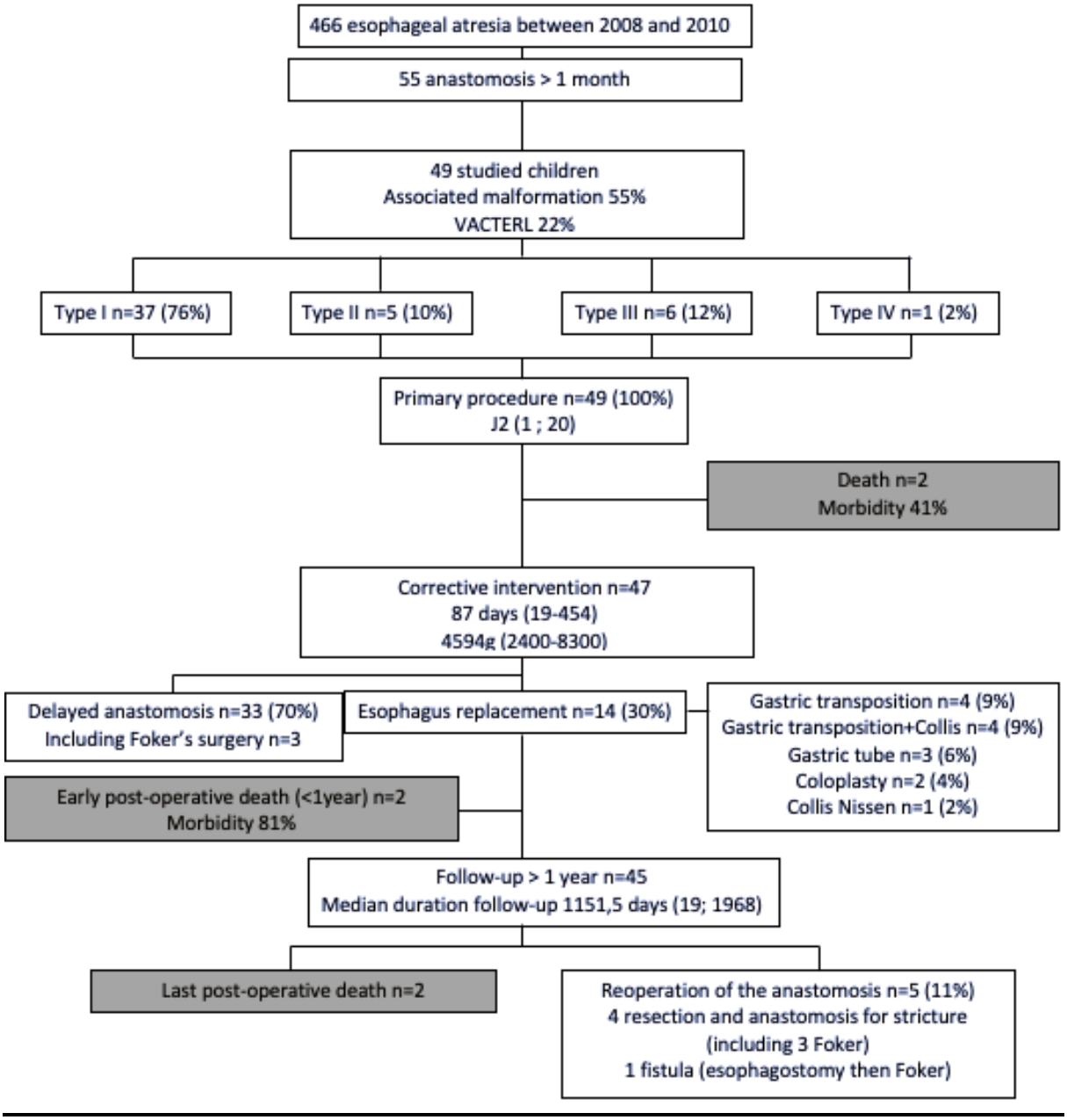


Table 1: Demographic Characteristics

DEMOGRAPHIC CHARACTERISTICS	n=49
Antenatal diagnosis (%)	37 (75)
Spontaneous pregnancy (%)	45 (92)
GA at birth in amenorrhea weeks (range)	36 (26,8; 41)
Vaginal delivery (%)	26/44 (59)
Spontaneous delivery (%)	27/44 (61)
Median birth weight in grams (range)	2072 (550; 3740)
Associated malformations (%)	26 (52)
Associated cardiac malformation (%)	12 (24)
VACTERL (%)	11 (22)
EA type according to the Ladd classification (%)	37 type I (76) 5 type II (10) 6 type III (12) 1 type IV (2)

Table 2: Characteristics of "native esophagus conservation" and "esophagus replacement" groups.

	Native esophagus conservation (n=33)	Esophagus replacement (n=14)	Statistical analysis
Median term in amenorrhea weeks (AW) (range)	36 (26.8; 39.8)	37 (31; 41)	p = 0,23
Median birth weight in grams (range)	2072 (1040; 3740)	2459 (550; 3025)	**p = 0,04 ***
Associated anomalies (%)	15 (45)	9 (64)	p = 0,34 CI 95% (0,1; 1,98)
Cardiac malformations (%)	7 (21)	4 (28)	p = 0,46 CI 95% (0,13; 3,87)
VACTERL (%)	7(21)	4 (28)	p = 0,46 CI 95% (0,1; 2,49)
Ladd classification (%)	25 type I (76) 3 type II (9) 4 type III (12) 1 type IV (3)	10 type I (71) 2 type II (14) 2 type III (14)	p = 0,46 CI 95% (0,22; 6,1)
Median age at primary intervention in days (range)	2 (1; 20)	2 (1; 19)	p = 0,37
Esophagostomy (%)	1 (3)	3 (21)	p = 0,07 CI 95% (0,01; 1,68)
Fistula closure (%)	5 (15) 4 type III 1 type IV	3 (21) 2 type III 1 type II	p = 0,68 CI 95% (0,11; 4,98)
Post-operative complications in %	42	43	p = 1 CI 95% (0,23; 4,29)

CI 95%: confidence interval to 95%

** statistically significant data*

Table 3: Corrective surgery

	Native esophagus conservation (n=33)	Esophagus replacement (n=14)	Statistical analysis
Median age at corrective surgery in days (range)	79 (19; 165)	98,5 (38; 454)	p = 0,27
Median weight at corrective surgery in grams (range)	4105 (2400; 6750)	5587 (2950; 8300)	**p = 0,04***
Presence of anastomotic tension (%)	22 (67)	6 (43)	p = 0,19 CI 95% (0,62; 11,75)
Elongation artifice (%)	3 (9)	0	p = 0,54 CI 95% (0,17; 2,08)

CI 95%: confidence interval to 95%

** statistically significant data*

Table 4: Post-operative information for "esophagus replacement" and "native esophagus conservation" groups.

