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Review

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Novel techniques for the management of esophageal anastomotic leaks

Andrés R. Latorre-Rodríguez, Sumeet K. Mittal

Norton Thoracic Institute, St. Joseph´s Hospital and Medical Center, Phoenix, AZ 85013, USA.

Correspondence to: Dr. Sumeet K. Mittal, Norton Thoracic Institute, St. Joseph´s Hospital and Medical Center, 500 W Thomas Rd. Suite 500, Phoenix, AZ 85013, USA. E-mail: sumeet.mittal@commonspirit.org

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Abstract

Anastomotic leaks (ALs) after esophageal resection remain a dreaded complication and are associated with high morbidity and mortality, along with an increased cost of care and prolonged hospitalization. Management strategies include confirming conduit viability, controlling sepsis with drainage/antibiotics, and maintaining nutrition. Traditional treatment of ALs has given way to nonoperative management including endoscopic and radiological techniques, which are associated with decreased morbidity. This article aims to review novel technologies and techniques for the management of esophageal ALs, including self-expandable metal stents, endoluminal vacuum therapy, leak content drainage, and radiology-guided drain placement.

Keywords: Anastomotic leak, postoperative complications, minimally invasive surgical procedures, digestive system surgical procedures, gastrointestinal endoscopy, esophagus

INTRODUCTION

Gastrointestinal resections require anastomosis to restore gastrointestinal (GI) continuity. Anastomotic leaks (ALs) are a dreaded complication, and their incidence, presentation, and management are driven by the organs involved and the location of anastomosis. ALs are more frequent after esophageal resection than after other digestive surgeries and are usually more challenging to manage due to their location in the mediastinum.

The reduction and management of perioperative complications includes three main strategies: (1) risk assessment and prevention through the appropriate selection of procedures and patients; (2) timely and early diagnosis of perioperative anastomotic complications; and (3) the adoption of less invasive endoscopic and radiological techniques to replace traditional major surgical interventions.

This paper aims to present the most recent information on fundamental concepts, including the definition, epidemiology, diagnosis, and management principles of esophageal ALs, and to introduce novel management techniques for this condition.

DEFINITION

Although ALs are widely regarded as the Achilles heel of esophageal resections, until recently, there was no uniform definition or grading. Recently, the Esophagectomy Complications Consensus Group (ECCG) defined ALs as a discontinuity in the anastomosis, staple lines, or conduits of the esophagus[1]. In other words, ALs are a failure of the anastomosis and may be caused by the surgical technique or intrinsic patient factors.

EPIDEMIOLOGY

ALs after esophageal surgery are believed to be the leading cause of postoperative morbidity, mortality, and prolonged hospitalization[2]. ALs can be associated with mediastinitis, sepsis, and acute respiratory distress syndrome[3]; however, it is difficult to know the precise incidence of ALs and their outcomes because, until recently, there was no accepted definition or standard method for recording, tracking, and defining complications[1,4]. More recently, the multicenter perioperative data collection platform for esophagectomies, ESODATA.org, was developed by the ECCG[5], and 79 surgical centers currently use it in more than 16 countries. Of 2704 esophagectomies registered on ESODATA.org between 2015 and 2016, ALs were the third most frequent complication with an incidence of 11.4%, preceded only by pneumonia (14.6%) and atrial arrhythmia (14.5%)[5].

The mortality rate among patients with ALs is higher (7.2%) than that of patients without this complication (3.1%)[2], and the incidence of ALs varies by the surgical anatomical location, being higher at the intracervical level (13.64%) than at the intrathoracic level (2.96%)[6]. In oncology patients, esophageal ALs are correlated with a significant reduction in overall survival and disease-free survival, as well as a greater likelihood of locoregional recurrences[7]. An important factor that may contribute to higher AL rates is surgeon inexperience[8], suggesting that the AL rate could be considered a key indicator of individual surgical expertise.

ETIOLOGY, RISK FACTORS, AND PREVENTION

Esophageal ALs can occur spontaneously with delayed clinical presentation, and a delay in diagnosis and management increases morbidity and mortality. Etiology is multifactorial; a clear or specific cause can rarely be established[9]. The recognized causes and risk factors of anastomotic leaks in the GI tract are classified into four groups: (1) intrinsic patient factors; (2) microbiota of the gastrointestinal tract; (3) tissue perfusion; and (4) technical or mechanical factors[2,9-12].

