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SUBJECT: SUBMISSION OF THE MANUSCRIPT TITLED "MANAGEMENT OF REFRACTORY ANASTOMOTIC STRICTURES FOLLOWING ESOPHAGEAL ATRESIA REPAIR. LITERATURE REVIEW

Zhenis N. Sakuov[1], https://orcid.org/0000-0002-9885-3778

Vasiliy M. Lozovoy[2], https://orcid.org/0000-0001-9193-7963

Asylzhan A. Yerekeshov[3], https://orcid.org/0009-0003-7793-9497

Meruyert S. Bokayeva[4], https://orcid.org/0009-0001-3359-6336

[1] National Research Center for Maternal and Child Health, "University Medical Center" CF, Astana, Republic of Kazakhstan;
[2] Astana Medical University, Astana, Republic of Kazakhstan;
[3] Scientific Center of Pediatrics and Pediatric Surgery, Almaty, Republic of Kazakhstan;
[4] School of Medicine, Nazarbayev University, Astana, Republic of Kazakhstan.

Abstract

Background: Refractory anastomotic strictures (AS) following esophageal atresia (EA) repair in children remain a challenging clinical issue, often resistant to standard endoscopic balloon dilatation (EBD). Despite multiple sessions, some patients experience persistent or recurrent symptoms, potentially associated with excessive fibrosis during healing process.

Objective: To evaluate novel, less invasive, and potentially more effective treatment strategies for managing refractory anastomotic strictures after esophageal atresia repair in pediatric patients..

Search strategy: A literature review was conducted using the Web of Science and PubMed databases, covering a 5-year period. The treatment modalities for refractory esophageal anastomotic strictures were categorized into seven groups: (1) intralesional corticosteroid injection (ICI), (2) systemic corticosteroid therapy, (3) topical application of mitomycin C (MMC), (4) endoscopic incisional therapy (EIT), (5) esophageal stenting, (6) cell-based therapies, and (7) magnetic recanalization.

Results: Contemporary treatment options for pediatric refractory esophageal strictures were analyzed. Intralesional corticosteroid injections, particularly triamcinolone, have been associated with reduced dilation frequency in short strictures, though potential complications include adrenal suppression and infectious risks. MMC has shown variable efficacy; some studies reported a reduction in stricture frequency, while others found no significant benefit. EIT has proven effective for short, asymmetric strictures but carries a high risk of esophageal perforation. Both esophageal stenting and systemic corticosteroid therapy remain controversial due to limited supporting evidence. Emerging techniques, including magnetic recanalization and cell-based therapies using autologous grafts or extracellular matrix scaffolds, are still in experimental stages but have shown promising outcomes in select cases.

Conclusion: There is no universally accepted treatment for refractory esophageal strictures. Intralesional corticosteroids and mitomycin C appear promising for short strictures, while novel therapies require further investigation. Prospective, comparative studies involving larger cohorts and long-term follow-up are essential to determine optimal treatment strategies, establish objective efficacy criteria, and confirm the safety of new therapeutic approaches.

Keywords: *esophageal atresia, anastomotic stricture, refractory and recurrent stenosis, adjunctive therapies, esophageal stenting.*

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Резюме

ЛЕЧЕНИЕ РЕФРАКТЕРНЫХ СУЖЕНИЙ АНАСТОМОЗА ПОСЛЕ КОРРЕКЦИИ АТРЕЗИИ ПИЩЕВОДА. ОБЗОР ЛИТЕРАТУРЫ

Женис Н. Сакуов[1], https://orcid.org/0000-0002-9885-3778

Василий М. Лозовой[2], https://orcid.org/0000-0001-9193-7963

Асылжан А. Ерекешов[3], https://orcid.org/0009-0003-7793-9497

Меруерт С. Бокаева[4], https://orcid.org/0009-0001-3359-6336

[1] "Национальный научный центр материнства и детства" КФ «University Medical Center», г. Астана, Республика Казахстан;
[2] НАО «Медицинский университет Астана», г. Астана, Республика Казахстан;

[3] АО «Научный центр педиатрии и детской хирургии», г. Алматы, Республика Казахстан;
[4] Школа медицины, Назарбаев Университет, г. Астана, Республика Казахстан.

Резюме: Рефрактерные стриктуры анастомоза (СА) после коррекции атрезии пищевода (АП) у детей остаются сложной проблемой, часто устойчивой к стандартной эндоскопической баллонной дилатации (ЭБД). Несмотря на повторные процедуры, у ряда пациентов наблюдается рецидив или стойкое персистирование симптомов, что может быть связано с усиленным фиброгенезом в процессе заживления.