	Native esophagus conservation n=33	Esophagus replacement n=14	Population n =47
Invasive ventilation in days (range)	0,5 (0; 53)	3 (0,5; 43)	1 (0; 53)
Non-invasive ventilation in days (range)	5 (0; 21)	0 (0; 15)	0 (0; 21)
Use of amines (%)	2/28 (7)	4/11 (36)	6/40 (15)
Parenteral nutrition (%)	24/27 (89)	11/11 (100)	35/38 (92)
Parenteral nutrition withdrawal in days after surgery (range)	21 (10; 123)	32 (6; 164)	27,5 (6; 164)
Complications (%)	26 (79)	12 (86)	38 (80)
Anastomotic fistula (%)	16 (48)	6 (43)	22 (47)
Anastomotic stricture (%)	20 (60)	8 (57)	28 (62)
Mortality (%)	1 (3)	1 (7)	2 (4)
Days of hospitalization before discharge (range)	151 (68; 317)	138 (59; 393)	139 (59; 393)

Figure 2: Cause of readmission before one year

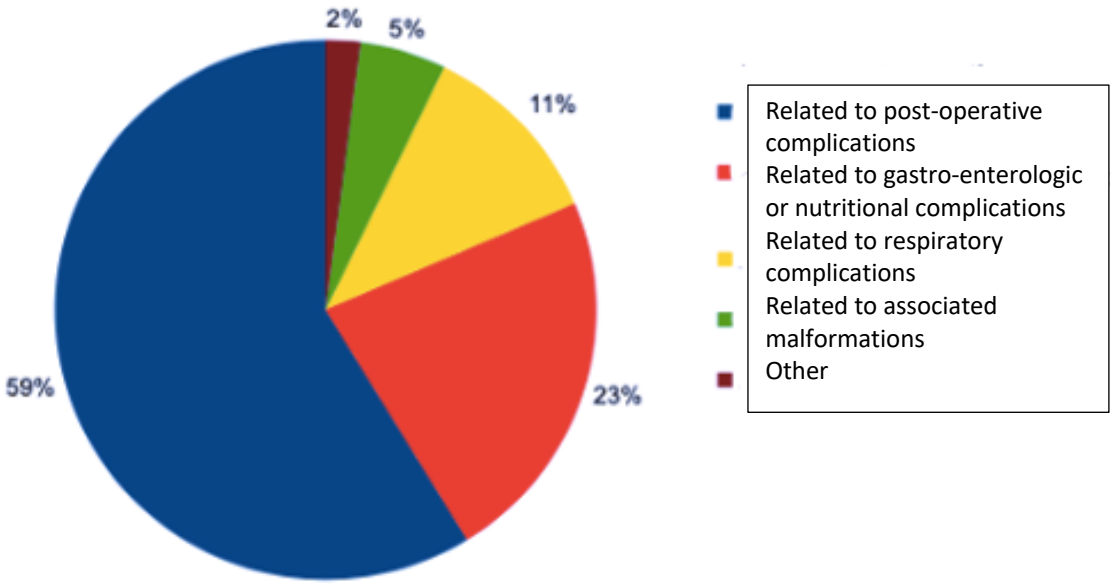
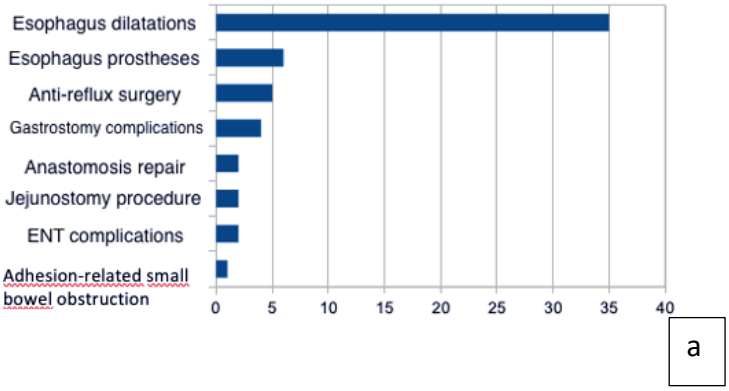


Figure 3: Complications, morbidity and readmission



a

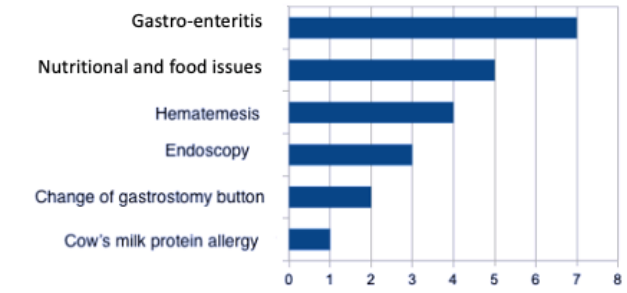
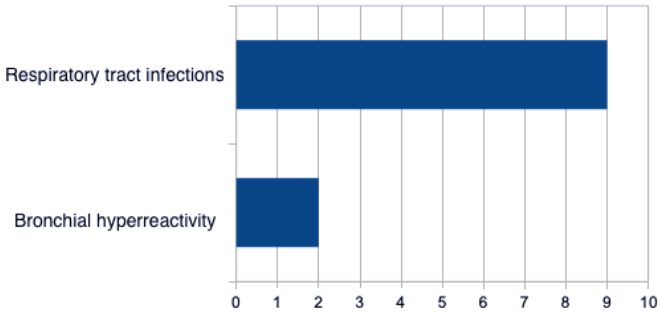


Figure 3: Gastro-enterologic and nutritional complications

b



c

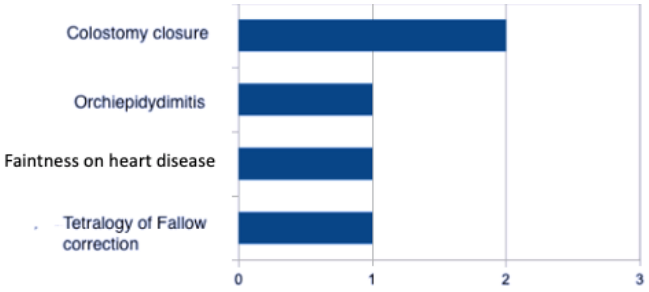


Figure 5: Hospitalizations due to associated malformations

d

a. Post-operative complications
b. Gastro-enterologic and nutritional complications
c. Respiratory complications
d. Hospitalizations related to associated malformations

Table 5: Outcomes at one year of "esophagus replacement" and "native esophagus conservation" groups.

	Native esophagus conservation n=32	Esophagus replacement n=13	Population n = 45
Rehospitalizations	25 (78%)	13 (100%)	38 (84%)
Number of rehospitalizations (extreme)	2,5 (0; 6)	3 (1; 7)	2,5 (0; 7)
Median duration in days (extreme)	9 (0; 148)	13 (0; 114)	9 (0; 148)
Total duration of hospitalization in days during the first year (extreme)	151,5 (86; 365)	160 (70; 365)	152 (70; 365)
Anti-reflux surgery	17 (53%)	6 (46%)	23 (51%)
Dysphagia	9/31 (29%)	3/12 (25%)	12/43 (28%)
GERD	25/32 (78%)	5/12 (42%)	30/44 (68%)
Oral disorder	18 (55%)	9 (69%)	27 (60%)
Intercurrent respiratory event	9 (28%)	5 (38%)	14 (31%)
Respiratory treatment	9/28 (32%)	6/13 (46%)	15/41 (37%)
Excusive oral feeding	16 (50%)	4 (31%)	20 (44%)

Annexe 2

Medium-term follow-up of a national cohort of long-gap esophageal atresia: analysis of orality and morbidity

BOURG A[1], AUGER-HUNAULT M[1], PARMENTIER B[1], GOTTRAND F[2], BECMEUR F[3], SCHNEIDER A[3], PIOLAT C[4], BONNARD A[5], SFEIR R[6], LEMELLE JL[7], ROUSSEAU V[8], SARNACKI S[8], SISSAOUI S[9], POUZAC M[10], DIMITROV G[11], ELBAZ F[12], JANNICK R[13], RAVASSE P[14], PETIT T[14], SAPIN E[15], MARTELLI H[16], BRANCHEREAU S[16], FOUQUET V[16], CARCAUZON V[17], MURE PY[18], GELAS T[18], KALFA N[19], ALLAL H[19], LECLAIR MD[20], DE NAPOLI S[20], POLI-MEROL ML[21], LARDY H[22], AUDRY G[23], IRTAN S[23], VARLET F[24], LEVARD G[1], POTOP D[1], THOMAS J[25]