Some risk factors that have been shown to have statistically significant associations with the development of ALs in the gastrointestinal tract include male sex, obesity, smoking, hypertension, vascular and coronary diseases, type 2 diabetes mellitus, chronic renal disease, chronic obstructive pulmonary disease, use of steroids, non-steroidal anti-inflammatory drugs or bevacizumab, previous abdominal surgery, or previous thoracic radiotherapy[2,9,10]. Adequate preoperative management and control of these risk factors through

pre-habilitation with physiotherapy and clinical follow-up is essential to decrease the likelihood of esophageal ALs after esophagectomy.

DIAGNOSIS

An early and timely diagnosis of esophageal ALs is critical in limiting deleterious outcomes. Delayed recognition and treatment of ALs lead to higher mortality and morbidity[13]. To date, there is no consensus on the best diagnostic modality. The clinical manifestations of ALs vary widely and range from asymptomatic presentation to complex scenarios such as sepsis or acute respiratory distress syndrome.

Common symptoms of esophageal ALs are fever, supraventricular tachyarrhythmias, dyspnea, chest pain, cough, peri-incisional erythema, cervical induration (cervical anastomosis), and symptoms related to mediastinitis or sepsis such as purulent discharge or enteric contents in the drains[4,14]. Several biomarkers have been studied for the diagnosis of esophagus ALs (e.g., c-reactive protein, calcitonin, erythrocyte sedimentation rate, and white blood cell count), but their systematic use is not standardized[4,15]. Depending on the availability and the specific scenario of each patient, the surgeon may use esophagography, computed tomography (CT), or endoscopy as diagnostic or confirmatory tools. However, in recent years CT plus endoscopy has become the standard method[4].

PRINCIPLES OF ESOPHAGEAL AL MANAGEMENT

The basic principles of managing esophageal ALs can be reduced to addressing sepsis (adequate drainage and broad-spectrum antibiotics), ameliorating the anastomotic defect, and providing nutritional support [Figure 1]. It is important to note that esophageal AL management must be individualized. First, it is imperative to determine the diagnosis and whether the patient needs to be transferred to an intensive care unit or supported in some way (e.g., ventilator, vasopressors). Second, the surgeon must determine if an intervention is required.

One of the most important challenges in the management of ALs is the control of sepsis or infectious complications that may lead to fatal outcomes. Infection control is based on two fundamental pillars: (*a*) drain any collection from the AL and limit continued leaking through the anastomotic defect, either by open surgery or minimally invasive procedures (endoscopic or percutaneous)[4]; and (*b*) provide early and correct broad-spectrum antibiotic treatment including anti-fungal coverage[4,16,17]. It is highly recommended to perform microbiological cultures, including blood cultures, to direct antibiotic therapy.

Another main goal during AL management is nutritional support. The key point is to determine the best type of nutritional support depending on the patient's condition. The preferred route is enteral and distal to the AL; some available options are the use of a nasojejunal, gastrostomy, or jejunostomy tube[4,13]. In addition, proton pump inhibitors, anticholinergics, and prokinetics are recommended to reduce salivary and leakage volume[4,18]. Nutritional support should be provided until the successful closure of the AL and the resumption of adequate oral intake[13,16,19].

SURGICAL MANAGEMENT

It is suitable and acceptable to perform an open or laparoscopic surgical intervention to correct both cervical and intrathoracic anastomotic defects in the following situations: (1) esophageal ALs detected within the first 72 h after surgery; (2) esophageal ALs in critically ill patients or those that are life-threatening; (3) in cases of necrotic or ischemic conduit; or (4) when previous endoscopic/radiological treatment has failed[4,13].