Цель: Изучить новые, менее инвазивные и более эффективные варианты лечения рефрактерных стриктур анастомоза после коррекции атрезии пищевода у детей.

Методы: Обзор литературы был проведен с использованием баз данных Web of Science и PubMed. Глубина поиска составила 5 лет. Методы лечения рефрактерных сужений анастомоза пищевода были разделены на семь групп: (1) внутриочаговая инъекция глюкокортикостероидов (ВИГ), (2) системная терапия глюкокортикостероидами (ГКС), (3) применение митомицина С (ММС), (4) эндоскопическая инцизионная терапия (ЭИТ), (5) стентирование пищевода, (6) клеточная терапия, (7) магнитная реканализация.

Результаты: Рассмотрены современные подходы к лечению рефрактерных анастомотических стриктур пищевода у детей после коррекции атрезии пищевода (АП). Внутриочаговое инъекции глюкокортикостероидов, особенно триамцинолона, показали снижение частоты дилатаций при коротких стриктурах, но сопровождаются рисками, включая супрессию надпочечников и инфекционные осложнения. Митомицин С, применяемый локально, продемонстрировал противоречивые результаты: в некоторых исследованиях отмечено уменьшение частоты стриктур, в других — отсутствие эффекта. Эндоскопическая инцизионная терапия эффективна при коротких и асимметричных стриктурах, но связана с высоким риском перфорации пищевода. Стентирование и системная терапия глюкокортикостероидами остаются спорными методами с ограниченной доказательной базой. Новые технологии, включая магнитную реканализацию и клеточную терапию с использованием аутологичных трансплантатов или внеклеточного матрикса, находятся на экспериментальной стадии, но демонстрируют обнадеживающие результаты в отдельных случаях.

Выводы: Не существует универсального метода лечения рефрактерных стриктур пищевода. Наиболее перспективны внутриочаговое введение глюкокортикостероидов и Митомицина С при коротких стриктурах, тогда как инновационные методы требуют дальнейших исследований. Необходимы последующие проспективные, сравнительные исследования с большим количеством пациентов и долгосрочным наблюдением для определения оптимальных стратегий, разработки объективных критериев оценки эффективности и подтверждения безопасности новых терапевтических подходов.

Ключевые слова: *атрезия пищевода, сужение анастомоза, рефрактерные и рецидивирующие стриктуры, вспомогательные методы лечения, стентирование пищевода*.

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Түйіндеме

ӨҢЕШ АТРЕЗИЯСЫН ТҮЗЕТУДЕН КЕЙІНГІ РЕФРАКТЕРЛІ АНАСТОМОЗДЫҚ ТАРЫЛУЛАРДЫ ЕМДЕУ. ӘДЕБИЕТТІК ШОЛУ.

Женис Н. Сакуов[1], https://orcid.org/0000-0002-9885-3778

Василий М. Лозовой[2], https://orcid.org/0000-0001-9193-7963

Асылжан А. Ерекешов[3], https://orcid.org/0009-0003-7793-9497

Меруерт С. Бокаева[4], https://orcid.org/0009-0001-3359-6336

[1] «Ұлттық ғылыми ана мен бала орталығы КФ «University Medical Center», Астана қ., Қазақстан Республикасы;
[2] КеАҚ «Астана медицина университеті», Астана қ., Қазақстан Республикасы;
[3] «Педиатрия және балалар хирургиясы ғылыми орталығы», Алматы қ., Қазақстан Республикасы;
[4] «Назарбаев Университеті» Медицина мектебі, Астана қ., Қазақстан Республикасы.

Кіріспе: Өңеш атрезиясын хирургиялық түзетуден кейінгі рефрактерлі анастомоздық стриктуралар (АС) балалар арасында эндоскопиялық баллонды дилатацияға (ЭБД) тұрақты жауап бермейтін күрделі мәселе болып қала береді. Қайталама процедураларға қарамастан, кейбір науқастарда симптомдардың қайта пайда болуы немесе тұрақты сақталуы байқалады, бұл жазылу процесіндегі күшейген фиброгенезбен байланысты болуы мүмкін.

Мақсаты: Өңеш атрезиясын түзеткеннен кейін дамитын рефрактерлі анастомоздық стриктураларды емдеудің тиімді әрі инвазивтілігі төмен жаңа әдістерін зерттеу.