1- Pediatric Surgery unit, University Hospital Center of Poitiers, 86000 Poitiers, France
2- Gastroenteroly unit, University Hospital of Lille Jeanne de Flandre, 59000 Lille, France
3- Pediatric surgery unit, University Hospital of Strasbourg, 67200 Strasbourg, France
4- Pediatric surgery unit, University Hospital of Grenoble, 38700 Grenoble, France
5- Pediatric surgery unit, Robert Debré Hospital APHP, 75019 Paris, France
6- Pediatric surgery unit, University Hospital of Lille Jeanne de Flandre, 59000 Lille, France
7- Pediatric surgery unit, University Hospital of Nancy, 54035 Nancy, France
8- Pediatric surgery unit, Necker Hospital APHP, 75015 Paris, France
9- Gastroenterology unit, Necker Hospital APHP, 75015 Paris, France
10- Pediatric surgery unit, Hospital of Orléans, 45100 Orléans, France
11- Gastroenterology unit, Hospital of Orleans, 45100 Orléans, France
12- Pediatric surgery unit, University Hospital of Rouen, 76000 Rouen, France
13- Pediatric surgery unit, University Hospital of Amiens-Picardie, 80054 Amiens, France
14- Pediatric surgery unit, University Hospital of Caen Normandie, 14000 Caen, France
15- Pediatric surgery unit, University Hospital of Dijon F.Mitterand, 21000 Dijon, France
16- Pediatric surgery unit, Bicetre Hospital APHP, 94270 Le Kremlin-Bicêtre, France
17- Pediatric surgery unit, Hospital of Le Mans, 72000 Le Mans, France
18- Pediatric surgery unit, University Hospital of Lyon HCL Women Mother Children Hospital, 69500 Bron, France
19- Pediatric surgery unit, University Hospital of Montpellier, 34295 Montpellier, France
20- Pediatric surgery unit, University Hospital of Nantes Hotel Dieu, 44093 Nantes, France
21- Pediatric surgery unit, University Hospital of Reims, 51100 Reims, France
22- Pediatric surgery unit, University Hospital of Tours, 37000 Tours, France
23- Pediatric surgery unit, Armand Trousseau Hospital APHP, 75012 Paris, France
24- Pediatric surgery unit, University Hospital of Saint-Etienne, 42270 Saint-Priest-en-Jarez
25- Gastroenterology unit, University Hospital Center of Poitiers, 86000 Poitiers, France

Corresponding author:

Agate BOURG
CHU de Poitiers, 2 rue de la Miletrie 86021 Poitiers
Tel : +33 5 49 44 42 44
Fax : +33 5 49 44 30 35
Email : agate.bourg@gmail.com

Abstract:

Introduction: Midterm long gap esophageal atresia (LGEA) morbidity is multifactorial. There is no standardized management of these children, making their medical care a real challenge for pediatric surgeons and pediatricians. The aims of this study were to analyze the midterm digestive and respiratory outcomes in this population focusing on the risk factors for nutritional disorders and the impact of surgical procedure on delayed morbidity.

Materials and Methods: A national prospective multicentric study was performed to evaluate midterm gastro-intestinal and respiratory morbidity. We collected data concerning growth, digestive and respiratory outcomes. A phone call assessment was performed to determine orality disorders using FOIS (Functional Oral Intake Scale) in all patients.

Results: Thirty-one patients were included. The age ranged from 7 to 10 years. Median follow-up was 9 years. Z-score median for weight was -0,97 (-3,52; 2,5). Eleven patients (35%) were treated by proton pump inhibitors (PPI) for gastro-esophageal reflux disease (GERD), 10 children (35%) had at least one endoscopic dilatation for anastomotic stricture with mean number of dilatations of 3 (0; 10) and 17 patients (55%) had food blockage. Three patients (10%) were dependent on enteral nutrition. FOIS was abnormal in 16 patients (52%). Ten children (30%) had asthma requiring long term treatment and 3 children (10%) had recurrent respiratory tract infections. Birth weight, term of birth, associated malformations, GERD, dysphagia, abnormal FOIS and asthma were not identified as risk factors for undernutrition. There were more oral disorders with native esophageal conservation than esophageal replacement (p=0,04). There was no significative difference for undernutrition, GERD, dysphagia, number of dilatations and asthma between the group with native esophageal conservation and the one with esophageal replacement.

Discussion: Midterm morbidity in this population concerns 80% of patients, principally marked by persistent GERD and dysphagia. Oral disorders were present for more than half of patients. Esophagus replacement surgical procedure seems to have better results regarding feeding disorder compared to native esophageal conservation.

Key words: esophageal atresia, long-gap esophageal atresia, gastro-esophageal reflux disease, dysphagia, orality, esophageal replacement.

INTRODUCTION:

Esophageal atresia (EA) is a congenital anomaly, with an incidence of 1.8 in 10000 newborns in France leading to 150 births per year in our country [1].

Since first successful surgery in 1941[2], anesthetic, surgical, and neonatal care have improved tremendously. Currently, long-term survival rate of these children approaches 100% in absence of other malformations[3,4,5].

Treatment of long gap esophageal atresia (LGEA) is still a major challenge[6,7,8,9,10] and even if the mortality is low, morbidity remains high.

Lack of studies doesn't allow to clearly evaluate the morbidity in subpopulation of LGEA. However, a recent study on LGEA over 30 years showed a median follow-up age of 5 years. Morbidity is essentially due to gastro-esophageal reflux disease (GERD) causing esophagitis, esophagus stricture and dysphagia[11].

The aim of this study is to describe midterm morbidity concerning: growth, digestive and respiratory status in a national cohort of LGEA.

The second aim is to evaluate risk factors for undernutrition and the impact of surgical procedure on this long-term morbidity.

MATERIALS AND METHODS

1. Population

EA is defined as a complete interruption of normal continuity of the esophagus. LGEA was defined as absence of restoration of esophageal continuity during neonatal period because of the important length of the inter-segment gap.

Between January 1st 2008 and December 31st 2010, all newborns who had delayed surgery for EA (after the age of 1 month) in France were included.

Patients were excluded if anastomosis was delayed for other reason than the length of the gap.

CRACMO (Centre de Référence des Affections Chroniques et Malformatives de l'Œsophage) was created in 2007 in Hospital Jeanne de Flandre at Centre Hospitalier Regional Universitaire of Lille. One of its goals is to ensure management of an EA epidemiological register in close collaboration with 38 centers responsible for treating this malformation in France.

Patients' inclusion in the register consisted of a collection sheet completed by the surgeon at the end of first neonatal hospitalization.

This study was under the agreement of CRACMO and its scientific council. National register of CRACMO is authorized by CNIL (commission nationale de l'informatique et des libertés).

This was a prospective, multicenter study.

2. Data

For all the patients that were included, all medical appointment and additional examination reports were collected. A letter was sent to all families to establish a phone meeting to evaluate orality using FOIS (Functional Oral Intake Scale).

Growth analysis was made by z-score calculation of weight for size (W/S) and size for age (S/A).

Digestive morbidity was analyzed by presence of gastroesophageal reflux disease (GERD) and paraclinical confirmation by eso-gastroduodenal transit (EGDT), eso-gastroduodenal fibroscopy (EGDF) or Ph-metry; food blockage; nutrition (enteral or oral); esophageal dilatations.

Orality was evaluated by FOIS including 7 states of orality.

Respiratory morbidity was evaluated by taking into consideration the long term treatment for asthma and recurrent respiratory infections (more than 2 episodes requiring antibiotics during the last year).

