Peer Review File

Article information: https://dx.doi.org/10.21037/tp-23-453

Reviewer A

Comment 1: The language is clear. The figures are relevant and clarify the intended message. The content of the article is important, fair to the literature and reported consicely. It was a pleasure to read this review article. My main comment/concern regards the lacking but critical point to management and that is follow-up care of patients with Long-gap Esophageal Atresia. I recommend the authors to provide a brief section, describing how postoperative including long-term follow-up care should be provided and/or is recommended by expert (or patient) stakeholders regarding the main areas of somatic and mental co-morbidity and quality of life.

Reply 1: Thank you for your careful review and feedback. We agree this section may be helpful to practitioners, and have accordingly added a section to the text.

Changes in the text: We have modified our text as advised, and included a new section entitled "Postoperative Management and Long-term Followup" (see Pages 18-19, Lines 393-416).

Reviewer B

Comment 1: This review is fluent and assesses many relevant issues in the management of long-gap esophageal atresia. Still I would think that ´management´ includes little more than definition, incidence, diagnosis and available surgical options and the most frequent complications.

Reply 1: Thank you for the feedback. In addition to the pre-existing "Preoperative Management" section, we have added a "Postoperative Management and Long-term Followup" Section to the text to provide additional guidance on management.

Changes in the text: We have modified our text as advised, and included a new section entitled "Postoperative Management and Long-term Followup" (see Pages 18-19, Lines 393-416).

Comment 2: The management of sequelae or complications – including vocal cord paralysis, tracheomalacia should be explained more. As well as the influence of associated anomalies on the choice of surgical treatment. The authors discuss of the merits of various techniques well enough maybe they could point out surgical management of LGEA should be tailored or planned individually by each patient.

Reply 2: Thank you for the comment. We agree surgical management of LGEA should be tailored to each patient individually, and have modified our text accordingly. We have also emphasized vocal cord paralysis and tracheomalacia as potential complications.

Changes in the text: We have modified our text as advised, and included a statement on vocal cord paralysis and tracheomalacia (see Pages 18, Lines 380-391, 396-397).

Comment 3: Thoracoscopic stretching techniques and magnet anastomoses have been mentioned. Maybe the authors could briefly also add whether or not tissue engineering has any future role.

Reply 3: Thank you for the suggestion; we have incorporated a paragraph on the current state and potential future role of tissue engineering in esophageal replacement.

Changes in the text: We have modified our text as advised, and included a section on tissue engineering (see Page 17-18, Lines 368-378).

Comment 4: I would like to hear more of the long term management and surveillance of GER and associated respiratory and nutritional issues as well as issues associated with quality of life and how it could be improved.

Reply 4: Thank you for the feedback; we have added a section on Postoperative Management and Long-term Followup, where we discuss long-term management, surveillance of GER and associated complications, respiratory and nutritional concerns, and referenced a systematic review discussing the quality of life in patients with long-gap esophageal atresia.

Changes in the text: We have modified our text as advised, and included a new section entitled "Postoperative Management and Long-term Followup" (see Pages 18-19, Lines 393-416).

Comment 5: On the whole this is a decent review and has definitely merits and interest maybe for a aspirating pediatric surgeon or pediatrician in a multidisclipnary follow-up team but as its present form lacks the in-depth issues that are of interest to an experienced surgeon.

Reply 5: Thank you for your accurate assessment of the paper. Since this is a broad and complex topic, the target audience for this Translational Pediatrics manuscript includes pediatric surgery trainees, less experienced surgical faculty, as well as all neonatology pediatricians. We have attempted to update the review in an effort to make it as comprehensive and helpful as possible for these audiences.

Changes in the text: N/A

Reviewer C

Comment 1: In general the review is OK, feels somewhat opinionated and not sure there is much "new information" or the "evidence-based' approach advocated in the abstract. Illustrations are somewhat old and of poor quality. Would suggest more "data" is presented

Reply 1: Thank you for your honest feedback. In this manuscript, we have attempted to provide a general review of long-gap esophageal atresia management that is accessible and useful to pediatric medical and surgical practitioners, without getting too detailed into the specifics of surgical technique, which falls outside the scope of this paper for Translational Pediatrics. One of the challenges in the management of long-gap esophageal atresia is the inherent lack of consensus and “evidence” due to the relative rarity, heterogeneity in clinical presentation, and practice pattern variations across institutions, which prevent the development of strong evidence-based recommendations. Accordingly, the literature is fraught with opinions. In an attempt to address these shortcoming, one of the major goals of the paper is to discuss the major consensus statements recently put forth by the three leading long-gap esophageal atresia associations: the American Pediatric Surgical Association (APSA), the European Reference Network for Rare Inherited Congenital Anomalies (ERNICA), and the International Network of Esophageal Atresias (INoEA). In response to your comments, we have done our best to emphasize these guidelines in our text and have incorporated additional data to support our text.