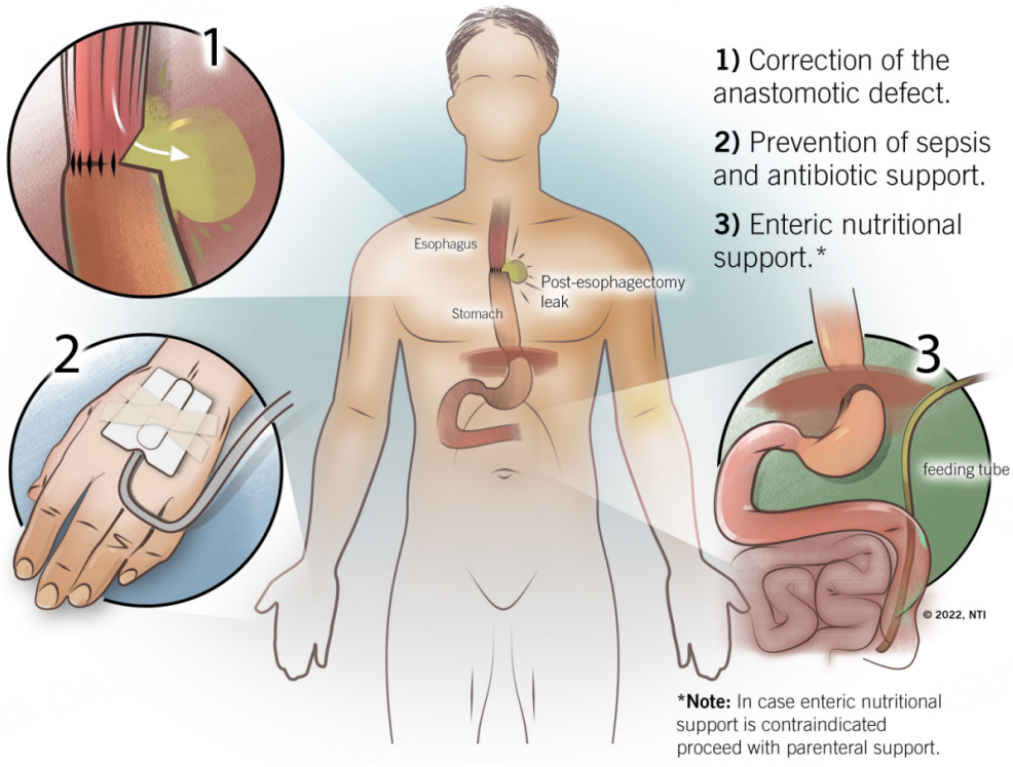

Figure 1. The basic principles of managing esophageal anastomotic leaks. (Used with permission from Norton Thoracic Institute, St. Joseph's Hospital, and Medical Center, Phoenix, Arizona).

The correct surgical approach must be reviewed and adjusted on a case-by-case basis. Some key factors that impact the choice of surgical technique are the presence or absence of empyema, conduit ischemia/necrosis, sepsis, and compromise of the gastric fundus[4,20,21].

The choice of open versus thoracoscopic surgical intervention depends on available surgical expertise; the presence of empyema, sepsis, or tissue necrosis generally requires an open procedure[4]. The contents of the leak must be drained, and the remaining tissue should be preserved[4,13]. Thoracoscopy, thoracotomy, cervicotomy, implantation of pedicle flaps, and gastric tube resection are some of the surgical management approaches used for esophageal ALs[4].

NOVEL TECHNIQUES

Major re-operative surgical interventions for ALs increase morbidity and the chance of GI tract diversion. Increasingly, less invasive management techniques are used to manage ALs. Advances in endoscopic techniques have made it possible to develop and adopt novel devices and technologies that stand out for their effectiveness and simplicity of use in clinical practice while adhering to the essential principles of AL management delineated above. As a result, the mortality rates associated with major ALs have decreased. Two endoscopic techniques that have become more common are self-expandable metal stents (SEMS) and endoluminal vacuum therapy (E-Vac). These endoscopic techniques, in addition to the availability of radiology-guided drain placement, have brought about a dramatic and welcome change in the management of ALs and the associated morbidity and mortality.

SEMS are partially or fully covered metal prosthetic biomedical devices that can be placed endoscopically. Their purpose is to cover the anastomotic defect while preserving an open lumen as the tissue is healing [Figure 2][4]. SEMS have been used within the GI tract since 1990 for the management of biliary obstruction of malignant origin[22,23] and are now widely used in the upper GI tract.

Clinical experience with the use of SEMS in the foregut is extensive; these devices are commonly used for the palliative management of dysphagia in patients with malignant esophageal obstruction and for treating esophageal ALs[24]. In general, SEMS are an adequate alternative for the management of symptomatic esophageal ALs for patients with symptomatic early ALs with < 70% esophageal diameter compromise without sepsis or critical comorbidities if there is a viable conduit and drainage site[4,25].

