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European Association for Cardio-Thoracic Surgery expert consensus statement on the prevention and management of mediastinitis

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Abstract

Mediastinitis continues to be an important and life-threatening complication after median sternotomy despite advances in prevention and treatment strategies, with an incidence of 0.25–5%. It can also occur as extension of infection from adjacent structures such as the oesophagus, airways and lungs, or as descending necrotizing infection from the head and neck. In addition, there is a chronic form of 'chronic fibrosing mediastinitis' usually caused by granulomatous infections. In this expert consensus, the evidence for strategies for treatment and prevention of mediatinitis is reviewed in detail aiming at reducing the incidence and optimizing the management of this serious condition.

Keywords: Mediastinitis • Cardiac surgery • General thoracic surgery • Treatment • Prevention • Guideline

BACKGROUND

Mediastinitis and deep sternal wound infection (DSWI) are devastating and life-threatening complications after median sternotomy. This involves the mediastinal–interpleural space within the chest. Despite advances in prevention and treatment strategies, its incidence remains significant and ranges between 0.25% and 5% [1–3, 58–61, 62, 63, 64]. Surgical wound infections may result from contamination during surgery from both the patient and the surgeon [65]. Blood-borne infection could represent an alternative route to the surgical wound [4], as well as extension of infection from adjacent structures such as the oesophagus (i.e. due to oesophageal perforation), airways (e.g. due to tracheobronchial perforation) and lungs (e.g. pleural empyema), or a descending necrotizing infection from the head and neck [e.g. descending necrotizing mediastinitis (DNM)]. In addition to the aforementioned acute types of mediastinitis, there is also a chronic form namely 'chronic fibrosing mediastinitis', which is very rare and usually caused by granulomatous infections. In the first part of the document DSWI is reviewed in detail, and in the second part other, less common, but important types and pathologies of mediastinitis are discussed.

† The first two authors contributed equally to this paper.‡ Chair of Clinical Guidelines Committee.¶ Chair of the EACTS Thoracic Domain.§ Chair of EACTS Working Group for Pleural Diseases.

METHODOLOGY

The European Association for Cardiothoracic Surgery (EACTS) Thoracic and Adult Cardiac Domain established a team of surgeons to produce a statement on the surgical treatment of mediastinitis. Initially, a set of key clinical questions was formulated on the epidemiology, diagnosis and classification of mediastinitis. Furthermore, two main groups of experts were formed in order to concentrate on the two main forms of mediastinitis: (i) mediastinitis after cardiac surgery and (ii) mediastinitis related to non-cardiac surgery. To obtain a body of scientific evidence, a systematic literature search was performed on medical databases Medline/PUBMED (National Library of Medicine, USA), EMBASE (Elsevier, Netherlands) and Cochrane Library (UK). The initial search was performed in January 2015. The search was limited to reference material published since 1938 (Table 1).

Levels of evidence are derived from published papers (Table 2) and recommendations classed by the strength of evidence (Table 3). The preliminary document was circulated among all the involved

Table 1: Methodology checklist

	Yes	No
Panel assembly		
• Experts from chest medicine and thoracic surgery	x	
• Experts vetted for conflict of interest	x	
• Patient representative	x	
• Expert methodologist	x	
Literature review		
• Performed in collaboration with librarian	x	
• Searched in multiple electronic databases	x	
• Reviewed reference list of retrieved articles (Medline/PUBMED,EMBASE, Cochrane Library)	x	
Evidence synthesis		
• Prespecified inclusion and exclusion criteria applied		x
• Evaluation of included studies for source of bias	x	
• Explicitly summarized benefits and harms	x	
• Grading system used		x
Included studies evaluated		
• Recommendations for clinical practice		x
• Summary/opinions	x	

Table 2: Levels of evidence

Level of Evidence A	Data derived from multiple randomized clinical trials or meta-analyses
Level of Evidence B	Data derived from a single randomized clinical trial or large non-randomized studies
Level of Evidence C	Consensus of opinion of the experts and/or small studies, retrospective studies, registries

members for further input and comments. A final version was then revised to incorporate all the pertinent comments suggested and submitted to the EACTS Thoracic domain for further input and implementation.

The manuscript has been approved by the Chair of the Clinical Guidelines Committee and by the Chair of the Pleural Diseases Working Group.

This statement describes the current evidence and practices for the management and prevention of mediastinitis.

GENERAL CONSIDERATIONS

Relevant anatomy

The mediastinum is limited bilaterally by the mediastinal parietal pleura and extends from the thoracic inlet superiorly to the diaphragm inferiorly. It is further artificially divided into three parts: the anterior, middle and posterior mediastinum.

The anterior mediastinum is bounded anteriorly by the sternum; posteriorly by the pericardium, aorta and brachiocephalic vessels; superiorly by the thoracic inlet; and inferiorly by the diaphragm. It includes the thymus, lymph nodes, adipose tissue and internal mammary vessels. The thyroid gland may also extend into the anterior mediastinum.

The middle mediastinum lies in between anterior and posterior mediastinum and is basically bounded anteriorly and posteriorly by the pericardium. Its contents include the heart and pericardium; the ascending aorta and aortic arch; the superior vena cava (SVC) and inferior vena cava; the brachiocephalic vessels; the pulmonary vessels; the trachea and main bronchi; lymph nodes; and the phrenic, vagus and left recurrent laryngeal nerves.

Table 3: Classes of recommendations

Classes of recommendations	Definition
Class I	Evidence and/or general agreement that a given treatment or procedure is beneficial, useful, effective
Class II	Conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the given treatment or procedure
Class IIa	Weight of evidence/opinion is in favour of usefulness/efficacy
Class IIb	Usefulness/efficacy is less well established by evidence/opinion
Class III	Evidence or general agreement that the given treatment or procedure is not useful/effective, and in some cases may be harmful

The posterior mediastinum is bounded anteriorly by the posterior trachea and pericardium, posteriorly by the vertebral column and the chest wall, respectively. It contains the oesophagus, descending aorta, azygos and hemiazygos veins, thoracic duct, vagus and splanchnic nerves, lymph nodes and fat.

Presentation

Mediastinitis manifests within a spectrum that ranges from the subacute, stable patient to the fulminant critically ill patient who requires immediate intervention in order to prevent death. Vital signs may generally show tachycardia and fever. In more advanced cases of sepsis, hypotension may be present and the patient may require intensive care support. Systemic signs of sepsis strongly suggest mediastinal involvement. Detailed diagnostic criteria are described later in detail.

Imaging studies

Delays in the diagnosis of mediastinitis greatly influence morbidity, mortality and overall outcome. The condition is typically recognized because of high clinical awareness in susceptible populations, including those with obesity, chronic obstructive pulmonary disease (COPD), diabetes, smoking, osteoporosis, re-exploration for bleeding, bilateral internal mammary artery (BIMA) use, redo surgery, prolonged intensive care stay and use of mechanical ventricular assist devices [5, 58, 64]. Contrast-enhanced computed tomography (CT)-scan (with additional oral contrast if an oesophageal lesion is suspected) is the diagnostic tool of choice in the diagnosis of mediastinitis. This does not only show the extent of infection but also helps in defining the underlying cause. Other imaging modalities can also be utilized that include magnetic resonance imaging (Fig. 1) and labelled white blood cell scan.