Әдістер: Web of Science және PubMed деректер базасы арқылы соңғы 5 жыл ішіндегі әдебиетке шолу жүргізілді. Өңеш анастомозы стриктураларын емдеу әдістері келесі жеті топқа бөлінді: (1) ошақішілік глюкокортикостероидты инъекция (ГКС), (2) жүйелі глюкокортикостероидты терапия, (3) митомицин С (ММС) қолдану, (4) эндоскопиялық инцизиялық терапия (ЭИТ), (5) өңешті стенттеу, (6) жасушалық терапия, (7) магниттік реканализация.

Нәтижелер: Өңеш атрезиясын түзеткеннен кейінгі рефрактерлі анастомоздық стриктураларды емдеудің қазіргі тәсілдері қарастырылды. Глюкокортикостероидтардың, әсіресе триамцинолонның ошақішілік инъекциялары қысқа стриктураларда дилатация жиілігін төмендеткенімен, бүйрек үсті безі функциясының тежелуі және инфекциялық асқынулар секілді қауіптермен байланысты. Митомицин С жергілікті қолданылғанда әртүрлі нәтижелер көрсетті: кейбір зерттеулерде стриктура жиілігі азайған, басқаларында әсері болмаған. Эндоскопиялық инцизиялық терапия қысқа және асимметриялық стриктураларда тиімді, бірақ өңештің перфорациясы қаупімен шектеледі. Стенттеу және жүйелі ГКС терапиясы дәлелдеме базасы жеткіліксіз, даулы әдістер болып қалып отыр. Жаңа технологиялар, соның ішінде магниттік реканализация мен аутологиялық трансплантаттар немесе жасушасыз матрикс арқылы жасушалық терапия әлі эксперименттік сатыда, бірақ жекелеген жағдайларда үміт күттіретін нәтижелер көрсетті.

Қорытынды: Рефрактерлі өңеш стриктураларын емдеудің әмбебап әдісі жоқ. Қысқа стриктураларда ГКС және ММС ошақішілік қолдану ең перспективті тәсілдер болып табылады, ал инновациялық әдістерді кеңірек зерттеу қажет. Емнің қауіпсіздігі мен тиімділігін дәлелдейтін, үлкен популяцияда жүргізілетін болашақ проспективті, салыстырмалы зерттеулер қажет.

Түйінді сөздер: *өңеш атрезиясы, анастомоздық стриктура, рефрактерлі және рецидивті стриктуралар, қосымша емдеу әдістері, өңешті стенттеу.*

Дәйексөз үшін:

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Introduction

Despite dilation treatment of postoperative esophageal stricture, some patients may experience recurrence or persistent symptoms. The causes of recurrent episodes or persistent anastomotic stenosis (AS) are not fully understood. The development of stricture is influenced by numerous initial conditions, as well as intra- and postoperative risk factors, which can significantly affect the outcome of the disease. The dilation procedure, in turn, may partially contribute to increased fibrogenesis during healing, which is an important factor in repeat interventions. Repeated dilation sessions increase the risk of complications and can have a negative impact on the psychological state of patients, especially children. If the stricture becomes resistant to dilation, it is preferable to adhere to a conservative approach before considering the patient as a candidate for surgical intervention [42]. Despite the lack of specialized controlled studies, various non-surgical methods of adjuvant treatment can be used in clinical practice for refractory and recurrent AS.

Search strategy

A comprehensive literature review was conducted using the PubMed and Web of Science databases, with a cutoff date of December 31, 2024. The search strategy included combinations of the following keywords: “esophageal atresia”, “anastomotic stricture”, “refractory”, “recurrent”, “adjunctive treatment”, and “esophageal stenting”.

Studies published between 2020 and 2024 were screened, with a particular emphasis on refractory or recurrent anastomotic strictures following esophageal atresia repair. Given the limited availability of pediatric data, additional studies were included if they addressed esophageal strictures of other etiologies - such as caustic injuries - that shared similar clinical behavior and treatment challenges.

Titles and abstracts were screened for relevance, followed by full-text assessment of potentially eligible articles. Studies were included if they reported outcomes of adjunctive or alternative therapies for refractory esophageal strictures in pediatric patients. Included interventions were categorized into seven groups: intralesional corticosteroid injection, systemic corticosteroid therapy, topical mitomycin C application, endoscopic incisional therapy, esophageal stenting, cell-based therapies, and magnetic recanalization.

Each treatment modality was evaluated based on its reported effectiveness and safety, the durability of response, the need for repeated dilatations, and the occurrence of complications. In cases where pediatric-specific data were lacking, relevant findings from adult populations were considered to supplement and contextualize the evidence base.