Changes in the text: Several changes have been made across the text in an attempt to address this point, with additional sections added to the text to present more evidence-based guidance on management, and updated references to the current literature.

Comment 2: Row 56: Would not say "never", change that to "rarely"
Reply 2: Thank you, this sentence has been removed at the suggestion of another reviewer.
Changes in the text: We have modified our text as advised. (see Page 3, Line 52).

Comment 3: Row 59: I actually think type B's are more common that type A's. What happens is that many proximal fistulas are missed and kids are incorrectly labeled as type A and only later in life to be found with missed proximal fistula. As surgeons learn how to perform more proper rigid bronchoscopy with ventilating bronchoscope and clear distension phase in order to find these proximal fistulas, maybe we will learn the true frequency of these. Just random thought as FYI, as there is no data yet for this, no need to change anything in your description.
Reply 3: Thank you for the feedback; this is an important and interesting consideration, and something we will be mindful of in our discussion of the incidence of Type A versus Type B defects. We agree that type Bs are more common than previously thought, but we are not aware of any study that has shown that type Bs are more prevalent than Type As.
Changes in the text: N/A

Comment 4: Prenatal diagnosis section should probably make a comment about counseling for possible premature birth/polyhydramnios and other concomitant anomalies of the VACTERL spectrum.
Reply 4: Thank you; we have updated the prenatal diagnosis section to include a statement on VACTERL counseling, including premature birth/polyhydramnios.
Changes in the text: We have modified our text as advised (see Page 4, 8; Lines 74-76, 153-161).

Comment 5: Row 115 You can NOT be that definitive about the esophagus not being able to be repaired at birth. There are some well nourished LGEA kids that can be repaired at birth and there is more and more interest (particularly in Europe) about early initiation of thoracoscopic staged internal traction even without a g-tube.
Reply 5: Thank you for the feedback. We agree with this oversight and have modified our revised manuscript to reflect a more nuanced approach to the early management of LGEA.
Changes in the text: We have modified our text as advised (see Page 6, Lines 108-119).

Comment 6: Row 120, it can be done laparoscopically as well but agree with cautioning about the small stomach and need for a carefully positioned tube with very little fluid in the balloon or a balloonless tube

Reply 6: Thank you. We have edited our text to reflect that the procedure may be done laparoscopically, and the importance of preventing iatrogenic gastric outlet obstruction.

Changes in the text: We have modified our text as advised (see Page 6, Lines 121-123).

Comment 7: Gapogram description should discuss on and off-tension assessments and the use of a ruler under the patient for standardization of measurements.

Reply 7: Thank you. We have added additional text to discuss the indications for on and off-tension assessments, and emphasized the importance of using a ruler in standardized measurements.

Changes in the text: We have modified our text as advised (see Page 7, Lines 134-143).

Comment 8: Row 154 - mention about pre-operative flexible nasolaryngoscopy for assessment of vocal fold movement impairments is essential as it establishes a baseline and some can be congenital in nature.

Reply 8: Thank you for the comment. We have added a statement encouraging practitioners to consider pre-operative flexible nasolaryngoscopy to establish a baseline for vocal fold movement.

Changes in the text: We have modified our text as advised (see Page 8, Lines 158-161).

Comment 9: Row 170 - You can mention here why its not widely practice as it has led to perforations and disasters.

Reply 9: Thank you for the suggestion; we have added this to our text.

Changes in the text: We have modified our text as advised (see Page 9, Lines 188-192).

Comment 10: Row 175: specify if this 2 cm thing is on- or off-tension assessment. I would say that if you are doing an esophagogram on-tension and you are still 2cm apart, it is still unlikely to be a good primary repair, yet if its only 2cm apart and the contrast study is off-tension (and in a virgin chest) then yes likely to be a good primary repair. This point is so critical as many surgeons embark on trying to repair these borderline kids and are fixated or only prepared to do a primary

repair, and open the chest only to find themselves not being able to do so and not prepared for a plan B for traction process initiation. Hence patient selection is critical. I strongly believe that if a surgeon is not experienced or comfortable with traction process they should not attempt to manage LGEA as one needs to be prepared to offer the full gamma of options. Early referral to a center with experience with LGEA management and one that can offer the full gamma of options should be strongly considered.