Treatment

Once a clinical diagnosis of mediastinitis is suspected or established, aggressive antibiotic therapy should be started after blood culture and consideration can be given to the surgical techniques available. In principle, control of the source of infection and surgical

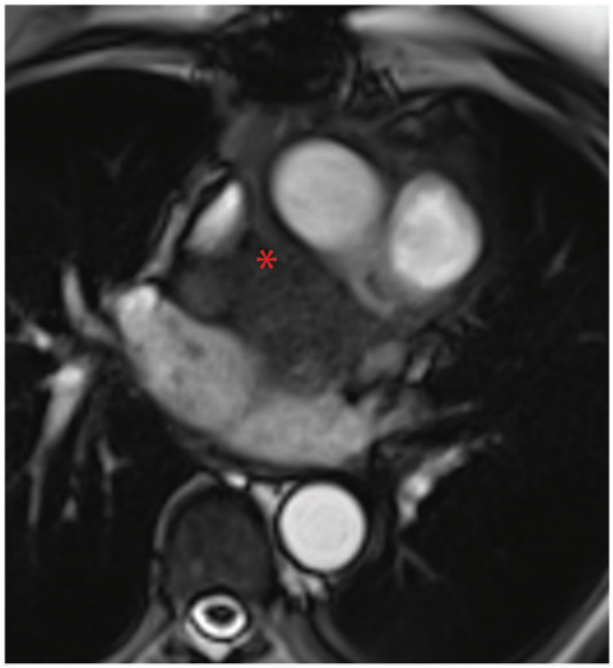

Figure 1: Magnetic resonance imaging of the mediastinum demonstrating infiltration and enhancement of the soft tissues indicative of mediastinitis.

debridement of affected tissue are the cornerstones of treatment [6, 7, 66, 67].

Outcome

The outcome strongly depends on rapid diagnosis and adequate treatment. It also depends on the underlying cause of the disease and the patients' comorbidities. Patients with DSWI have a worse short- and long-term outcomes, with an associated mortality rate reported between 10% and 47% [4, 8, 59, 63, 64, 68–70]. The impact of this complication on both healthcare and hospital budgets is significant [4, 8, 69].

Prevention

Many preventative measures are suggested as effective for reducing the incidence of surgical site infections (SSIs), such as preoperative screening for carriage of multiresistant organisms [e.g. methicillin-resistant *Staphylococcus aureus* (MRSA)], antimicrobial prophylaxis, preoperative skin preparation, accurate surgical technique and wound management.

MEDIASTINITIS AND DEEP STERNAL WOUND INFECTION AFTER MEDIAN STERNOTOMY

Definition

According to Centers for Disease Control and Prevention (CDC) guidelines [9], the definition of mediastinitis requires at least one of the following criteria:

- Patient has organisms cultured from mediastinal tissue or fluid.
- Patient has evidence of mediastinitis on gross anatomical or histopathological examination.
- Patient has at least one of the following signs or symptoms: fever (>38°C), chest pain or sternal instability.

And at least one of the following:

- Purulent drainage from mediastinal area;
- Mediastinal widening on imaging.

The definition of post-sternotomy mediastinitis by van Wingerden et al. [10] is:

Infection occurring within 1 year following surgery, regardless of whether an implant is in place or not,

AND infection appears related to the operative procedure,

AND, at least one of the following criteria:

1. Patient has organisms cultured from mediastinal tissue or fluid obtained during a surgical operation or needle aspiration.
2. Patient has evidence of mediastinitis seen during a surgical operation or histopathological examination.
3. Patient has at least one of the following signs or symptoms with no other recognized cause: fever (>38°C), chest pain or sternal instability.

AND at least one of the following:

a. Purulent discharge from the mediastinal area;
b. Organisms cultured from blood or spontaneous discharge from the mediastinal area;
c. Radiological evidence of an infective process in the mediastinum.

Sternal wound infections can also be divided into 'superficial' infections and 'deep' infections, based on the depth of the infection. Early infections include both 'superficial' infections, reaching the dermis and subcutaneous tissue, and DSWIs that reach under the sternum and the anterior mediastinum. Thus, a DSWI can present either 'early'—more common—or as a 'late' infection. 'Late' infections often comprise a combination of superficial and deep infection and they include osteomyelitis, subcutaneous abscess and sternocutaneous fistulas.

Risk factors

The pathogenesis of mediastinitis is complex and multifactorial. Several risk factors have been identified and of those, diabetes and obesity remain most important [62]. Preoperative, intraoperative and postoperative variables have been described.

Preoperative risk factors include diabetes mellitus [1, 11–13, 59, 64, 71–85], obesity [1, 11, 59, 64, 71, 72, 74–77, 80–82, 84, 86–94], advanced age [75–77, 82, 90, 95, 96], COPD [59, 81, 84, 91, 97–99], heart failure and left ventricular dysfunction [1, 77, 81, 86, 95, 100], smoking [1, 12, 82, 89], female sex [75, 79, 95, 96, 101], elevated serum creatinine level or patients undergoing haemodialysis [77, 81, 95, 100], peripheral vascular disease [1, 13, 80], prolonged preoperative stay in hospital [59, 78, 101], emergent or urgent surgery [82, 99, 102].

Intraoperative risk factors include use of BIMA grafts [1, 11, 64, 72, 81, 86, 91, 92], prolonged duration of surgery, perfusion time and aortic cross clamp time [11, 13, 72, 77, 79–81, 86, 95–97], redo cardiac surgery and reoperation [12, 58, 59, 64, 87, 90, 101–105].

Postoperative risk factors include postoperative respiratory failure [1, 12, 59, 71, 85, 90, 92, 97] and prolonged intensive care stay [64, 73, 80, 85, 106].

Diagnosis

Signs and symptoms of mediastinitis typically present within 30 days of cardiac surgery. Local signs include purulent drainage from the sternal wound and sternal instability. Often patients present with fever, raised inflammatory markers and reporting slow or no recovery. One of the most reliable signs of DSWI is sternal instability, which can be easily appreciated on physical examination and is often reported by the patients themselves [107]. It may be difficult to distinguish on physical examination between DSWI and superficial infection. When a high index of suspicion is present, early wound opening and inspection with appropriate sampling of tissue for bacteriologic assessment are strongly advised.