Results

An analysis of contemporary approaches to the treatment of refractory anastomotic strictures following esophageal atresia (EA) repair over the past five years has identified seven main techniques, which are presented below.

Intralesional injection of glucocorticosteroids (GCS)

The administration of GCS into the stricture area, in addition to dilation, was proposed for the prevention of recurrence more than 50 years ago. Despite extensive clinical experience, the mechanism of action remains poorly understood. GCS are effective in hypertrophic scars and keloids, making them potentially useful in recurrent anastomotic strictures. The administration of GCS, such as triamcinolone acetonide (TAC), reduces collagen synthesis, enhances its breakdown, and reduces fibrous healing after dilation, preventing cross-linking of collagen molecules and the formation of contractures in scar tissue, improving long-term treatment outcomes [3,44].

The most commonly used steroid for intralesional injections is triamcinolone acetate or acetonide; betamethasone and dexamethasone preparations are also used [25]. TAC is usually injected using a standard sclerotherapy needle into four quadrants of the esophagus along the proximal edges of the stricture prior to dilation, as described in *Ramage et al.* [38]. In some cases, an additional injection is made directly into the scar tissue if its thickness is uneven. The concentration used varies from 10 to 40 mg/ml according to different sources. The authors

prefer 10 mg/ml, as 40 mg/ml is more viscous and requires dilution before use [50]. Steroids can be administered before and after dilation therapy. The optimal number of injections remains controversial, but some experts limit themselves to three procedures, since further administration does not provide any additional effect and is also associated with an increased risk of systemic and local complications [45].

A systematic review and meta-analysis involving more than 3,000 patients demonstrated the efficacy of intrafocal glucocorticosteroid injections (IGI) in the treatment of esophageal anastomotic strictures. On average, patients required 2.1 injections, and the number of dilations decreased from 5.2 to 1.13 after steroid administration [45]. *Gandhi et al.* described a series of 12 patients, 5 of whom underwent correction of esophageal atresia and received IGI in combination with dilation, which resulted in long-term remission of symptoms. [21]. Two retrospective studies have shown that intralesional steroid injections for benign esophageal strictures in children are more effective in short-segment lesions, reducing the frequency of dilations and increasing the intervals between them. No significant improvement was observed in long strictures, indicating that the effectiveness of the method depends on the length of the stricture [11,14].

Potential complications of esophageal steroid injections include adrenal suppression, esophageal perforation, intramural infection, candidal infection, mediastinitis, pleural effusion, and growth retardation [45]. In addition, there is a separate report of spontaneous rupture of the right aortic arch, presumably associated with weakening of the arterial wall under the influence of steroids [28]. *Annefleur et al.* report in a meta-analysis that the overall incidence of adverse effects was moderate at 7.1%, with most adverse effects being local in nature and not requiring additional treatment (approximately 10%), while systemic complications were less common (0.7%) and were associated with adrenal insufficiency, Cushing's syndrome, or growth retardation [45]. Therefore, careful clinical monitoring and assessment of growth curves in patients receiving IGI is necessary.

In conclusion, it should be noted that since studies investigating the efficacy and safety of intralesional steroid therapy are few, uncontrolled, and heterogeneous, it is difficult to draw definitive conclusions about the benefit of steroids in reducing recurrent stricture formation in patients with EA. The guidelines for pediatric gastrointestinal endoscopy do not recommend the routine use of intrafocal steroids for refractory esophageal strictures in children [26,42]. Prospective, comparative studies need to be conducted before intralesional steroid injection is recognized as a safe and effective method.

Systemic therapy with glucocorticosteroids

Systemic GCS therapy is considered a possible alternative treatment for refractory esophageal strictures in cases where standard approaches, such as intralesional steroid injections and dilation, prove ineffective. However, the use of this technique in endoscopic dilation has been described only in isolated clinical cases.

Hishiki et al. reported a patient with esophageal atresia (EA) who developed refractory anastomotic stricture (AS), requiring surgical resection of the stenosed segment followed by anastomotic reconstruction. The secondary AS was resistant to balloon dilation but regressed after two short courses of intravenous dexamethasone (1 mg/kg) [24].

Morikawa et al. described the use of high doses of methylprednisolone in a patient with refractory AS who was scheduled for surgery. The patient underwent a stepwise dose reduction regimen: methylprednisolone was administered intravenously (25, 15, 10, 5, and 2 mg/kg daily for 4 days each) after balloon dilatation with intrafocal steroid injection, and then sequentially replaced with oral prednisolone (2, 1, and 0.5 mg/kg daily for 1 week each). As a result of this therapy, the AS finally regressed [36].