Risk factors for malnutrition were explored: term of birth, weight of birth, associated malformation, surgical technique used for esophageal reparation, GERD, dysphagia, FOIS and asthma.

We also compared patients with esophageal replacement to those with native esophageal conservation for GERD, FOIS, dysphagia, number of dilatations and asthma.

Patients were excluded if a phone call assessment with the family was not possible.

3. Statistics

Most data were converted to quantitative binary data mode to realize medians of binary variables and an expression of results with values of extremes.

Birth term, birth weight and size, age at data collection, z-score for weight and size, number of esophagus dilatations, number of months since the last dilatation and FOIS were analyzed quantitatively and results of descriptive statistics were expressed as medians and values of extremes.

Nonparametric tests were used to search for malnutrition risk factors and comparison between groups who underwent different surgical procedures.

Mann-Whitney test was used to compare quantitative and qualitative variables, Fisher exact test was used to compare 2 qualitative variables.

$P< 0,05$ was considered statistically significant.

Results:

The included patients were described in *Figure 1.* Characteristics of patients were described in *Table 1*

Median of z-score for weight in midterm was -1 (-3,52; 2,5). Undernutrition was present in 7 patients (23%) defined by a z-score for weight <-2 standard deviation (SD).

Fifty-five percent of patients had an anti-reflux surgery, and 23% among them had recurrent symptoms. In the group of patients without surgery, 6 (43%) had a clinical GERD and 4 had a confirmation by further examination. In total, 35% of patients were treated for reflux, 12 (38%) underwent surgery and 8 (27%) did not have any sign of GERD (*Figure 2).*

Ten children (35%) never had dilatations for stricture.
For the others, the median number of dilatations was 2 (0; 10). Median time between dilatations was 62 months (3; 114). Five children had at least one dilatation in the past year and all had a native esophageal conservation.

Food blockage concerned 17 patients (55%). Sixteen children had feeding disorder (FOIS <7) (52%). (*Figure 3*)

Ten children had asthma requiring a background treatment (32%). Recurrent infection (> 2 infections per year requiring antibiotics) concerned 3 children (10%) (*Figure 3*).

Prematurity and low birthweight were not associated with midterm undernutrition (*Figure 4*). Associated malformations at birth, esophageal replacement or native esophageal conservation, GERD, food blockage, oral disorder and asthma were not statistically associated with undernutrition. (*Figure 5*)

The result of FOIS was significatively poorer for children with native esophageal conservation. (*figure 6*). There was no significant difference between the group with native esophageal conservation and the group with esophageal replacement for undernutrition, GERD, dysphagia and asthma. There was no significant difference between the two groups concerning the number of dilatations. (*Figure 7*)

DISCUSSION:

Due to the rarity of the pathology, the literature provides only few evidences on the midterm morbidity of LGEA group of patients. The optimal follow up of these patients is still debated. We report a national cohort of 31 patients. LGEA concerned only 11% of EA in France, which represent 16 children per year in France. These data are equivalent to the literature rate of LGEA[12]. Delayed morbidity is complex and multifactorial. We analyzed the morbidity regarding undernutrition, GERD, anastomotic strictures and asthma.

Feeding disorder is a relatively recent field of clinical research and analysis of anthropometric data highlighted chronic undernutrition in our population. A specific study between delayed undernutrition and premature birth did not allow to define it as a risk factor. This study showed a partial dependence on enteral nutrition with gastrostomy in 7% of cohort. Even if a great majority of children was enteral nutrition free, food blockage was present in 57% of population. This is coherent with the results described in the literature[13]. The incidence of dysphagia is higher than the anastomotic stricture requiring dilatations. We can explain this by frequent dysmotility of esophagus in EA[14,15].

Oral disorder for EA is underestimated although feeding and swallowing rehabilitation is more often considered[16]. If the introduction of an oral diet is delayed, the acquisition of feeding and swallowing abilities is impaired. Recent studies highlight adjustments of food consistency in 65% of patients with EA[17]. In the present study, 50% of children still have oral disorders at the age of 6. Despite the consensus among pediatric surgeons that the conservation of native esophagus is associated with the best postoperative results, oral disorder is higher in case of native esophagus conservation compared to replacement surgery.

Regarding digestive morbidity, medium-term GERD was present in one third of patients. *Koivulaso and al.* showed a GERD rate of 44% at the age of 5 years[18] in children born with EA and eso-tracheal fistula. In long-gap subpopulation, prevalence of GERD was 48% at 5 years and 66% at 13 years[11,19]. In adulthood, a study by *Taylor and al.* including 132 patients with EA shows a prevalence of anti-reflux surgery for 11% of patients and 60% of clinical reflux[20]. The prevalence of GERD in our study is lower. This difference could be explained by the subjective evaluation of GERD by the

patient[21]. An objective assessment with PH-metry could be more precise. In our study, all patients except two (18%) underwent PH-metry.

To prevent persistence of GERD responsible of esophageal metaplasia, anti-reflux surgery can be proposed[22]. In this study, 55% of patients had an anti-reflux surgery and a quarter of operated children had recurrent GERD. A previous study shows a recurrent GERD in 42%[23]. Esophagus reconstruction surgical procedure did not have an impact on the prevalence of GERD. This data is similar with those in the literature[24].

GERD and anastomotic strictures are closely linked. It requires early intervention to prevent feeding disorders. Anastomotic stricture was present in 65% of children in this cohort. Thirty five percent of patients with LGEA never had dilatation after surgery. In the study, incidence of dilatations was higher than in the literature[25] but median number of dilatations was equivalent to previous studies[26].

However *Stenstrom et al.* showed that anastomotic stenosis was an early morbidity[27]. Prolonged feeding difficulties may contribute to persistence of oral disorders and undernutrition.

It appears important that follow-up for these children focuses not only on gastrointestinal pathologic condition but also on respiratory pathologic condition. In this study, prevalence of children with asthma requiring treatment was 32%, as in literature[28]. This condition is not improved with the age[29]. Persistent respiratory symptoms may be sustained by long term gastrointestinal complication such as GERD.

Some authors have estimated that costal synostosis after thoracotomy or associated chest malformations may participate in development of restrictive syndrome[30]. Both inflammatory process and intrinsic airway hyperresponsiveness may also contribute to this remodeling process, which may indorse impaired lung function. In addition, a study has shown a correlation between inter-fragmentary length, GERD or respiratory pneumonitis and restrictive syndrome[31]. We think that the pathophysiology of these respiratory sequelae is multifactorial. To explain the respiratory outcome, we have to mention the tracheomalacia, the frequent inhalations linked to esophageal dysmotility and the lack of pulmonary maturation during childhood[32].

This work presents the results of mid-term follow-up of a cohort of patients with a homogeneous management in time and space. Major limitation of this work is

the size of the cohort, due to the rarity of the pathology. It was not possible to obtain significant differences in statistical analyzes, even if some trends are highlighted. Better knowledge of mid-term morbidity of these patients seems essential to prenatal information for these patients and families. In addition, evaluation of follow-up practices on a national multicenter cohort should improve the global and multidimensional care of these children. We propose that some factors should be used to identify patients who will benefit from a more intensive medical follow-up program.

Regarding the frequency of complications in our population of LGEA, it appears to us that a study comparing mid-term morbidity in children with LGEA and children with non-long gap esophageal atresia should be important to assess the differences between these two individual groups of patients.