Radiographic imaging can support the clinical diagnosis and is included as part of the CDC guidelines for defining mediastinitis [14]. A simple postero-anterior chest radiograph can show the presence of air between the sternal edges. Furthermore, lateral displacement of one or more sternal wire could represent an indirect sign of fractured or separated sternum [108]. CT-scanning provides excellent detail and is the investigation of choice when a diagnosis cannot be easily established by clinical examination alone [15, 109]. It is also valuable in guiding surgical planning. The typical CT findings in cases of mediastinitis are sternal disruption, free gas bubbles underneath the sternal plate and mediastinal fluid collection [110].

Perioperative prevention measures

The principles of prevention are to (i) minimize the intraoperative wound contamination with skin bacteria, (ii) avoid contamination with more virulent pathogens (*S. aureus*, Gram-negative bacteria), (iii) reduce preconditions for secondary haematogenous contamination of bacteria, (iv) optimize the local conditions for wound healing and optimize the general host defence and (v) prevent development of infection by contaminating bacteria (antibiotic prophylaxis). Different measures can be applied during the preoperative phase for reducing DSWI rate. These include preoperative screening for carriage of multiresistant organisms (e.g. MRSA), antimicrobial prophylaxis, preoperative skin preparation and accurate surgical technique.

Staphylococcus aureus nasal carriage. The anterior nares are the commonest area for *S. aureus* colonization. Approximately 20% of the general population are persistently colonized, whereas 30% represent an intermittent carrier and the remaining 50% appear not to be susceptible to *S. aureus* carriage for unclear reasons [16]. Methicillin-sensitive *S. aureus* (MSSA) lives on the skin of humans as a commensal. Nasal colonization with strains of methicillin-resistant *S. aureus* (MRSA) is estimated at around 1% of the total population [111] and is more frequent in certain sub-groups such as elderly people, immunosuppressed patients, diabetics and those who are frequently hospitalized. *Staphylococcus aureus* is the most common causal microorganism for wound infections in general, causing up to 80% of post-surgical mediastinitis [17, 112].

Compared with MSSA mediastinitis, MRSA mediastinitis has up to 11-fold increase in mortality rate [61, 75]. As a result of the association between colonization and subsequent infection, numerous studies have focused on decolonization strategies in order to reduce the risk of infection and transmission of the organism to others. Topical mupirocin is the most commonly used method for MRSA eradication. It is safe, well tolerated and not systemically absorbed, which makes it an ideal agent for decolonization. However, there is growing evidence of increasing mupirocin resistance and treatment failure, especially in those individuals colonized with MRSA in multiple sites. In a large international cohort of patients undergoing cardiac surgery, which were observed prospectively, invasive postoperative *S. aureus* infections occurred in 1% of adult patients despite modern perioperative management. The corresponding mortality rates were 3% for MSSA and 13% for MRSA infections. Preoperative nasal colonization with *S. aureus* increased the risk of postoperative infection 3-fold [113].

San Juan et al. [114] showed that endogenous nasal colonization often precedes methicillin-susceptible *S. aureus* post-sternotomy mediastinitis, which suggests that preoperative decontamination is adequate for preventing methicillin-susceptible *S. aureus* post-sternotomy mediastinitis, whereas hospital infection control measures seem to be the major factor for preventing MRSA post-sternotomy mediastinitis.

A meta-analysis by van Rijen et al. [18] included four randomized controlled studies to assess the use of mupirocin preoperatively in patients who were *S. aureus* nasal carriers. In the largest of these studies, Perl et al. [19] reported a significant effect of mupirocin on the *S. aureus* rate. In the studies of Garcia et al. [20], Kalmeijer et al. [115] and Konvalinka et al. [116], no significant effect was found. Meta-analysis of these four studies demonstrated a significant effect of mupirocin on the *S. aureus* infection rate after surgery in carriers [relative risk (RR) 0.55, 95% confidence interval (CI): 0.34–0.89]. In surgical patients who were not carrying *S. aureus*, the treatment had no significant beneficial effect (RR 1.09, 95% CI: 0.52–2.28). Using molecular typing techniques, Perl et al. reported that 85% of the *S. aureus* infections were endogenous. The study by Kalmeijer et al. concurs with a percentage of 86%. The authors concluded that the effectiveness of mupirocin is related to carriers only, because in proven nasal carriers a significant and effective reduction in the rate of *S. aureus* infection was found.

The review by Trautmann et al. [21] analysed four randomized and seven sequential open cohort studies. Three of the five studies carried out in cardiac surgery patients showed a significant reduction in sternotomy site infections. However, all three studies were open sequential cohort studies. In contrast, a prospective, randomized, double-blind study in cardiac surgical patients showed no benefit of mupirocin.

A meta-analysis by Kallen et al. [22] included seven studies: three randomized controlled trials (RCTs) and four before-and-after studies. When cardiothoracic surgery studies were analysed, mupirocin was found to reduce infection compared with controls in both the RCTs and non-randomized studies although the difference was not statistically significant in the former. The authors concluded that perioperative intranasal mupirocin appeared to reduce the incidence of SSI in non-general surgery patients, but had no apparent effect in general surgery.

The Society of Thoracic Surgeons (STS) practice guidelines [23] recommend routine mupirocin nasal administration for all patients undergoing cardiac surgical procedures in the absence of a documented negative testing for staphylococcal colonization; the duration of mupirocin therapy for suppressing *S. aureus* nasal carriage is 5 days (Class I, Level of Evidence A). In general, cardiothoracic patients are considered at high risk for serious MRSA infection and therefore should be routinely

screened at the time of admission or preferably prior to admission. It is recommended that carriers of MRSA, who are receiving prophylaxis for an operation, should undergo nasal decolonization with mupirocin [24].

Skin antiseptic preparation. Skin antiseptic preparation is aimed at reducing bacterial colonization of the skin and the risk of wound contamination during the surgical procedure. Iodophor [such as povidone-iodine (PI)] and chlorhexidine gluconate (CHG) are the main types of antiseptics and can be mixed with either alcohol or water. Chlorhexidine reduces skin bacterial colony counts to a greater extent than PI does or other agents that have been studied [117, 118]. Adjunctive means to reduce contamination include measures to reduce airborne contamination in the operating room by use of tight scrub-suits and laminar airflow. The use of plastic adhesive drapes on the skin is commonly practiced but should be questioned, as it has in fact not been shown to reduce SSIs and might even increase the recolonization of the skin.

The role of preoperative shower or bath with antiseptic agents in reducing bacterial colonization is largely debated. A recent systematic review supports the idea that presurgical showering with CHG is effective in reducing bacterial burden, but the effect on SSIs was inconclusive [119].

Two previous systematic reviews [25, 26] reported mixed findings for the reduction of skin flora and SSIs with presurgical showering. Jakobsson et al. examined 10 studies and, while they were unable to produce definitive recommendations due to the different study designs, they concluded that preoperative disinfection showers with CHG are effective from a microbiological point of view as eight of the reviewed studies demonstrated a sharp reduction in skin flora. On the other hand, Webster et al. reviewed seven trials, which provided no clear evidence of benefit for preoperative showering or bathing with chlorhexidine over other wash products in reducing the rate of SSI.