Yokota et al. investigated the efficacy of intravenous pulse therapy with steroids after balloon dilatation for the prevention of restenosis. In their study, none of the patients experienced serious side effects such as adrenal insufficiency, gastrointestinal ulcers, or severe infections, indicating the relative safety of short-term use of systemic GCS [52].

To date, the use of systemic GCS in refractory AS remains limited, as this strategy requires careful assessment of potential risks. The literature reports cases of adrenal suppression even with local administration of steroids, especially in the context of AS treatment after BP correction. In this regard, dynamic monitoring of patients receiving steroid therapy is recommended, with monitoring of adrenal function and replacement therapy if necessary [5].

Mitomycin C

Mitomycin C (MMC) is an antibiotic isolated in 1958 from Streptomyces caespitosus. In addition to its antimicrobial and well-known antineoplastic properties, it has antiproliferative effects, reducing collagen synthesis and scar formation [6]. In this regard, MMC has been proposed as an additional method for treating esophageal strictures.

The method of MMC administration is an important aspect that requires special attention. The drug should act strictly on the stenotic segment without having a potentially dangerous effect on the surrounding healthy mucous membrane. The most common method is the local application of MMC solution using a cotton swab under endoscopic control [42]. To protect the mucosa from contact with the drug, methods using tubes, caps, and ligators for varicose veins of the esophagus have been described. The use of a microporous polytetrafluoroethylene catheter balloon with drug elution, inserted through the stricture under fluoroscopic control, has also been proposed [23]. Alternative methods include direct instillation[55] and MMC injections into the walls of the stenosis after its dilation [56].

MMC is usually prepared immediately before use. According to a recent systematic review, the concentration of the drug ranged from 0.1 to 1 mg/ml, the volume was 1–3 ml, and the number of procedures ranged from 1 to 12, with a median of 1–2 applications. When re-administered, the intervals between procedures ranged from 1 week to 13 months, with a median of 4 weeks [39]. A concentration of 0.4 mg/ml is the most commonly used [8]. However, recent studies have not revealed any significant differences in the effectiveness of MMC depending on the method of application or concentration [29].

The efficacy of MMC in anastomotic strictures remains a subject of debate. One study reported a 71% efficacy rate in patients with esophageal atresia (mainly type C), where

success was defined as a reduction in the frequency of endoscopic dilations after administration of the drug [29]. Another study showed that injectable MMC after at least two dilations in patients with recurrent stenosis was highly effective. Factors that increased the success of therapy were short and single stenosis, as well as Esophageal atresia (EA) type C [12]. At the same time, *Divarci et al.* did not find any effect of stricture length on the effectiveness of MMC [15].

Similarly, based on a study involving 31 patients reported in 11 publications (clinical cases and small series of patients), the authors concluded that MMC was effective (defined as clinical improvement) in 68% of patients [6]. An analysis of 24 studies involving both children and adult patients showed that a complete response was achieved in 73% of patients receiving MMC as treatment for refractory strictures of the gastrointestinal tract [39].

Mitomycin C has demonstrated its effectiveness in several prospective studies on post-burn strictures. In a double-blind RCT, El-Asmar et al. showed that 80% of patients with short caustic esophageal strictures experienced complete resolution of strictures, compared with 35% in the placebo group [16]. In a similar study of long caustic strictures, the efficacy reached 85.7% when using 0.5 mg/ml MMC [17].

However, a number of studies have shown low efficacy of MMS. *Chapuy et al.* compared the use of MMS with repeated dilations in patients with severe forms of EA types A and C. Stricture resolution was observed in 73% of patients after 1.9 sessions with MMS, while in the group without MMC, successful treatment was achieved in 90% of children after 3 balloon dilations [12].

Zimmer et al. report a 55% success rate, where the length of the stricture ranged from 2 to 8 mm and successful treatment was defined as endoscopic resolution of the stricture, whereas in many studies the clinical dysphagia score was used. The authors determined that the response rate to mitomycin C was 60% in patients with stenosis less than 4 mm and 50% in children with stenosis greater than 4 mm [32]. *Rosseneu et al.* obtained similar results [55]. In addition, a systematic review and meta-analysis of the efficacy of MMC in post-burn strictures did not reveal statistically significant differences in the total number of dilations between groups with and without the use of the drug [18].