The clinical success rate associated with endoscopic management of ALs with SEMS is close to 85%, and there is no statistically significant difference in the clinical success rate between fully covered and partially covered SEMS (85% and 86%, respectively, $P = 0.97$)[26]. The average healing time after SEMS placement is 4 to 8 weeks[27]; however, the result depends directly on the defect size and the time since diagnosis[4,16,28]. The use of SEMS is recommended in small-to-medium diameter leaks with a smaller luminal opening size. On the other hand, the use of this device for the management of proximal (cervical) esophageal ALs is related to a higher risk of failure due to challenging fixation in the proximal esophagus[4]. Healing of ALs uniformly leads to strictures, but the use of stents may decrease the extent and prevalence of anastomotic strictures associated with AL healing.

Complications related to the use of SEMS occur in 34% to 78% of patients. The highest risk is stent migration, occurring in 16% to 62% of cases[26,28]; other adverse events include post-extraction esophageal stenosis, tissue overgrowth, enlargement of the anastomotic defect, bleeding, esophageal perforation, tracheal perforation, vascular compression, discomfort, pain, fistula development, reflux, and aspiration pneumonia[4,13].

E-Vac is a more recent novel technique for the endoscopic management of esophageal ALs. Although this technology was already widely used in the field of GI surgery for the management of intestinal perforations, its use for the management of esophageal AL only began in 2005, with the first clinical trial results in 2010[29].

E-Vac uses an endoscopically placed tube to administer negative pressure to the anastomotic leak location. A polyurethane endosponge that provides suction and seals the leak cavity is located in the distal end of the device, which is suitable for intracavitary or intraluminal placement [Figure 3][30]. Currently, the commercial product Endo-SPONGE (B. Braun SE) is not widely available worldwide, including in the United States. However, several centers in the U.S. have reported improvising the device with a wound-vac sponge (GranuFoam; 3M) at the end of a nasogastric tube[31].

As the use of E-Vac for the management of esophageal ALs has increased, it has proven to be a safe therapeutic option, and the reported clinical success in the closure of esophageal ALs is 67% to 78%[32,33]. Studies on the prophylactic use of E-Vac have shown a reduction in the incidence of ALs after esophagectomy[34,35].

The use of E-Vac is indicated for but not limited to large ALs, early or late ALs, ALs with cavitary collections, and symptomatic or asymptomatic patients in critical condition[4,30]. The endosponge should be replaced every 3 to 4 days, and therapy must continue until the defect is corrected and there are no signs of