The CDC guidelines recommend that patients shower or bath with an antiseptic solution the night before surgery and that the skin is prepared with 'an appropriate antiseptic agent' [16]. Clinical practice guidelines from the National Institute for Health and Clinical Excellence recommend that patients shower or have a bath using soap, either the day before or on the day of surgery. There is no evidence of a difference of effect on SSI rate between chlorhexidine as a cleansing agent and plain detergent or soap. In addition, chlorhexidine has been found not to be cost-effective. They also recommend preparing the skin at the surgical site with antiseptic immediately before incision, but they do not indicate a preference for CHG or PI [120].

Prophylactic antibiotic therapy. Perioperative antimicrobial prophylaxis is the cornerstone of SSI prevention. The benefits of appropriately administered prophylactic antibiotic therapy in patients undergoing cardiac surgery have been clearly demonstrated and preoperative antibiotics should be administered to all patients to reduce the risk of postoperative infection (Class I, Level of Evidence A) [27, 121, 122].

However, the choice of antibiotic, optimal dose, duration and timing of antimicrobial prophylaxis protocol remains controversial. The STS Practice Guidelines on antibiotic prophylaxis in cardiac surgery [23] indicate a beta-lactam antibiotic as a single antibiotic of choice for standard cardiac surgical prophylaxis in populations that do not have a high incidence of MRSA (Class I Level of Evidence A). For patients who are considered beta-lactam or penicillin allergic, vancomycin is recommended as the primary prophylactic antibiotic (Class I, Level of Evidence A) with additional Gram-negative coverage (Class IIB recommendation, Level of Evidence C).

In order to reach adequate antibiotic serum concentration and effective tissue level, the time of administration is proven to be an important aspect of antibiotic prophylaxis. In patients for whom cefazolin is the appropriate prophylactic antibiotic for cardiac surgery, administration within 60 min of the skin incision is indicated (Class I, Level of Evidence A). In patients for whom vancomycin is the prophylactic agent of choice, a dose of 1–1.5 g or a weight-adjusted dose of 15 mg/kg administered intravenously slowly over 1 h, with completion within 1 h of the skin incision, is recommended (Class I, Level of Evidence A). For patients who receive an aminoglycoside (usually gentamicin, 4 mg/kg) in addition to vancomycin before cardiac surgery, the initial dose should be administered within 1 h of the skin incision (Class I, Level of Evidence C).

The 2011 American College of Cardiology/American Heart Association (ACC/AHA) guideline for CABG surgery [2] recommends a first- or second-generation cephalosporin for prophylaxis in patients without MRSA colonization (Class I, Level of Evidence A) and vancomycin alone or in combination with other antibiotics to achieve broader coverage is recommended for prophylaxis in patients with proven or suspected MRSA colonization (Class I, Level of Evidence B).

Duration of antibiotic prophylaxis is another point of debate. Ideally, short courses of antibiotic prophylaxis are preferred to longer courses to reduce risks of drug toxicity, infection with *Clostridium difficile*, the emergence of resistant pathogens and cost [28, 93, 94, 123, 124]. On the other hand the rationale given for prolonging the duration of antibiotic prophylaxis in cardiac surgery includes the pharmacokinetic/pharmacodynamic changes caused by the use of cardiopulmonary bypass, hypothermia and blood loss. The STS Practice Guidelines on antibiotic prophylaxis recommend that the duration of a prophylactic antibiotic regimen is limited to the shortest amount of time required to effectively minimize the probability of postoperative infection. They recommend postoperative prophylactic antibiotics to be given for 48 h or less (Class IIa, Level B).

Lador et al. [29] in a recent systematic review and meta-analysis of RCTs comparing one antibiotic regimen versus another in cardiac surgery found that shorter duration of prophylaxis was associated with a higher rate of DSWI. The difference originated from studies in which the short-duration arm was $\leq$24 h postoperation. There were no significant differences between short versus longer prophylaxis when the short-duration arm provided more than 24 h postoperative coverage. In this group of studies, the mean postoperative prophylaxis duration in the short-duration arm was 48 h (range: 30–60). The same trends were observed for all other SSI categories, with a statistically significant benefit for longer versus $\leq$24 h postoperative prophylaxis for any sternal wound infection.

In a recent systematic review and meta-analysis, Mertz et al. [30] compared the relative effectiveness of short-term (<24 h) and long-term (24 h or more) antibiotic prophylaxis in cardiac surgery. In this review, longer term prophylaxis reduced the risk of sternal SSIs by 38% with a greater reduction in risk when analysis was restricted to four trials comparing the same drug regimens (a total of 12 trials were eligible). The study concluded that long-term antibiotic prophylaxis may be more effective than short-

term regimens in preventing sternal SSIs in patients undergoing cardiac surgery, but no definite conclusion could be drawn because of heterogeneity in antibiotic regimen and risk of bias in the published studies.

Local antibiotic prophylaxis with collagen–gentamicin has been evaluated since 2005 in several studies including four large RCTs, retrospective studies and in meta-analyses [31]. In brief, all RCTs but one [32] showed a reduction in SWI. The divergent result in this multicentre RCT has later been questioned for the technique of soaking the sponges in saline prior to implant. Recent meta-analyses support the technique concluding that implantable gentamicin–collagen sponges significantly reduce the risk of sternal wound infection after cardiac surgery [31].

In summary, antibiotic prophylaxis reduces the SSI rate to approximately 1/5 compared with placebo and is recommended for all cardiac surgery [27]. Antibiotics need to be present in the tissues before contamination occurs and the first dose should be given immediately preoperatively. There is no additional effect of extending the prophylaxis to more than 48 h and a duration of 24 h may be sufficient and is generally practiced in many centres.

Local application of vancomycin, in addition to intravenous (IV) prophylactic antibiotics and tight glycaemic control, has been shown to be very effective to substantially decrease the incidence of sternal wound infection after cardiac surgery [125] and may become recommended part of multifaceted prophylactic strategy to prevent sternal wound infections. There are however concerns regarding potentially high serum levels and the risk of selection of resistant strains to this important antibiotic.

Control of hyperglycaemia. The maintenance of physiologic blood glucose levels is an important strategy to decrease DSWI rate. Diabetes mellitus has been established as an independent risk factor for postoperative surgical wound infection, with infection rates two to five times more prevalent than in non-diabetic population [1, 11–13, 59, 64, 71–85, 126]

Diabetic patients undergoing cardiac surgical procedures, before use of IV insulin, were more likely to have worse short- and long-term survival and higher rates of DSWI [33, 71, 72, 93, 127–131]. Furthermore, post-sternotomy mediastinitis in diabetic patients after cardiac surgery increases operative mortality 2- to 3-fold [34].

Furnary et al. [127] found the average blood glucose level over the first two postoperative days to be the strongest predictor of any DSWI in diabetic patients who have undergone cardiac surgery.