Bibliographie :

1. Sfeir, R. *et al.* Esophageal atresia: Data from a national cohort. *J. Pediatr. Surg.* **48**, (2013).
2. Nakayama, D. K. The history of surgery for esophageal atresia. *J. Pediatr. Surg.* (2020).
3. A. Pini Prato, *et al* A cross-sectional nationwide survey on esophageal atresia and tracheoesophageal fistula, *J. Pediatr Surg*, **50** (2015)
4. Orford, J., Cass, D.T. & Glasson, M.J. Advances in the treatment of oesophageal atresia over three decades: the 1970s and the 1990s. *Ped Surgery Int,* **20** (2004)
5. Shaw-Smith C. Oesophageal atresia, tracheo-oesophageal fistula, and the VACTERL association: review of genetics and epidemiology, *Journal of Medical Genetics* **43** (2006).
6. Séguier-Lipszyc, E. *et al.* The management of long gap esophageal atresia. *J. Pediatr. Surg.* **40**, (2005).
7. Shieh, H. F. & Jennings, R. W. Long-gap esophageal atresia. *Semin. Pediatr. Surg.* **26**, (2017).
8. John E. Foker, Tara C. Kendall, Kirsti Catton, Khalid M. Khan, A flexible approach to achieve a true primary repair for all infants with esophageal atresia, *Seminars in Pediatric Surgery*, **14** (2005)
9. Foker, J. E., Kendall Krosch, T. C., Catton, K., Munro, F. & Khan, K. M. Long-gap esophageal atresia treated by growth induction: the biological potential and early follow-up results. *Semin. Pediatr. Surg.* **18** (2009).
10. Gallo, G., Zwaveling, S., Groen, H., Zee, D. V. der & Hulscher, J. Long-Gap Esophageal Atresia: a Meta-Analysis of Jejunal Interposition, Colon Interposition, and Gastric Pull-Up. *Eur. J. Pediatr. Surg.* **22** (2012).
11. Friedmacher, F. & Puri, P. Delayed primary anastomosis for management of long-gap esophageal atresia: a meta-analysis of complications and long-term outcome. *Pediatr. Surg. Int.* **28** (2012).
12. Saud Al-Shanafey, John Harvey. Long gap esophageal atresia: an Australian experience,

Journal of Pediatric Surgery, **43** (2008)

13. Tomaselli, V. *et al.* Long-term evaluation of esophageal function in patients treated at birth for esophageal atresia. *Pediatr. Surg. Int.* **19** (2003).
14. Legrand C., Michaud L. *et al* Long-term outcome of children with oesophageal atresia type III. *Archives of Disease in Childhood*. **97** (2012)
15. Tambucci, R. *et al.* Anastomotic Strictures after Esophageal Atresia Repair: Incidence, Investigations, and Management, Including Treatment of Refractory and Recurrent Strictures. *Front. Pediatr.* **5** (2017)
16. Conforti, A., Valfré, L., Falbo, M., Bagolan, P. & Cerchiari, A. Feeding and Swallowing Disorders in Esophageal Atresia Patients: A Review of a Critical Issue. *Eur. J. Pediatr. Surg.* **25** (2015).
17. 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.* **64** (2017).
18. Koivusalo, A., Pakarinen, M. P. & Rintala, R. J. The cumulative incidence of significant gastrooesophageal reflux in patients with oesophageal atresia with a distal fistula—a systematic clinical, pH-metric, and endoscopic follow-up study. *J. Pediatr. Surg.* **42** (2007)
19. Sri Paran, T., Decaluwe, D., Corbally, M. & Puri, P. Long-term results of delayed primary anastomosis for pure oesophageal atresia: a 27-year follow up. *Pediatr. Surg. Int.* **23** (2007)
20. Taylor, A. C. F. *et al.* Gastroesophageal Reflux and Related Pathology in Adults Who Were Born With Esophageal Atresia: A Long-Term Follow-up Study. *Clin. Gastroenterol. Hepatol.* **5** (2007)
21. Tomaselli V., Volpi M., Dell'Agnola C. et al. Long-term evaluation of esophageal function in patients treated at birth for esophageal atresia. *Ped Surgery Int* **19** (2003)

22. Koivusalo, Antti I. *et al* Endoscopic Surveillance After Repair of Oesophageal Atresia Longitudinal study in 209 patients. *Journal of Ped Gastro and Nutn*. **62** (2016)
23. Harry Lindahl, Risto Rintala, *et al* Failure of the nissen fundoplication to control gastroesophageal reflux in esophageal atresia patients, *J. Pediatr. Surg*. **24** (1989)
24. Lee, H. Q., Hawley, A., Doak, J., Nightingale, M. G. & Hutson, J. M. Long-gap oesophageal atresia: comparison of delayed primary anastomosis and oesophageal replacement with gastric tube. *J. Pediatr. Surg.* **49** (2014)
25. Koivusalo, A. *et al.* Is routine dilatation after repair of esophageal atresia with distal fistula better than dilatation when symptoms arise? Comparison of results of two European pediatric surgical centers. *J. Pediatr. Surg.* **39** (2004)
26. Serhal, L. *et al.* Anastomotic stricture after surgical repair of esophageal atresia: frequency, risk factors, and efficacy of esophageal bougie dilatations. *J. Pediatr. Surg.* **45** (2010)
27. Stenström, P., Anderberg, M., Börjesson, A. & Arnbjörnsson, E. Dilations of anastomotic strictures over time after repair of esophageal atresia. *Pediatr. Surg. Int.* **33** (2017)
28. Gatzinsky, V., Jönsson, L., Ekerljung, L., Friberg, L.-G. & Wennergren, G. Long-term respiratory symptoms following oesophageal atresia. *Acta Paediatr.* **100** (2011)
29. Sistonen, S. *et al.* Repaired oesophageal atresia: respiratory morbidity and pulmonary function in adults. *Eur. Respir. J.* **36** (2010)
30. Kovesi, T. & Rubin, S. Long-term Complications of Congenital Esophageal Atresia and/or Tracheoesophageal Fistula. *Chest* **126** (2004)
31. Dittrich, R., Stock, P., Rothe, K. & Degenhardt, P. Pulmonary outcome of esophageal atresia patients and its potential causes in early childhood. *J. Pediatr. Surg.* **52** (2017)
32. Fragoso, A. C. & Tovar, J. A. The Multifactorial Origin of Respiratory Morbidity in Patients Surviving Neonatal Repair of Esophageal Atresia. *Front. Pediatr.* **2** (2014)

ACKNOWLEDGEMENTS

The authors are grateful to Luke Harper and Diana Potop for reviewing the English text.

AUTHOR CONTRIBUTIONS

CRACMO for data, Julie Thomas, Frederic Gottrand and all participative centers for data collection and management, Julie Thomas for data analysis, Julie Thomas, Agate Bourg et Marie Auger Hunault for manuscript writing, Frederic Gottrand for project development.

COMPLIANCE WITH ETHICAL STANDARDS

All the authors declare that they have no conflict of interest.