The most dangerous systemic side effects of MMC are changes in heart rate or blood pressure, allergic reactions, and bone marrow suppression[27]. Among local complications, there is an increased risk of iatrogenic perforation. Chapuy et al. suggested that in their study, the appearance of reflux could be associated with subclinical perforation caused by MMC [12]. In another study by this group, perforation was recorded during the procedure, which was treated conservatively [12].

Another complication of MMC injection is the formation of peptic ulcers [22], which makes local application more preferable. However, Wishahy et al. did not record ulcer formation in their study [47].

Since mitomycin C is a cytostatic drug, one of the potential side effects may be dysplasia of healthy tissues after accidental exposure during application. This risk is expected to increase, especially with repeated use. Cases of de novo gastric metaplasia in the anastomosis area after local application of mitomycin C have been reported. Ley et al. found one case of gastric metaplasia in a child with caustic stenosis, but were unable to determine its exact cause - whether it was caused by mitomycin C, cauterization, or dilations [29]. Dysplastic lesions of the upper gastrointestinal tract have not been described in the literature, but the limited number of observations requires long-term endoscopic monitoring with biopsy.

Although the data obtained in the pediatric population are promising, large randomized clinical trials (RCTs) are needed before the administration of mitomycin C becomes the standard of care for children with benign recurrent esophageal stricture.

Endoscopic incisional therapy (EIT)

Endoscopic incisional therapy (EIT) is used for congenital strictures, strictures that have developed as a result of chemical burns, and postoperative complications following correction of esophageal atresia. The method is based on the understanding that many strictures, especially anastomotic ones, have an asymmetrical structure with areas of varying degrees of scar tissue thickness. While balloon dilation can lead to rupture in areas with thinner scar tissue, EIT allows selective treatment of denser fibrous areas, which increases the effectiveness of treatment [50].

The procedure is performed using an electrosurgical needle knife and involves a series of radial incisions parallel to the longitudinal axis of the esophagus in the area of the stricture, followed by endoscopic balloon dilation. All stages of the procedure are performed under direct endoscopic visualization. This method is considered to be most effective for strictures less than 1 cm in length [33].

Tan Y. et al. reported a case of successful treatment of refractory esophageal stricture using a combination of endoscopic incisional therapy (EIT) and esophageal stenting. In a recent retrospective study involving seven pediatric patients, sustained clinical improvement in dysphagia symptoms was observed in 71.4% (5 out of 7) during a follow-up period ranging from 1 to 21 months. Based on the hypothesis that longer strictures are associated with a higher risk of recurrence, three patients with strictures exceeding 1.5 cm received additional esophageal stenting as part of their management strategy [43].

Manfredi et al. reported favorable outcomes following endoscopic incisional therapy (EIT) in a cohort of 42 patients, including 40 with anastomotic strictures. Treatment effectiveness was observed in 78% (32 out of 41 cases) at 6 months and 64.5% (20 out of 31 cases) at 12 months post-intervention. Procedural success was defined as requiring no more than five dilations within six months following EIT, while long-term success was defined as needing no more than six dilations within 12 months. The overall incidence of esophageal perforation associated with the procedure was 4.4% [33].

In another study involving 58 patients, EIT achieved stricture resolution in 76% of patients during 2 years of follow-up. In the subgroup of patients with refractory strictures, the efficacy of the method was 61%, and the incidence of perforations was 2.3% [34].

In a study by *Yasuda et al.,* the incidence of perforations during balloon dilation without EIT in patients with congenital esophageal stenosis was 2.5% (3/118 endoscopies), while the incidence of perforations during

endoscopic interventions involving EIT reached 29% (17/58 endoscopies). As expected, the risk of complications was significantly higher in procedures involving EIT [51].

Although the complication rate remains low, its significance requires special attention. It is necessary for the endoscopist to be prepared to repair esophageal perforation using appropriate endoscopic techniques (e.g., EVAC or stenting) and to have experience in surgical correction of complications.

Esophageal stenting

Esophageal stenting relies on the same fundamental principle as balloon dilation - applying continuous circumferential radial pressure to mechanically widen the esophageal lumen [28]. Early reports described the use of silicone tubes [13] and polytetrafluoroethylene (PTFE) stents [4,37], which were externally fixed via the nasal passage to maintain positioning. More recent studies have focused on the use of self-expanding stents, which can be placed either endoscopically or under fluoroscopic guidance. Various types of self-expanding stents have been employed in pediatric patients, including plastic [9], metallic [53] and biodegradable stents [46], depending on the specific clinical context and stricture characteristics.