There is therefore convincing evidence that the presence of perioperative hyperglycaemia adversely affects the DSWI rate and continuous insulin infusions should represent the standard of care for glycometabolic control in all patients undergoing cardiac surgery (Class I, Level of Evidence B).

Surgical technique. Adherence to basic surgical principles is intuitive. These include careful median sternotomy, control of bleeding, parsimonious use of diathermy, gentle and limited tissue handling and dissection. Meticulous haemostasis is particularly important, as postoperative bleeding represents a major risk for mediastinitis [62]. Moreover, paramedian sternotomy is strongly associated with postoperative chest instability [132] causing deep wound dehiscence favouring mediastinitis [35]. Sternal instability or dehiscence may be a consequence of an SSI but also by itself promotes bacterial growth. In cardiac surgery, a mechanically rigid fixation of the sternal halves reduces infection rate. Several new techniques with wires, plates or other devices have been published although more evidence from adequately powered, prospective, controlled studies is needed. The technique with lateral reinforcement (Robicsek), however, did not reduce the incidence of sternal wound complications in high risk patients in a large randomized controlled multicentre trial [36]. The risks of mediastinitis and sternal osteomyelitis from the liberal application of bone wax have been a source of concern. Recently, a prospectively randomized study on 400 patients undergoing isolated coronary bypass surgery has shown no detrimental effect of the use of bone wax on wound healing and infection rate [37].

Although the use of bilateral mammary artery (BIMA) may improve long-term survival in CABG patients, its use has long been considered a risk factor for DSWI when compared with the use of a single left internal mammary artery (LIMA) [133]. This is thought to be related to decreased vascularization of the sternum following BIMA harvesting [134]. The perceived risk of infection is considered the main reason for the low use of BIMA despite its survival benefit, probably one of the reasons why in the USA it is used in <5% of isolated CABG operations [135]. In a large meta-analysis by Dai et al. [136], the use of BIMA was shown to increase the relative risk of DSWI by 62% when compared with LIMA. This increased risk was most prominent in patients with diabetes and in the elderly. The risk for all levels of sternal wound infections (superficial and deep infections including mediastinitis) was similarly increased in the BIMA group. Importantly, however, the use of skeletonized BIMA was not associated with increased risk of DSWI [136–140].

Furthermore, the association of the use of BIMA and DSWI was recently challenged in a large study using US national outcome data from the Nationwide Inpatient Sample. In over 1.5 million CABG cases from 2002 to 2008, the use of BIMA was not an independent risk factor for DSWI except in patients with chronic complications of diabetes mellitus [135, 141].

Management principles

Antibiotics. Microbial identification and antibiotic susceptibility should be established as soon as possible after the diagnosis of sternal wound infection. Expeditious treatment with broad-spectrum antibiotics should be started [6]. The dosing of antimicrobial agents should be adjusted in obese patients to ensure adequate tissue levels [142]. Zeitlinger et al. showed that in patients undergoing surgical revascularization, IMA harvesting significantly diminishes antimicrobial penetration into the peristernal tissue suggesting the need for dosing adjustment following IMA harvesting [143].

Sternal SSI is therefore initially treated with IV antibiotics. As Coagulase-negative Staphyloccocus (CoNS) is often multiresistant and MRSA is common in some centres, first-line antibiotic treatment is commonly IV vancomycin, until results from antimicrobial susceptibility tests become available. Cloxacillin and other β-lactamase-resistant staphylococcal antibiotics are commonly used when infection with either *S. aureus* or CoNS has been established.

Surgical strategies. Many approaches have been described for the surgical treatment of post-sternotomy mediastinitis. These include: revision with open dressings, primary closure, closed

irrigation, negative pressure wound therapy (NPWT) and reconstruction with vascularized soft tissue flaps (e.g. omentum, pectoral muscle).

Surgical treatment is generally necessary for DSWI. Although the most appropriate surgical approach for the treatment of sternal SSI is still debated, there is a consensus that at least wound debridement is necessary. Two approaches are most common to close the wound: (i) primary intention, i.e. the wound is closed by drawing the wound edges together, or (ii) tertiary intention or delayed primary closure, i.e. the wound is debrided and left open for treatment and observation, and is then closed a few days later. A secondary intention approach, i.e. there is no direct closure and the wound granulates and heals, however, is rarely used for DSWI. When either primary intention or delayed primary closure is used, the sternal halves can often be rewired in a fashion similar to that in a primary operation—or more securely, if there is risk of fracture, using the Robicsek technique [144].

The earliest treatment for DSWI was revision of the wound, followed by either open wound dressings or closed irrigation. Open wound dressing changes involve frequent changes of paraffin gauzes and close observation of the wound. The first adjunct therapy to debridement and open wound dressing was the use of antibiotic irrigation of the wound, or closed irrigation [145].

Stability of the sternum before delayed primary closure is of great importance regardless of the treatment method. Cases of right ventricle perforation during conventional treatment have been described that are often believed to be related to rupture due to the sternal halves tearing the ventricular wall [146]. Furthermore, pulmonary function of patients with an open wound is impaired, often requiring them to remain intubated for prolonged periods of time. For delayed closure of the wound, a steel plate can be used for fixation of an unstable sternum after extensive debridement for DSWI [147].

Soft tissue flap transposition is often required to fill a sternal defect resulting from repeated treatment interventions, or to directly fill a sternal wound after debridement. Use of the omentum as a soft tissue flap was first described in 1976 [148]. After subtotal sternectomy, followed by transposition of highly vascularized greater omentum to the sternal defect, the wound is then closed by delayed primary intention. Instead of an omental flap, a muscle flap is more commonly used today, most often the pectoralis muscle. This was first described in 1980 by Jurkiewicz et al. [149] in patients who had not responded to either open wound dressing or closed irrigation. The pectoralis major, and in some cases the rectus abdominis muscle, is transposed to fill up the sternal defect with good results.

Recurrent sternal SSI is not uncommon and can be challenging to manage. This is seen more frequently following open wound dressing treatment, irrigation and other forms of older treatment methods compared with the newer treatment using negative-pressure [38, 150, 151].

A particularly difficult problem following sternal reconstruction using muscle flaps is chronic pain and/or sternal instability, which has been reported in over 40% of cases as well as commonly reported long-term muscle weakness [152]. Abdominal hernias following omental transfer can occur, and may require surgical intervention.

Negative-pressure wound therapy, introduced in the late 1990s, is a newer treatment modality that can stabilize the sternum and promote granulation of the wound. In 1999, Obdeijn et al. [39] were the first to describe successful use of NPWT in three patients with deep sternal SSI. Since then, numerous reports have been published providing stronger empirical evidence of the use of NPWT in the treatment of sternal SSI.