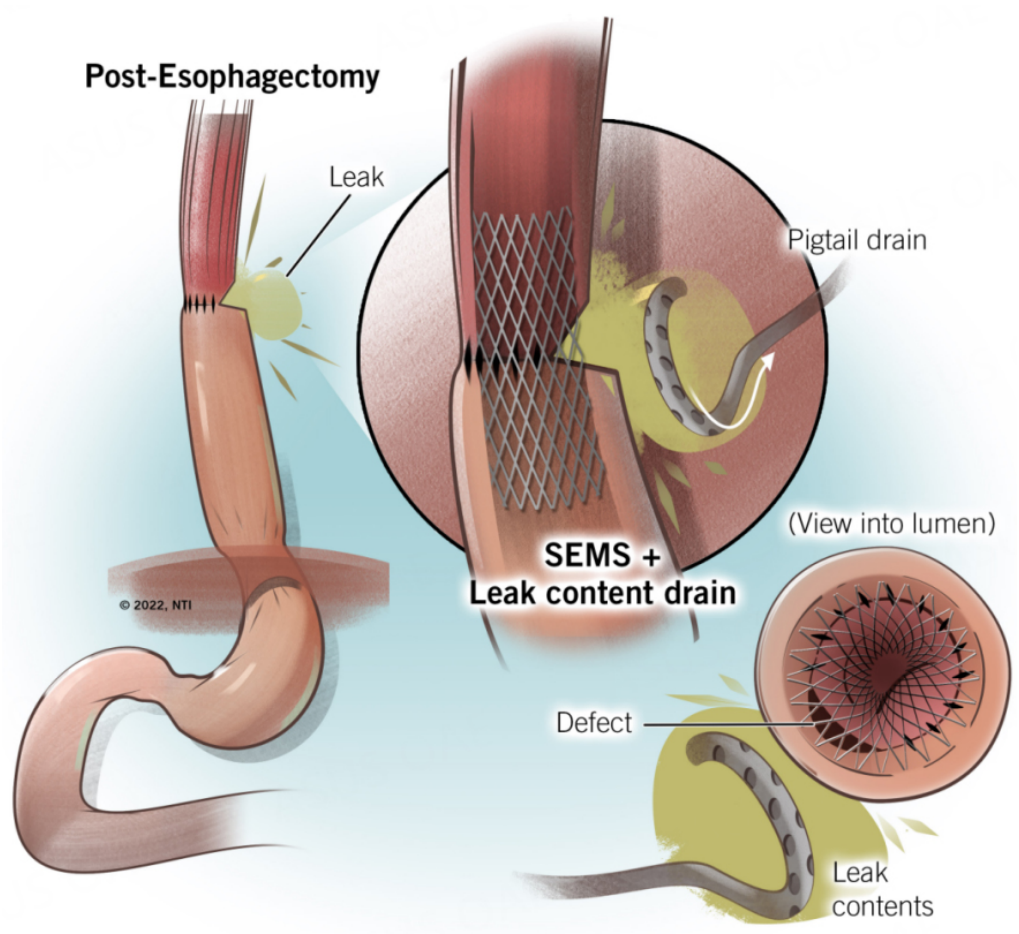

Figure 2. Illustration of a self-expandable metallic stent (SEMS) used for the endoscopic management of esophageal anastomotic leaks. (Used with permission from Norton Thoracic Institute, St. Joseph's Hospital, and Medical Center, Phoenix, Arizona).

ischemia or necrosis. The average length of E-Vac therapy is between 12 and 36 days[4]. Risks and complications associated with this treatment are rare. The most common complication is esophageal stenosis secondary to tissue granulation; other documented complications include bleeding, rupture of the descending aorta, and formation of new fistulas[4,30]. Endoscopic management with E-Vac is 2.5 times less expensive than open surgical management, making it a cost-effective option[36].

It is possible that combining the use of SEMS and E-Vac will lead to better clinical outcomes and also increase safety. In clinical practice, this novel technique has been called stent-over-sponge[37]. A clinical trial and registration of the VAC-Stent device (VAC Stent Medtec AG), which hybridizes SEMS and E-Vac, is currently underway[38].

Another technique for managing esophageal ALs endoscopically is leak-content drainage, although this is a non-standardized technique and has multiple variations according to the experience of each surgical center. It was first described in 1993 and entailed endoscopically locating the defect to advance a nasogastric tube to the abscess cavity, subsequently verifying its permeability and maintaining continuous suction; relocation of previously placed drains can also be performed[39]. Moreover, in 2021 Hallit *et al.*[40] reported the use of internal endoscopic drainage with double pigtail stents (i.e., draining the leaked content through and around the double pigtail stent while maintaining the defect open), with a 100% success rate (38/38). In this