Reply 10: Thank you; this is an important point and we have clarified our text accordingly to reflect that these measurements reference off-tension assessments. Additionally, we have added a section to the text emphasizing the importance of early patient transfer for surgeons who do not routinely manage LGEA.

Changes in the text: We have modified our text as advised (see Page 10, 18; Lines 197-201, 380-391).

Comment 11: Row 335, incorrect, 3 anastomosis are not usually required, mostly its just 2, the esophagojejunal anastomosis in the neck and the jejuno-jejunostomy in the belly, particularly with the roux-&-y approach. Only reason for 3 anastomosis is if you are connecting jejunum straight to stomach or using it as a true interposition between esophageal ends, which we don't routinely perform as can lead to poor conduit emptying as these kids often have small/dysfunctional stomachs with delayed gastric emptying. I would also not say that complications are the norm, with experience, these can go very well.

Reply 11: Thank you for the feedback. We have revised the jejunal conduit section to clarify that the jejunum may be used either as a conduit in complete esophageal replacement, or in a Roux-en-Y approach. We have also softened our statement that complications are the norm in jejunal conduits.

Changes in the text: We have modified our text as advised (see Page 16, Lines 339-342).

Reviewer D

Comment 1: 19: better definition would be newborn period by a single operation, because LGEA can be repaired in certain newborns using traction or other options

Reply 1: Thank you for the feedback, we have edited our text to reflect this point.

Changes in the text: We have modified our text as advised (see Page 1, Lines 19).

Comment 2: 45: better word for viable maybe acceptable long term outcome

Reply 2: Thank you for the suggestion; we agree that this is better phrasing and have modified this sentence as recommended.

Changes in the text: We have modified our text as advised (see Page 3, Line 43).

Comment 3: 49: left or right bronchus

Reply 3: The text has been edited to reflect the fistula may be in either the right or left bronchus.

Changes in the text: We have modified our text as advised (see Page 3, Line 46).

Comment 4: 115: this is not necessarily true, early repair becoming more common even without gtube creation

Reply 4: Thank you. We have modified our text to reflect that early repair without g-tube creation may be appropriate for a select group of patients at experienced centers.

Changes in the text: We have modified our text as advised (see Page 6, Line 109-119).

Comment 5: 117: gtube not mandatory, we currently favor repair of long gap for babies weighing close to 3kg without gtube, starting soon after birth, using traction

Reply 5: Thank you. We have modified our text to reflect that early traction without g-tube creation may be appropriate for a select group of patients at experienced centers.

Changes in the text: We have modified our text as advised (see Page 6, Line 109-119).

Comment 6: 119: open gtube not mandated as the approach, we prefer Rothenberg laparoscopic approach with Malekot type tube, I call it laparoscopic assisted mini open gtube

Reply 6: Thank you. We have modified our text to reflect that an open g-tube is not the mandatory approach, and that it may be placed laparoscopically.

Changes in the text: We have modified our text as advised (see Page 6, Lines 121-123).

Comment 7: 129: retrograde EGD best for bigger babies, directed contrast injection can be performed with feeding tubes or dilators. Also metal dilators can be used for gap assessment with pressure

Reply 7: Thank you for the comments. We have updated our text to reflect retrograde EGD as an optimal tool in the assessment of LGEA gap length both on- and off-tension.

Changes in the text: We have modified our text as advised (see Page 7, Lines 134-143).

Comment 8: 176: we have found that unless gap assessment with tension can get pouches nearly touching, then primary repair without creation of hiatal hernia is not likely

Reply 8: Thank you; we have added this caveat to our text.

Changes in the text: We have modified our text as advised (see Page 10, Lines 199-201).

Comment 9: 334: internal mammary usually rather than intercostal

Reply 9: Thank you; we have changed intercostal to internal mammary.

Changes in the text: We have modified our text as advised (see Page 16, Lines 350-351).

Comment 10: 486: better more recent JI paper: Thompson K, Zendejas B, Svetanoff WJ, Labow B, Taghinia A, Ganor O, Manfredi M, Ngo P, Smithers CJ, Hamilton TE, Jennings RW. Evolution, lessons learned, and contemporary outcomes of esophageal replacement with jejunum for children. Surgery. 2021 Jul;170(1):114-125. PMID: 33812755

Reply 10: Thank you for the reference; we have reviewed and referenced this study in our section on jejunal conduits.

Changes in the text: We have modified our text as advised (see Page 16, Line 347).