Negative-pressure wound therapy promotes healing in different types of wounds through removal of excess fluids and other debris by creating negative pressure, often referred to as vacuum, in a well-sealed wound. The proposed mechanisms by which NPWT aids wound healing are numerous; increased perfusion of the wound, facilitated granulation tissue formation, and removal of fluid. A recent review by Glass et al. suggests that promotion of wound healing occurs by modulation of cytokines to an anti-inflammatory profile, and mechanoreceptor- and chemoreceptor-mediated cell signalling, culminating in angiogenesis, extracellular matrix remodelling and deposition of granulation tissue [40].

When NPWT is used for DSWI, multiple layers of paraffin gauze are placed at the bottom of the sternal wound after debridement in order to prevent damage to the right ventricle of the heart. Following placement of the paraffin gauzes, polyurethane foam is cut to fit the wound and a sterile wound drape covers it; a tube for transmission of pressure is attached through a hole in the drape. The negative pressure applied to the wound has been shown to increase microvascular blood flow a few centimetres from the wound, whereas hypoperfusion has been seen close to the edge of the wound [153]. Recent studies have shown that gauze may be used, with similar results as for polyurethane foam [154].

The negative pressure in a sternal wound is most often applied at a continuous pressure of -125 mmHg. However, in a rat model, continuous pressures of -50, -75 or -125 mmHg were shown to be similarly effective at reducing the wound area [155]. Furthermore, in a porcine model the stability of the sternum was found to be similar at pressures of -75, -125 and -175 mmHg but diastasis of the foam was more pronounced at pressures less than -100 mmHg [156]. The finding that -75 mmHg leads to optimal contraction of the wound has been confirmed, but it was observed that if the wound fluid volume was high, an initial pressure of -125 mmHg could be regarded as optimal [157]. Instead of continuous pressure, cyclical (or intermittent) application of negative pressure may sometimes be more convenient and it may even have advantages for wound healing [154]. However, this has limited use in DSWI due to the lack of added stability to the wound.

The wound is usually reopened after 2–4 days after treatment with negative pressure. Based on both clinical observations and parameters of inflammation (such as neutrophil count and C-reactive protein), the clinician can determine whether the wound is sterile and the proliferative stage of wound healing has begun [158]. If the wound is not healed, new foam is placed with negative pressure. Patients with DSWI most often require a total of two to four dressing changes as part of the NPWT treatment. This includes the initial debridement where the foam is first placed, and wound closure [159]. After the wound is healed and all signs of infection are gone the sternum is rewired and the skin closed. In this way, a delayed primary closure can be achieved in most cases [160]. A few reports have described the use of NPWT for secondary intention as method of closure of the wound, but this has generally led to a worse outcome [41].

Complications related to NPWT when used for sternal SSIs are most often minor, and they most often involve pain at the edges of the wound, which usually subsides shortly after initiation of the negative pressure. In-growth of granulation tissue into the

foam can also cause light bleeding upon removal. Other, mostly preventable, minor wound complications include pressure sores caused by mislaid evacuation tubes and erosion of the wound edges caused by the foam being laid out over the wound edge onto healthy skin [161]. Major bleeding has been reported and is a potentially fatal complication of NPWT in the sternal wound; it can be seen when negative suction is introduced to the sponge or when the sponge dressings are changed. There is concern that rupture of the right ventricle is more likely when using NPWT than with other methods [146] due to displacement of the heart towards the thoracic wall and possible contact of the right ventricle with the edge of the sternum. Other causes of major bleeding during NPWT have also been reported such as infectious erosion of the ascending aorta and mobile sternal wires.

In a recent and comprehensive review, van Wingerden et al. [10] classified post-sternotomy mediastinitis into four groups, suggesting surgical approaches based on the available evidence (see Table 4).

The authors divided post-sternotomy mediastinitis according to sternum stability viability, and available bone stock. Types 1 and 2 are characterized by a reasonably stable sternum, whereas Types 3 and 4 by an unstable sternum. In Type 1 (relatively stable sternum and minimal bone loss) the use of NPWT is advised. Clear evidence for the use of NPWT therapy is provided by two systematic reviews and two meta-analyses (Class I, Level B) [7, 42, 66, 67, 162–167].

In Type 2 (relatively stable sternum with sufficient and viable bone stock), direct closure is proposed. This can be done with or without a bridge of conservative management with NPWT. The recent reports are in favour of delayed closure, as the use of NPWT allows better definition of the extent of the infection and better assessment of sternal viability. Furthermore, antibiotic therapy can be administered in the conservative phase of the treatment and surgical risks related to the debridement and closure can be mitigated by a delayed approach [168–170] (Class I, Level B).

In Types 3 and 4 there is sternal instability. The viability of the sternum differentiates these two entities. In Type 3 (viable sternum), sternal stabilization can be achieved with plates or clips [171–176]. Complete reconstruction can be achieved with or without the use of pectoral flaps or omentum (Class IIb, Level B).

For the above-mentioned reasons, delayed closure with bridge therapy with topical negative pressure (TNP) seems a sensible approach. Even when rewiring only is compared with rewiring and suction irrigation system, the outcome seems to be better with the latter; a recent study showed the superiority of TNP system when compared with closure and suction–irrigation drainage [177]. The use of pectoral muscle flaps or omentum following sternal stabilization could be recommended although in some cases removal of the plates due to infection is necessary [179].

In Type 4 the sternum is necrotic; therefore, debridement of necrotic tissue followed by flap reconstruction provides vascularized tissue cover, some sternal stability and obliteration of dead space (Class IIb Level B). Muscle flap (pectoralis and rectus abdominis) and omentum flap have been described and recommended for this type of reconstruction [179–183].

There is no consensus regarding the timing for surgical reconstruction. Concerns still remain about the necessity for obtaining negative cultures at the time of closure. Two recent studies found that the presence of positive tissue cultures does not influence the rate of readmissions with recurrent infection [43].

Outcomes of treatment

Historically, mortality due to deep sternal SSIs was 20–45% before more advanced surgical techniques were developed [184]. In contemporary reports, the mortality is reported to range between 1% and 14% [159, 185, 186]. Patients treated surgically for sternal SSIs most often require lengthy hospitalizations, with numerous procedures required for resolution of the infection. They do not have improved quality of life after surgery to the same degree as patients without sternal SSI.

Long-term outcome is negatively associated with DSWI. In a long-term study, the adjusted hazard ratio for all-cause mortality 10 years after the primary operation in patients with deep sternal SSIs who survived the first 6 months was almost doubled. Furthermore, early sternal SSI increases the risk of late chronic infections [184].

Already established advantages of NPWT are both improved sternal stabilization and earlier mobilization of patients. However, it has been debated whether NPWT is indeed superior to older techniques for the treatment of DSWI. A systematic review of NPWT for various acute or chronic wounds concluded that there was no evidence to support that NPWT was superior to conventional treatment, and the authors called for more RCTs [44]. Randomized trials comparing NPWT and conventional treatment are few and concerns about publication bias have been raised. Despite this lack of evidence, currently many institutions prefer NPWT for the treatment of sternal SSIs.