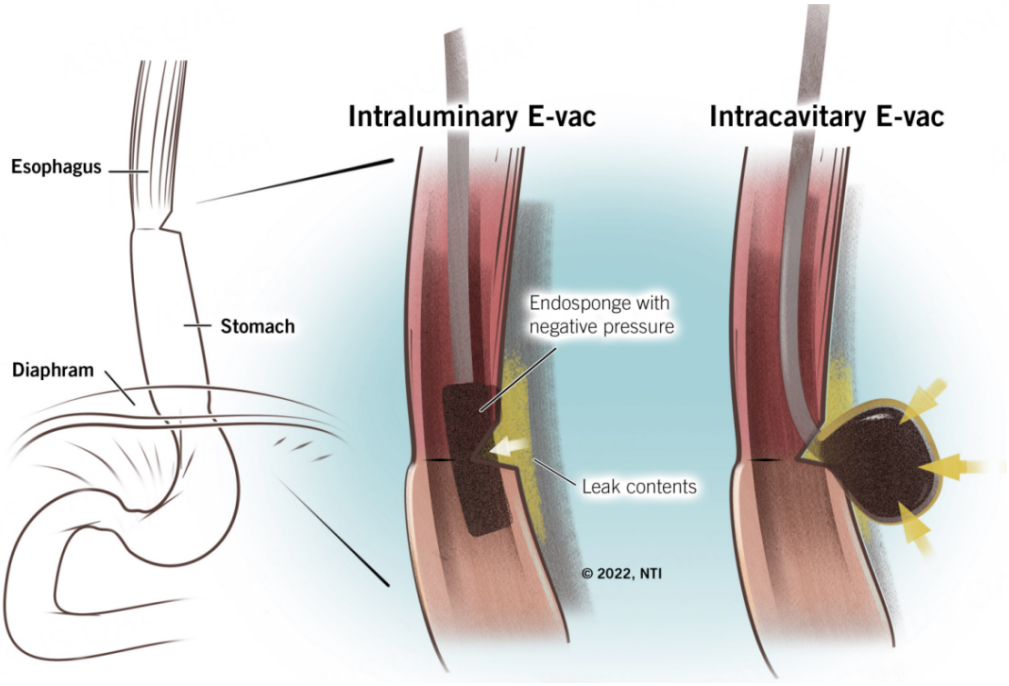

Figure 3. Illustration of the (A) intraluminal and (B) intracavitary placement of the E-vac device in the endoscopic management of esophageal anastomotic leaks. (Used with permission from Norton Thoracic Institute, St. Joseph's Hospital, and Medical Center, Phoenix, Arizona).

same study, SEMS placement had a 77% (23/30) success rate. Additional recent alternatives for the minimally invasive management of esophageal ALs, including the use of endoscopic clips, endoscopic overstitch systems like OverStitch (Apollo Endosurgery, Inc.), and continuous suture systems, have had limited success[4].

Interventional radiology or image-guided procedures have boomed in recent decades due to the increasing availability of expertise and decreasing complications and costs. In the field of thoracic surgery, multiple successful attempts at percutaneous CT-guided drainage of mediastinal or peri-esophageal abscesses have been reported and appear to be associated with higher success rates than SEMS; however, interventional radiology management for esophageal ALs is still unstandardized and a very uncommon (stand-alone) procedure[41]. Furthermore, clinical trials are required to elucidate the full risks and benefits of this approach[41].

The management of ALs of the foregut is focused on prevention, the use of minimally invasive endoscopic technologies, and personalized therapies. One interesting preclinical study that decreased the rate of ALs was performed in an animal model and used gene therapy with recombinant human vascular endothelial growth factor by direct injection of a non-viral plasmid-based delivery system[42]. Furthermore, early clinical and preclinical studies have shown promising results from the peri-anastomotic administration of biologics, such as porcine fibrin sealant[43], as well as cell therapy, such as autografting stromal cells in fibrin scaffold[44] and mesenchymal stem cells with or without platelet-rich plasma[45,46].

CONCLUSIONS

ALs after surgical intervention in the gastrointestinal tract, including the esophagus, are an infrequent

complication but are associated with high morbidity and mortality. The surgeon must be familiar with the clinical symptoms and diagnostic methods to detect and treat this complication early under the basic principles: correct the anastomotic defect, prevent or treat sepsis, and provide adequate nutritional support.

Given the complexity and wide variation in the clinical presentation of ALs, there is currently no consensus or clinical practice guidelines to direct the appropriate treatment for each patient. The current trend is away from aggressive surgical management of ALs, limiting this option to cases of necrosis or uncontrolled sepsis. On the contrary, the use of new minimally invasive management technologies, especially E-Vac and SEMS, which have shown satisfactory results in the management of non-critical symptomatic cases, is increasing.

Currently, there are multiple clinical trials underway to identify and apply more robust intraoperative preventive techniques, and new technologies for the minimally invasive management of ALs have been introduced. Additional study results are expected in the next decade, and new devices for endoscopic management of ALs, including hybrid devices (SEMS + E-Vac) and cell and gene therapies, may be adopted; however, more preclinical and clinical trials assessing the safety and effectiveness of these therapies are required.

DECLARATIONS

Authors' contributions

Made substantial contributions to the concept, scope, literature review, writing, and revisions: Mittal SK, Latorre-Rodriguez AR

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Conflicts of interest

Both authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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