Reviewer E

Kunisaki and his team reviewed current concepts of treatment of long-gap esophageal atresia. The manuscript is well written and easy to read and I particularly enjoyed the provided images and sketched procedures. As the current piece is a review, I do miss a clear recommendation in the conclusion, which I feel is appropriate as the team has the necessary expertise to do so and the evidence, on the typically low level of pediatric surgery, is available, too.

Comment 1:

I am not sure if the statement on true esophageal hyperplasia is backed by data. Reference 32 investigates uniaxial tension on isolated organs from an abbatoir, so this by no means a proof of the statement made in lines 206-208. The other two references are from rats, which is a particular drawback, as the anatomy of the rat esophagus is substantially different: Rodent esophagus is longer per se, it is composed of skeletal muscle cells and highly keratinised and thus anatomically different to an omnivor's esophagus (discussed by the team of Oliver Muensterer in DOI: 10.1016/j.jpedsurg.2018.10.085). This is relevant for the statement, because Sullins and co-workers (DOI: 10.1016/j.jpedsurg.2015.03.011) were not able to demonstrate this effect in pigs, which are anatomically much more similar to humans. Therefore, I feel that the statement is not substantiated.

Reply 1: Thank you for the careful review and comments. We agree that studies have not yet investigated this in humans, and have decided to remove this sentence from our paper.

Changes in the text: We have modified our text as advised (see Page 11, Lines 228-230).

Comment 2: The paragraph discussing the different definitions of what a long-gap esophagus is, is confusing. While I agree that the functional definition is the "correct" or most appropriate one, I am not sure whether selectively discussing only some opinions is the right way to go. The number of definitions is long and consists of the use of centimeters, more than two (reference 33) up to more than 5 centimetres (DOI: 10.1016/j.athoracsur.2008.05.056), and the use of vertebral bodies, but not only three, but between two (DOI: 10.1186/1750-1172-2-24) and four vertebral bodes (reference 25). I would suggest to limit it to the functional definition and just state that there are plenty more. Otherwise, a more exhaustive review on the definitions would be preferrable and the use of a table might be advisable.

Reply 2: Thank you for the feedback. To limit confusion, we have removed the paragraph discussing various LGEA definitions, and emphasized the functional definition.

Changes in the text: We have modified our text as advised (see Pages 3-4, Lines 50-59).

Comment 3: I disagree on the explicit recommendation for a computed tomography to exclude a vascular ring. Although I am aware that the issue of radiation exposure is more of a continent thing, it has been shown that MRI is equally suitable (DOI: 10.1159/000492080) and can even prenatally

diagnose a vascular ring (DOI: 10.3389/fped.2023.1159130). A recommendation for cross-sectional imaging instead of computed tomography might thus be preferrable.

Reply 3: Thank you for the feedback; we agree that cross-sectional imaging is a better phrasing for this recommendation, and have edited our text accordingly.

Changes in the text: We have modified our text as advised (see Page 6, Lines 101-102).

Comment 4: I am not sure whether the citation to reference 15 is suitable to support the statement in lines 169-170. Reference 15 is essentially just the opinion of 24 people and the statement on bougienage was not discussed at all there. Although one might argue it had been somehow outdated, it reappeared in the literature recently (DOI: 10.1007/s00383-022-05138-7 & 10.1016/j.jpedsurg.2017.12.009), we frequently use it at our centre too, and I am aware of at least two other centres here that also use it for long-gap Vogt type II esophageal atresias.

Reply 4: Thank you for the comments and references. We have updated our statement to reflect that while bougienage has largely fallen out of favor in the United States, it does remain common in other places, with recent studies supporting the use for esophageal elongation. We also incorporated your updated references.

Changes in the text: We have modified our text as advised (see Page 9, Lines 189-192).

Comment 5: I do find the statement that gap measurements are not well-standardized between institutions (lines 124) and the fact that there is a recommendation to use just these gap lengths to time surgery in delayed primary repair slightly inconsistent. Not only because of the different approaches to gap length measurement, but also due to the different definitions of what would constitute a long-gap. In addition, there are many more approaches to gap length measurement, for example applying traction from both esophageal ends in order to verify that the ends can be brought together under pressure (DOI: 10.3389/fsurg.2021.701609), which is a comment method in my home country. Again, instead of just using examples, it would be preferrable to just state that there are different methods or present all of them.