The overall cost of sternal SSI treatment is generally no higher when NPWT is used than when conventional treatment is used. Mokhtari et al. [186] showed that the total cost of treatment was

Table 4: AMSTERDAM classification (Assiduous Mediastinal Sternal Debridement & Aimed Management) [10] Reproduced with permission from Biomed Central

Type	Sternal stability	Bone viability and stock	Reconstruction	Staging of reconstruction
1	Stable	Reasonable	TNP	Class I, Level B
2a			Local muscle flap	Primary (Class II, Level B)
2b			Muscle or omentum flap	Delayed (Class I, Level B)
3a	Unstable	Viable & sufficient	Rewiring/osteosynthesis	Primary delayed (Class IIb, Level B)
3b			Rewiring/osteosynthesis and Muscle or omentum flap	
4a		Necrotic and insufficient	Muscle flap	Primary/delayed (Class IIb, Level B)
4b			Omental flap	
4c			Muscle and omental flap	

2.5 times higher for deep sternal SSI cases treated with NPWT than for non-SSI patients, which was similar to conventional treatment. Although the material cost is often greater using NPWT, it is less laborious, as the wound is only changed two or three times a week, resulting in similar or even reduced total cost [187].

Summary of recommendation for prevention and management of post-sternotomy mediastinitis

In the absence of documented negative testing for staphylococcal colonization, routine prophylactic topical mupirocin is recommended for 5 days

(Class I, Level of Evidence A)

A shower or bath using soap, either the day before or on the day of surgery should be considered

(Class IIa, Level of Evidence B)

A beta-lactam antibiotic as a single antibiotic of choice in patients without MRSA colonization is recommended

(Class I, Level of Evidence A)

For patients who are considered beta-lactam or penicillin allergic or with proven or suspected MRSA colonization, vancomycin is recommended as the primary prophylactic antibiotic with additional Gram-negative coverage

(Class I, Level of Evidence B)

It is recommended that administration of antibiotic prophylaxis should be completed within 1 h of the skin incision and start of surgery

(Class I, Level of Evidence A)

Use of continuous IV insulin to achieve and maintain an early postoperative glycometabolic control is indicated to reduce the incidence of DSWI

(Class I, Level of Evidence B)

Skeletonized IMA dissection is recommended in patients with diabetes or when bilateral IMAs are harvested

(Class I, Level of Evidence B)

Negative pressure wound therapy is recommended either as a destination or as a bridge prior to final surgical closure in cases of post-sternotomy mediastinitis

(Class I, Level of Evidence B)

The use of muscle or omental flap in case of sternal instability or insufficient bone stock may be considered

(Class IIb, Level of Evidence B)

OTHER TYPES OF MEDIASTINITIS

Descending necrotizing mediastinitis

Background. Descending necrotizing mediastinitis describes an infection with its origin from a head and neck source, most commonly an oropharyngeal or odontogenic focus, which then spreads in the fascial spaces of the head and neck and descends downward into the mediastinum. The most common origins of DNM infection include peritonsillar, dental or odontogenic abscesses. In general, the mortality rate is high, with reports ranging from 11% to 40% [45, 46] as mediastinal infection rapidly leads to sepsis and multiorgan failure if not treated early and appropriately.

The criteria for diagnosis of DNM established by Estrera et al. [46] include: (i) clinical manifestations of severe infection; (ii) demonstration of characteristic roentgenographic features; (iii) documentation of the necrotizing mediastinal infection at operation or post-mortem examination, or both; (iv) establishment of the relationship of oropharyngeal or cervical infection, with the development of the necrotizing mediastinal process.

The extent of infection directly affects the mortality rate, which is around 10% in localized (above the tracheal carina) and 30% in diffuse disease (extending below the tracheal carina) [45].

Descending necrotizing mediastinitis results from infections of polymicrobial origin (most commonly *Streptococcus* and *Bacteroides* species [188]), reflecting the process of oral bacteria entering through disruptions of mucosal and tissue barriers and spreading along the deep fascial planes, from the neck downward into the mediastinum. The different anatomical neck spaces from which infection spreads to the mediastinum are the pretracheal and the retropharyngeal space, respectively.

The pretracheal space ends inferiorly at the pericardium and parietal pleura at carinal height. In about 8% of DNM cases this space is a possible pathway for infections of the airways, i.e. epiglottitis/laryngitis and the thyroidea to the anterior and middle mediastinum. Odontogenic infections tend to spread posteriorly towards the vascular space and from there, in 12% of cases of DNM, further to the anterior mediastinum. The retropharyngeal space drains directly into the posterior mediastinum and is, with an estimated incidence of 70%, one of the main spreading routes especially for oropharyngeal infections in DNM [60]. However, as each of these potential spaces contains loose areolar tissue that lacks defence cells and is poorly vascularized, and therefore allows the unopposed spread of any cervical infection along and across them, any cervical infection can potentially involve the entire mediastinum. Downward spread is additionally facilitated by gravity, breathing and negative intrathoracic pressure [46, 47, 190].

Other potential causes of DNM, besides dental infections and common oropharyngeal infections such as tonsillitis and epiglottitis, include pharyngitis, primary neck infections (including posttraumatic), cervical lymphadenitis, suppurative thyroiditis, parotitis [191], traumatic endotracheal intubation (with DNM usually occurring in the early postoperative period) and jugular IV drug use/abuse [192].

Descending necrotizing mediastinitis appears to affect men as well as women with a mean age of around 50 years, but the disease can affect patients from an age of a few months up to the eighth decade [193].

History

Patients usually have experienced and present with symptoms and signs of an oropharyngeal/odontogenic infection and fever. Neck and chest pain together with dyspnoea are other potential findings. Further course of the disease can be rather dramatic, rapidly evolving into systemic sepsis.

Diagnosis

Besides oropharyngeal examination, liberal use of contrast-enhanced cervicothoracic CT-scan [184] is essential for the early detection of DNM.

Typical CT features of DNM are increased density of the adipose tissues (>25 Hounsfield units), cervical lymphadenopathy, mediastinal fluid collections and pleural and/or pericardial fluid collections (Fig. 2). Furthermore, myositis and vascular thrombosis can be seen [194].

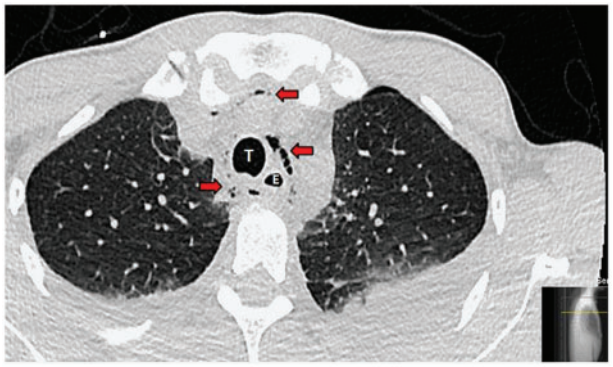

Figure 2: CT-scan showing mediastinal air (arrows) and bilateral pleural effusions as a sign of anterior and posterior descending mediastinitis in a 33-year-old male patient with peritonsillar abscess. E: oesophagus; T: trachea.