LEGENDS

Figure 1: Flow chart
Table 1: Characteristics of patients
Figure 2: Study of GERD
Figure 3: Digestive and respiratory prevalence
Figure 4: Association between undernutrition-Birth term and birth weight
Figure 5: Undernutrition associated factors
Figure 6: Surgical procedures associated factors
Figure 7: Surgical procedure – dilatation number association

Figure 1: Flow chart

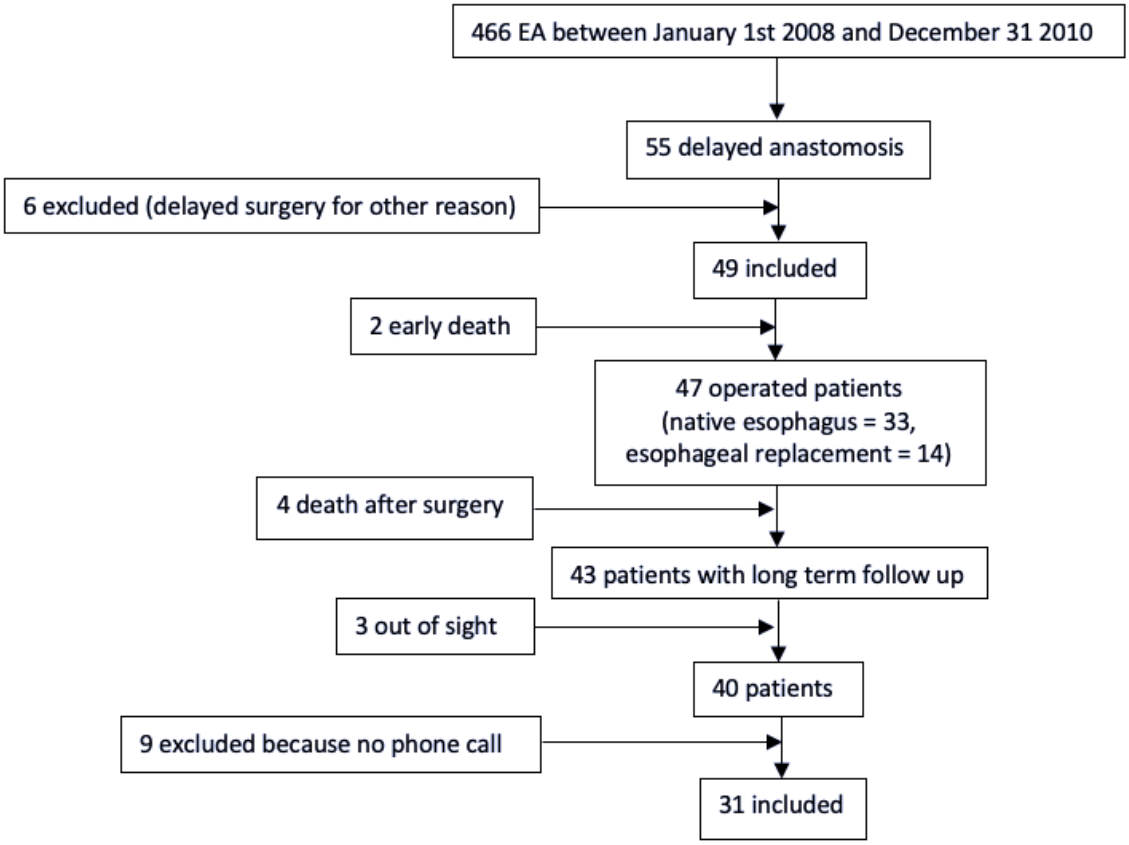
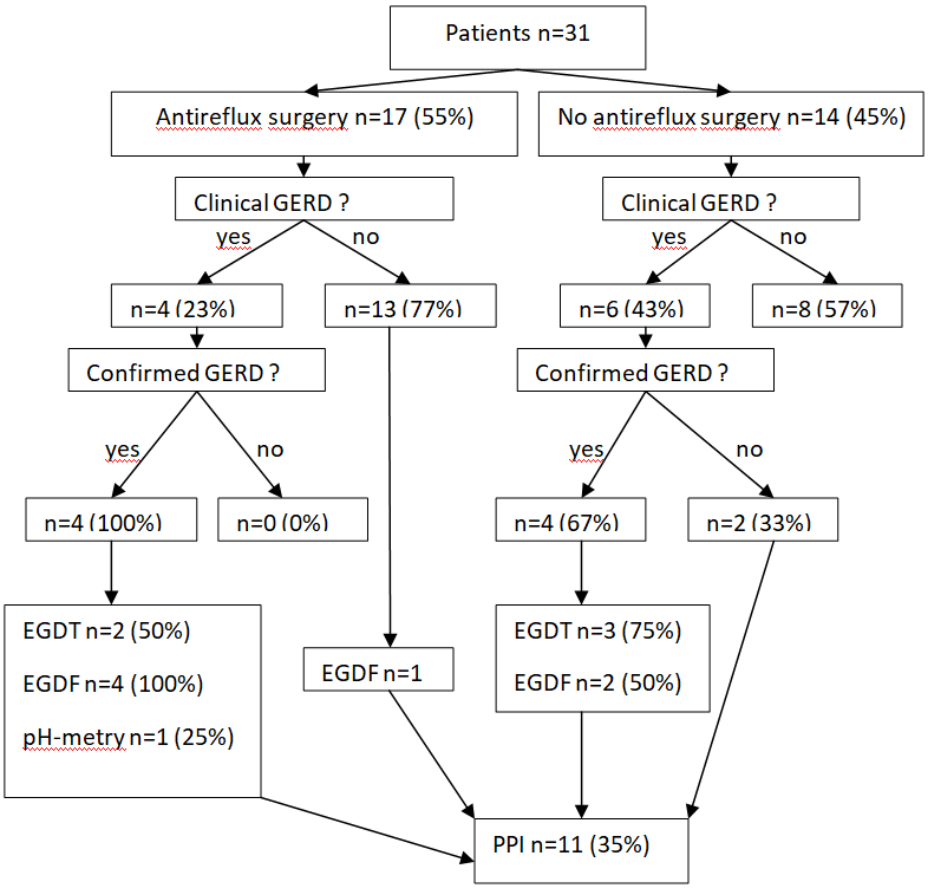


Table 1: Characteristics of patients

Characteristics of patients	**n=31 (%)**
Boys	n=16 (52)
Term of birth (gestational age (GA)) (min; max)	37 (26,8; 39,8)
Weight of birth (grams) (min; max)	2260 (1040; 3260)
Associated malformations	n = 13 (42)
Native esophageal conservation	n = 22 (71)
Esophageal replacement	n = 9 (29)
Median age at study (years) (min; max)	9 (7; 10)