Reply 5: Thank you for the feedback. The measurement of gap length varies by technique, institution, and surgeon, and leaves room for additional standardization; however, there is increasing attention towards the use of gap measurements to optimize the approach and timing of surgery. For these reasons, we believe it is important to discuss the current variation in how gap

lengths are measured to develop treatment algorithms that will be helpful for surgeons who do not perform these operations with much frequency. However, to mitigate confusion, we have removed the text from this paragraph and instead emphasized it in a more appropriate section of our paper.
Changes in the text: (see Page 7, Lines 129-143).

Comment 6: The statement in lines 243-246 is not supported by the two provided references 15 and 42. The first one is just a consensus statement and the second one an opinion piece. I do agree that the results from specialist centres such as the Boston group for the Foker procedure or the Wroclaw group for internal traction (DOI: 10.1016/j.jpedsurg.2022.10.017) are successful. However, this does not translate to success in routine care outside these centres: Our colleagues from the British Isles reported rather devastating results for both the Foker procedure (DOI: 10.1016/j.jpedsurg.2021.10.039) and internal traction (DOI: 10.1016/j.jpedsurg.2022.05.008). Although there are favourable reports from different centres (DOI: 10.3389/fsurg.2021.701609), they have used traction procedures not in neonates, but in infants in whom delayed primary repair did not allow a primary anastomosis, even under tension.
Reply 6: Thank you for the comments and insightful references. We agree that traction procedures are high-risk for unfavorable outcomes, and should be considered with a high degree of caution by centers and surgeons with limited prior experience. We have modified our text accordingly.
Changes in the text: We have modified our text as advised (see Page 13, Lines 263-267).

Comment 7: With regard to other techniques, such as the magnets, there is not only this approach, but also the one (connect-ea) from Mainz/Munich/UCLA (DOI: 10.1542/peds.2020-049627 & 10.1016/j.jpedsurg.2023.09.00). Moreover, there are still no long-term results available for patients treated with that method. As a reminder, patients treated by Zaritsky's method had severe and long-lasting issues with recurrent strictures for years, which has partially been reported (DOI: 10.1016/j.jpedsurg.2020.01.022).
Reply 7: Thank you for the feedback and references. We have modified our text to emphasize the limitations of magnamosis, specifically the recurrent strictures requiring serial endoscopic esophageal dilations, and eventual surgical revision. As there are several magnets reported in the literature, we have removed the reference to a specific manufacturer/device, and opted to reference the concept of magnamosis in more general terms.

Changes in the text: We have modified our text as advised (see Page 13, Lines 270-280).

Comment 8: With regard to the statement that the majority of patients were operated around being three months old, this might not be the worldwide standard: Although rather old, it was 146 days in Australia (DOI: 10.1016/j.jpedsurg.2007.12.001), but more recent with five months in Belgium/Luxemburg (DOI: 10.1016/j.jpedsurg.2016.11.010) and there are even case reports in the literature in which suregons have waited for more than a year (which is also reported in the Belgian experience) or four months in the Nordics (DOI: 10.1016/j.jpedsurg.2018.07.023)

Reply 8: Thank you for the feedback. Although we typically perform delayed repairs around 3 months of age in the United States, this may not be the case at all centers or in all countries. As such, we have revised our text and incorporated your references to demonstrate the variability of timing of repair.

Changes in the text: We have modified our text as advised (see Page 10, Lines 195-196).

Comment 9: As I have already stated in my introductory sentence, it is unclear to me why you opted to have such a verbose conclusion without a clear recommendation. Not only has the APSA recommended delayed primary repair, as you have stated (lines 183-184), you have described that it is the standard of care in the United States (DOI: 10.1016/j.surg.2023.03.005), but also on the continent (DOI: 10.1016/j.jpedsurg.2016.11.010) and the method for which we have the most available data (DOI: 10.1016/j.jpedsurg.2019.06.017). Consequently, it is unclear to me why there is no clear recommendation for delayed primary repair. Every other method is niche and requires substantial experience, which is likely not available in the vast majority of centres. Which also applies to thoracoscopic surgery, as your group has demonstrated (DOI: 10.1016/j.jpedsurg.2021.04.006). Therefore, the evidence supporting these rather strong conclusions is available and should thus guide the reader. Moreover, the aspect of centralization is rather not a conclusion of your review, so it should be avoided, too.

Reply 9: Thank you for the detailed feedback and references. We agree there is sufficient data, including a statement by APSA, recommending delayed primary repair as the first-choice management for LGEA. We have revised our conclusion to include a stronger statement advocating for delayed primary repair, and have removed references to centralization.

Changes in the text: We have modified our text as advised (see Pages 19-20, Lines 419-442).