Self-expanding metal stents (SEMS) are cylindrical mesh devices composed of woven, knitted, or laser-cut metallic structures, typically made of nitinol, an alloy of nickel and titanium. These stents are designed to self-expand to a predetermined diameter. To minimize tissue ingrowth through the stent mesh, SEMS may be fully or partially covered with a plastic or silicone membrane [1]. Self-expanding plastic stents (SEPS) consist of a woven polyester framework entirely encased in a silicone membrane. Radiopaque markers located at both ends and the midsection allow for precise fluoroscopic guidance during placement [1]. Biodegradable stents (BDS) are constructed from biodegradable polymers that gradually dissolve in vivo, thereby eliminating the need for endoscopic removal. These stents typically retain their structural integrity and radial force for approximately 6 weeks, with complete degradation occurring within 11 to 12 weeks post-implantation [2]. While all three stent types etallic, plastic, and biodegradable - have been utilized in the management of refractory benign esophageal strictures in adults, only SEPS are currently approved for use in children [41]. Pediatric data on esophageal stenting remain limited and heterogeneous, with reported clinical success rates ranging from 26% to 86% depending on patient selection and procedural technique [7,9,19,35]. Data on stenting specifically in children with esophageal atresia (EA) are even more scarce. *Manfredi et al.* reported outcomes in 23 pediatric patients with EA who underwent 40 esophageal stenting procedures. The reported success rates were 39% at ≥30 days and 26% at ≥90 days following stent removal. Both bare metal stents (used in 14 patients) and fully covered stents (used in 26 patients) were included in the analysis. The mean duration of stent placement was 9.7 days, with a range from 2 to 30 days [35].

In conclusion, esophageal stenting represents a promising therapeutic option for the management of recurrent and refractory anastomotic strictures. Its main advantages include prolonged maintenance of luminal patency and improved oral intake. However, stent tolerance may be suboptimal in pediatric patients, and complications such as stent migration and other adverse events may occur. The long-term efficacy and safety of esophageal stenting in children require further confirmation through prospective clinical studies.

Magnetic recanalization

Magnetic recanalization and magnetic compression anastomosis (MCA) are emerging techniques for the treatment of refractory esophageal strictures in children. The first successful pediatric case of magnetic recanalization for esophageal stenosis was reported by *Bulyhin et al.* in 1993 [54]. These techniques utilize magnetic devices and magnetic force to eliminate scar tissue at the site of the anastomosis without injuring the muscular layer of the gastrointestinal tract [31]. MCA involves positioning magnets on either side of the stricture; once aligned, the magnetic attraction induces localized ischemia, leading to necrosis and sloughing of the fibrotic tissue, thereby re-establishing esophageal patency. Key technical parameters include the orientation, strength, and intermagnetic distance. Increasing the length of the cylindrical magnet array proportionally enhances the magnetic flux density and, consequently, the attractive force. An expert consensus has been established to guide the clinical use of MCA, addressing aspects such as patient selection, magnetic device design, surgical approach, perioperative care, and prevention of complications. Indications for magnetic recanalization include short-segment esophageal stenosis - postoperative, congenital, or caustic in origin - typically measuring less than 2 cm, though limited use in 2–3 cm lesions has been described. Contraindications include the presence of a tracheoesophageal fistula, esophageal perforation, stenotic segments longer than 4 cm, and ectopic tracheal cartilage in cases of congenital stenosis [30].

The literature describes cases of successful use of magnetic compression stricturoplasty in children with refractory strictures after repair of esophageal atresia. A study by *Woo et al.* reports the successful treatment of two patients with refractory strictures using neodymium magnets. Additional interventions, such as balloon dilation and stenting, were required after the procedure, but after 31 months, both patients had sustained esophageal patency without dysphagia[48].

In conclusion, magnetic recanalization and MCA are promising methods for treating refractory esophageal strictures in children. Further research and accumulation of clinical experience will allow this technology to be optimized and its long-term effectiveness to be determined. Knowledge of the fundamental principles of magnetism is crucial for the successful application of magnets in surgery.

Cell therapy

In the search for more effective and less invasive treatment strategies, cell therapy and tissue engineering—particularly those involving somatic stem cells—have emerged as promising areas of investigation. One actively explored approach is the transplantation of cell sheets derived from autologous oral mucosa. This technique is based on the concept of cell sheet engineering, which enables the cultivation and harvesting of intact cellular layers without the use of proteolytic enzymes, thereby preserving the extracellular matrix and facilitating seamless engraftment.