Figure 2: Study of GERD



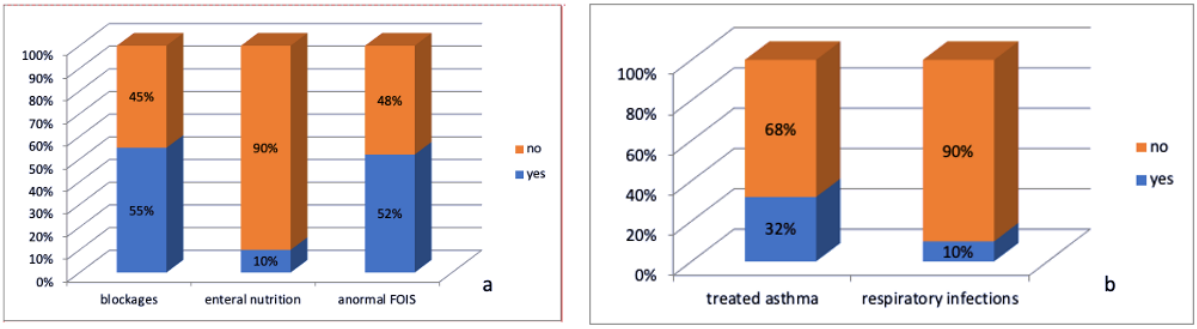
GERD: Gastroesophageal reflux disease

PPI: Proton pump inhibitor

EGDT: esophageal-gastro-duodenal transit

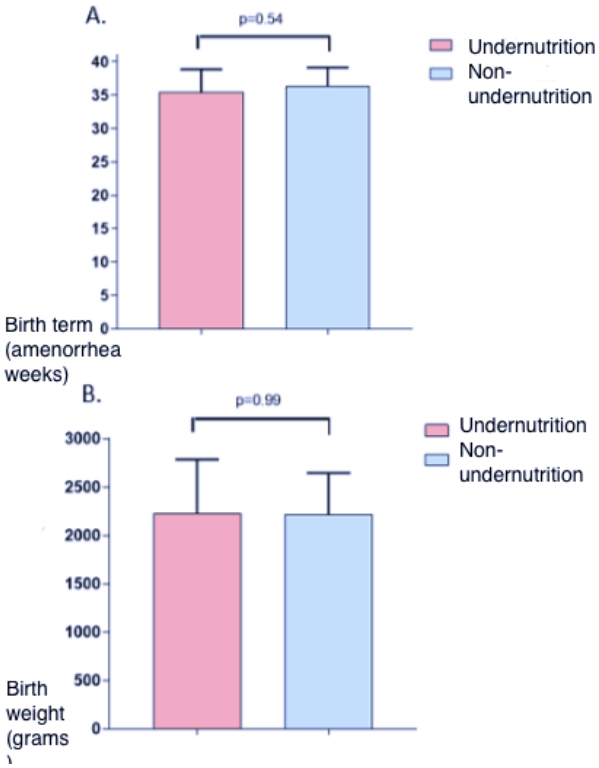
EGDF: esophageal-gastro-duodenal fibroscopy

Figure 3: Respiratory and digestive prevalence



a. Food blockage, enteral nutrition and oral disorders
b. Asthma and respiratory infections

Figure 4: Association between undernutrition-Birth term (A) and birth weight (B).

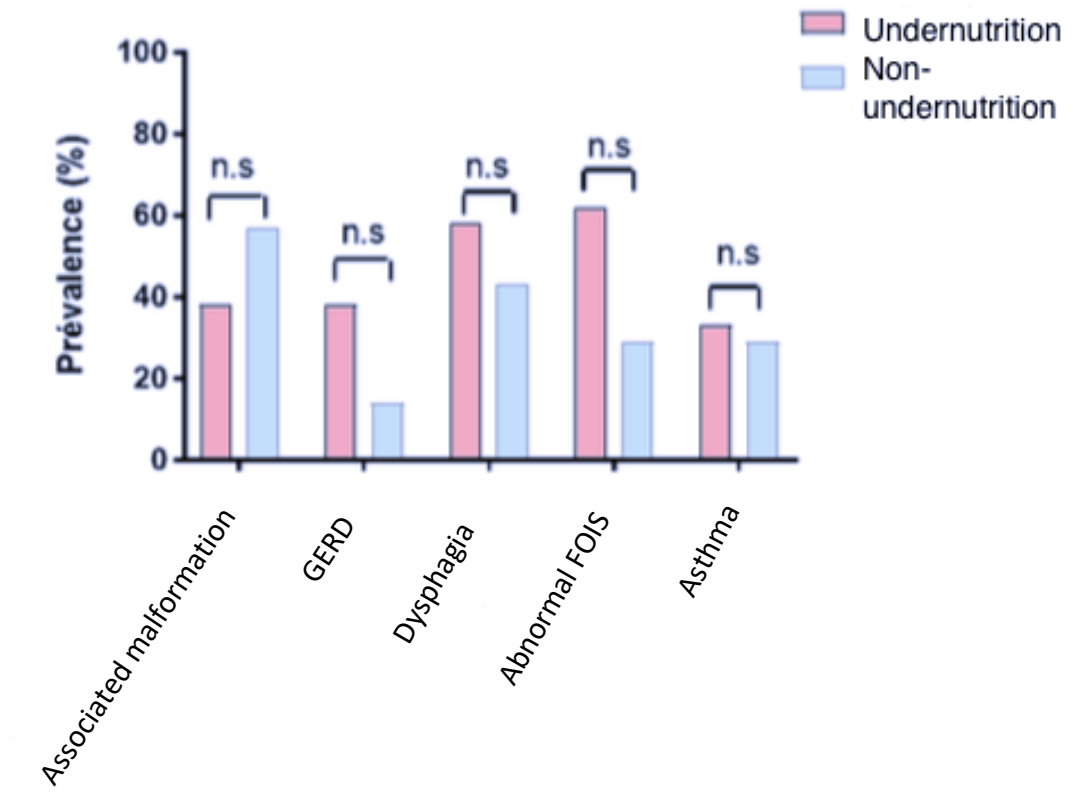


Birth term in amenorrhea weeks: undernutrition median (n=24) = 36,5 (26,9; 39,8) and non-undernutrition (n=7) = 37,8 (32; 38,7), p= 0,54 (A).

Birth weight in grams: undernutrition median (n=24) = 2268 (1680; 2820) and non-undernutrition (n=7) = 2260 (1040; 3260), p=0,99 (B).

Mann-Whitney non-parametric test.

Figure 5: Undernutrition associated factors



Undernutrition : n=24. Non-undernutrition n = 7.

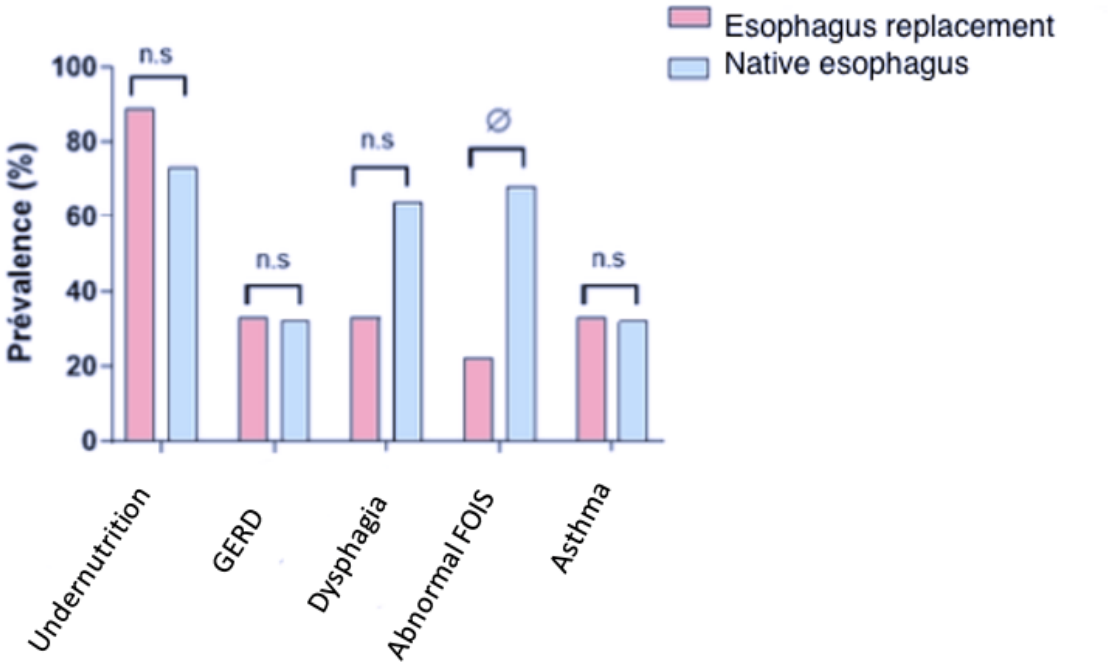
Associated malformations : undernutrition n=9 (38%) vs non-undernutrition n=4 (57%). OR = 0,46 (0,05 ; 3,43), p= 0,41 ;

GERD : undernutrition n=9 (38%) vs non-undernutrition n=1 (14%), OR = 3,47 (0,05 ; 3,43), p = 0,38 ;

Dysphagia : undernutrition n=14 (58%) vs non-undernutrition n=3 (43%), OR = 1,83 (0,25 ; 15,40), p=0,67 ; Abnormal FOIS : undernutrition n=15 (62%) vs non-undernutrition n=2 (29%), OR=3,97 (0,52 ; 50,06), p=0,20 ; Asthma : undernutrition n=8 (33%) vs non-undernutrition n=2 (29%), OR = 1,24 (0,16 ; 15,78), p=1.

Non-parametric Fisher test.

Figure 6 : Surgical procedure associated factors



Esophagus replacement : n=9, native esophagus : n=22.

Undernutrition : esophagus replacement n=8 (89%) vs native esophagus n=16 (73%), OR =2 ,91 (0,27 ; 154,84), p=0,64 ;

GERD : esophagus replacement n=3 (33%) vs native esophagus n=7 (32%), OR = 1,07 (0,13 ; 7,06), p=1 ;

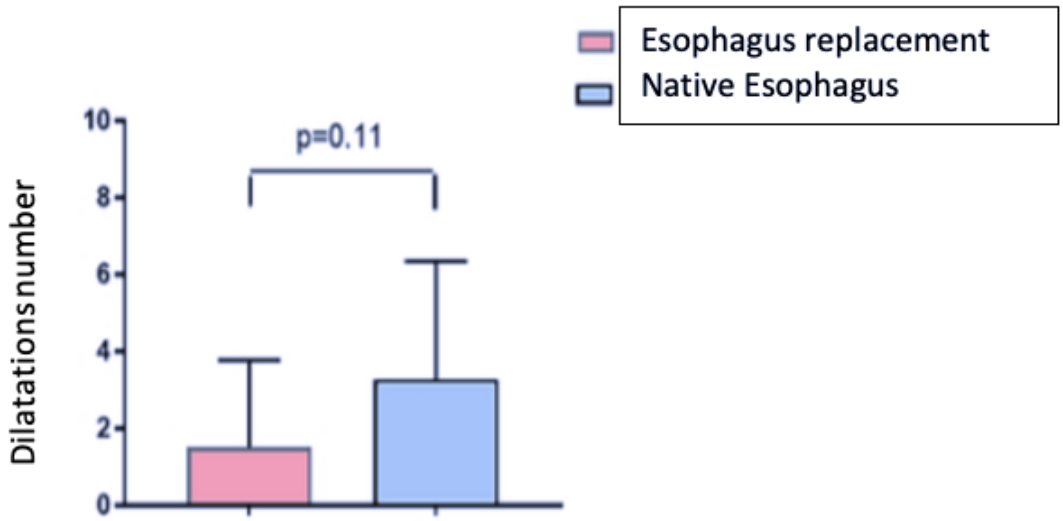
Dysphagia : esophagus replacement n=3 (33%) vs native esophagus n=14 (64%), OR = 0,50 (0,10 ; 2,44), p=0,48 ;

Abnormal FOIS : esophagus replacement n = 2 (22%) vs native esophagus n=15 (68%), OR = 0,14 (0,01 ; 1,01), p=0,04 ;

Asthma : esophagus replacement n=3 (33%) vs native esophagus n=7 (32%), OR = 1,07 (0,13 ; 7,06), p=1.

Non-parametric Fisher test.

Figure 7: Surgical procedure – dilatation number association



Median: esophagus replacement (n=8) = 0 (0; 5) and native esophagus (n=22) = 3 (0; 10), p=0,11. Non-parametric Mann-Whitney test

Résumés et mots-clés

Introduction: Esophageal atresia (EA) is a rare congenital malformation. The initial surgery depends on the length of the gap. Nowadays, the survival rate of operated children is high but medium and long-term morbidity is still important. The aim of this study was to compare morbidity at 6 years between long gap esophageal atresia (LGEA) and non-long gap esophageal atresia (NLGEA).

Materials and Methods: We performed a multicentric retrospective study of patients with EA between 2008 and 2010 with a follow-up until the age of 6. For each LGEA, 2 NLGEA were included. The digestive, respiratory and orthopedic morbidity at 6 years were collected from all the medical records in association with CRACMO (Centre de Référence des Affections Chroniques et Malformatives de l'Oesophage).

Results: Thirty-one patients with LGEA and sixty-two with NLGEA were included. There were more esophagitis cases in LGEA group than in NLGEA one (45% vs 15%, p=0.005). More anti-reflux surgeries were performed in LGEA group (65% for LGEA vs 19% for NLGEA, p<0.001). LGEA group had more digestive symptoms like bolus impaction in the esophagus or dysphagia (68% vs 33%, p=0.003) and more complications such as anastomotic stricture (71% vs 38%, p=0.006). There was no significant difference between the two groups regarding respiratory symptoms. NLGEA group had more tracheomalacia than LGEA group (33% vs 6,6%, p=0.006). NLGEA group had more spine deformation than LGEA group (23% vs 3,2%, p=0.026).

Discussion: The 6-year morbidity was higher for LGEA group especially the digestive comorbidity. In the long-term, the follow-ups should be scrutinized closer for these children.

Key words: Esophageal atresia, Long-gap esophageal atresia, Complications, Midterm outcome.

SERMENT

En présence des Maîtres de cette école, de mes chers condisciples et devant l'effigie d'Hippocrate, je promets et je jure d'être fidèle aux lois de l'honneur et de la probité dans l'exercice de la médecine. Je donnerai mes soins gratuits à l'indigent et n'exigerai jamais un salaire au-dessus de mon travail. Admis dans l'intérieur des maisons mes yeux ne verront pas ce qui s'y passe ; ma langue taira les secrets qui me seront confiés, et mon état ne servira pas à corrompre les mœurs ni à favoriser le crime. Respectueux et reconnaissant envers mes Maîtres, je rendrai à leurs enfants l'instruction que j'ai reçue de leurs pères.

Que les hommes m'accordent leur estime si je suis fidèle à mes promesses ! Que je sois couvert d'opprobre et méprisé de mes confrères si j'y manque !

ABSTRACT

Introduction: Esophageal atresia (EA) is a rare congenital malformation. The initial surgery depends on the length of the gap. Nowadays, the survival rate of operated children is high but medium and long-term morbidity is still important. The aim of this study was to compare morbidity at 6 years between long gap esophageal atresia (LGEA) and non-long gap esophageal atresia (NLGEA).

Materials and Methods: We performed a multicentric retrospective study of patients with EA between 2008 and 2010 with a follow-up until the age of 6. For each LGEA, 2 NLGEA were included. The digestive, respiratory and orthopedic morbidity at 6 years were collected from all the medical records in association with CRACMO (Centre de Référence des Affections Chroniques et Malformatives de l'Oesophage).

Results: Thirty-one patients with LGEA and sixty-two with NLGEA were included. There were more esophagitis cases in LGEA group than in NLGEA one (45% vs 15%, p=0.005). More anti-reflux surgeries were performed in LGEA group (65% for LGEA vs 19% for NLGEA, p<0.001). LGEA group had more digestive symptoms like bolus impaction in the esophagus or dysphagia (68% vs 33%, p=0.003) and more complications such as anastomotic stricture (71% vs 38%, p=0.006). There was no significant difference between the two groups regarding respiratory symptoms. NLGEA group had more tracheomalacia than LGEA group (33% vs 6,6%, p=0.006). NLGEA group had more spine deformation than LGEA group (23% vs 3,2%, p=0.026).

Discussion: The 6-year morbidity was higher for LGEA group especially the digestive comorbidity. In the long-term, the follow-ups should be scrutinized closer for these children.

Key words: Esophageal atresia, Long-gap esophageal atresia, Complications, Midterm outcome.