Previous clinical studies in adults with esophageal squamous cell carcinoma have demonstrated the efficacy of autologous oral mucosal cell sheet transplantation in preventing post-procedural esophageal stenosis following

extensive endoscopic submucosal dissection. These findings provide a rationale for further investigation into the application of this method in the pediatric population, particularly in cases of refractory or recurrent esophageal strictures [49].

The use of this method in children with refractory postoperative anastomotic stenosis after correction of esophageal atresia and stenosis was investigated in a clinical trial. In one of the three patients, despite two transplants, the effect was temporary and limited, which ultimately led to the need for surgical resection of the stenosis due to severe fibrosis and thickening of the submucosal layer. The researchers suggest that the high degree of scarring and the large number of previous endoscopic balloon dilations (more than 100 procedures) in this patient may have limited the effectiveness of the therapy. However, in two other patients, cell sheet transplantation was more successful: they did not require endoscopic balloon dilation for at least 48 weeks, and one of them for more than two years, allowing them to return to a normal diet. These results confirm that cell sheet transplantation can be effective in some cases of refractory anastomotic stenosis [20].

Another emerging approach involves tissue engineering using biocompatible scaffolds to reconstruct esophageal defects. A systematic review and meta-analysis of preclinical studies in animal models demonstrated that this strategy holds significant promise for esophageal tissue regeneration, although it remains associated with considerable challenges [40]. The most commonly reported postoperative complications in experimental models included graft stenosis (46%), postoperative dysphagia (15%), and anastomotic leakage (12%).

Various types of scaffolds have been investigated, including non-absorbable materials (e.g., silicone or collagen-based), absorbable polymers (e.g., polyglycolic acid combined with collagen), and decellularized extracellular matrices. Seeding these scaffolds with mesenchymal stem cells (MSCs) appears particularly promising, as MSCs possess multipotent differentiation capacity and may support the regeneration of functional esophageal tissue.

Despite their potential, critical limitations—such as graft stenosis and the lack of peristaltic motility in bioengineered esophageal segments—remain major obstacles and require further investigation in preclinical settings before transitioning to large-scale clinical trials. Nevertheless, a clinical case report has described the successful use of a decellularized extracellular matrix scaffold for treating recurrent esophageal stricture in a child, suggesting potential feasibility in select cases [10].

Overall, cell-based therapies and tissue engineering approaches represent promising strategies for the treatment of refractory esophageal anastomotic strictures. However, these modalities require further refinement and the conduct of well-designed prospective clinical trials to validate their long-term efficacy and safety, as well as to establish the optimal indications and treatment protocols for pediatric patients.

Discussion

The management of refractory anastomotic strictures (AS) in children following esophageal atresia (EA) repair often requires the application of various treatment modalities. Although several adjunctive and experimental techniques have been described, none has yet emerged as a universal standard of care. The lack of controlled and methodologically homogeneous studies makes it difficult to draw definitive conclusions regarding the efficacy and safety of most available interventions.

Further prospective, comparative studies with larger patient cohorts and long-term follow-up are necessary to identify optimal treatment strategies, establish objective criteria for assessing clinical outcomes, and confirm the safety of novel therapeutic approaches.

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Information about the authors:

Zhenis Nurtazinovich Sakuov – Master of Medical Sciences, Head of the Department of Neonatal Surgery, "National Research Center for Maternal and Child Health" of the Corporate Fund "University Medical Center", PhD candidate at the Department of Pediatric Surgery, Astana Medical University, Astana, Republic of Kazakhstan. E-mail: zhenissakuov@gmail.com, https://orcid.org/0000-0002-9885-3778

Vasiliy Mikhailovich Lozovoy – Doctor of Medical Sciences, Professor at the Department of Pediatric Surgery, Astana Medical University, Astana, Republic of Kazakhstan, v.m.loz@mail.ru, https://orcid.org/0000-0001-9193-7963

Asylzhan Abubakirovich Yerekeshov – Candidate of Medical Sciences, Associate Professor, Deputy Chairman of the Board for Clinical Affairs, Scientific Center of Pediatrics and Pediatric Surgery JSC, Almaty, Republic of Kazakhstan. https://orcid.org/0009-0003-7793-9497

Corresponding Author:

Meruert Spanovna Bokayeva – Pediatric Surgeon, Master's student in Molecular Medicine School of Medicine, Nazarbayev University, Astana, Republic of Kazakhstan

Mailing address: 5/1 Kerei and Zhanibek Khans Street, Astana 010000, Republic of Kazakhstan

Phone: +7 771 192 2220

Email: meruyert.bokayeva@nu.edu.kz