CT-scan can also be a helpful tool in identifying any clinically suspected progression or persistence of infection in the postoperative period [195–197].

Management principles. Administration of IV broad-spectrum antibiotics with coverage for aerobic and anaerobic bacteria as soon as possible is mandatory considering the high mortality rates of up to 85% in the preantibiotic era [189]. In case of severe sepsis and/or septic shock, early ICU admission for optimal management is strongly advisable. After treatment of the pharyngeal or dental focus and airway management, prompt and adequate drainage of the neck and the mediastinum should be performed [198, 199]. Airway compromise due to inflammatory oedema is a common finding in DNM that should be anticipated and treated with early tracheotomy, which can serve a dual role of opening fascial planes and securing the airway. The surgical strategy is usually determined according to the expected extent of disease: For localized infection of the upper mediastinum above the tracheal carina, cervicotomy and transcervical drainage may be sufficient, whereas further downward spread should be treated by additional subxiphoidal drainage (in localized disease and stable patients only) or even more aggressively by median sternotomy and proper debridement of necrotic tissue [198]. The posterior mediastinum can be accessed either by a clamshell approach, uni-/bilateral thoracotomy and/or uni-/bilateral video-assisted thoracoscopic surgery (VATS) in selected cases. As a general principle on which most authors agree [47–49, 190, 192, 200], optimal treatment should include radical surgical debridement of affected tissue, i.e. pericardial fat and thymic tissue, through an open thoracic approach. Corsten et al. [190] were the first to identify a statistically significant difference in survival in a meta-analysis, between patients undergoing only transcervical mediastinal drainage (53%) and those receiving transthoracic mediastinal debridement (81%). Ten years later, Misthos et al. [48] showed that early combined transthoracic mediastinal and cervical debridement and drainage was the only favourable factor for survival compared with cervical drainage and/or transcervical mediastinal drainage alone, in 27 patients with DNM extending into the lower anterior mediastinum.

Median sternotomy [48, 201, 202] is a fast and simple approach to the anterior mediastinum, whereas a clamshell approach [203] allows good exposure of the whole mediastinum, and both pleural cavities with the possibility of early bilateral decortications and debridement of the entire mediastinum. Nevertheless, a clamshell incision is associated with significant morbidity in these already compromised patients.

Sternotomy has the problem of limited access to the posterobasal mediastinum, especially on the left side, which can be overcome by single-lung ventilation (double lumen tube, bronchial blocker), as well as using short-term apnoea or ventilation with small tidal volumes if single-lung ventilation is not tolerated. Possible reported adverse events after median sternotomy or clamshell incision include phrenic nerve palsy, sternal dehiscence or even sternal osteomyelitis. Although in the series reported by Kocher et al. [202] none of the 16 patients treated by median sternotomy ($n = 8$) or clamshell ($n = 8$) suffered from any of these complications.

As posterolateral thoracotomy is described as a standard approach by some authors [49, 195, 204], others reported their experience with less-invasive approaches such as subxiphoidal drainage or VATS drainage [205–207] similarly to the management of oesophageal perforations.

However, as addressed before, systematic debridement and broad opening of involved fascial spaces are essential in preventing persistent or even progressive disease, and with that, the need for reoperation and the risk of severe complications [47–49, 190, 192, 197, 200, 208, 209]. Most studies that report less invasive approaches such as simple drainage [192] or VATS drainage [205], or unilateral thoracotomy [186] show reoperation rates between 20% and 30%. Also unilateral thoracotomy and continuous postoperative irrigation have been described, again with a reoperation rate of 10% and an early mortality rate of 20% [196].

Obviously, each of the abovementioned techniques offers potential advantages and disadvantages, and presumably, the surgical approach has to be carefully chosen according to the patients' condition, the extent of disease and the surgeons' experience in order to maintain a low rate of complications, reoperations and mortality.

Comorbidities, especially of immunosuppressive character, i.e. diabetes, alcoholism, malnutrition, corticosteroid therapy and prior chemotherapy, might not only predispose to development of DNM but also lead to more complicated courses of the disease [45, 188, 190, 192–194].

Summary of recommendations for prevention and management of descending necrotizing mediastinitis.

- Diagnosis is made by oropharyngeal examination and contrast-enhanced cervicothoracic CT-scan (Class I, Level of Evidence C).
- Immediate treatment with IV broad-spectrum antibiotics with coverage for aerobic and anaerobic bacteria (Class I, Level of Evidence C).
- Prompt surgical management is indicated including systematic debridement of affected tissue and broad opening of involved fascial spaces:
  1. Treatment of the pharyngeal or dental focus (Class I, Level of Evidence C);
  2. Airway management—tracheotomy maybe considered (Class IIb, Level of Evidence C);
  3. Uni- or bilateral cervicotomy should be performed depending on the origin and extent of infection (Class IIa, Level of Evidence C);

4. Mediastinal management may include one or several of the following steps (Class IIb, Level of Evidence C):
   - Transcervical drainage for confined disease of the upper mediastinum;
   - Median sternotomy for main involvement of the anterior mediastinum;
   - Uni-/bilateral thoracotomy or VATS in selected cases for involvement of the posterior mediastinum;
   - Contained abscess formations in stable patients maybe only drained (e.g. transcervical and/or subxiphoidal for retrosternal abscess, VATS or CT-guided for pleural abscess).

Mediastinitis after oesophageal perforation

Background. Depending on the aetiology and the course of disease, oesophageal perforations can be a diagnostic and therapeutic challenge. Mediastinitis can result from cervical as well as from thoracic oesophageal perforations and is associated with high mortality rates.

It has to be noted that this document mainly focuses on the diagnosis and treatment of oesophageal perforation and not on oesophageal anastomotic leakage after oesophageal surgery.

The majority of perforations occurs at areas of physiologic narrowing, for example at the cricopharyngeus muscle or at the oesophagogastric junction. Approximately half of all oesophageal perforations are iatrogenic and most of them occur during endoscopic procedures [50, 213]. The incidence of perforation from simple endoscopy is <0.5%, but with additional pneumatic dilatation for achalasia the incidence increases to rates of approximately 6% [214]. Especially interventions that involve the use of rigid oesophagoscopy seem to be associated with an increased risk of iatrogenic perforation [215]. A common location of perforation from endoscopy as well as from foreign body ingestion, which is the reason for perforation in approximately 12% of patients, is at the first narrowing at the cricopharyngeus muscle [216]. When oesophageal dilatation is performed, the location is often proximal to or at the stricture [50].

Spontaneous perforation (Boerhaave's syndrome) accounts for 15% of perforations, which are usually located at the left posterolateral aspect of the distal oesophagus. Other causes for oesophageal perforation include trauma in 9% (blunt or penetrating), intraoperative injury (2%) or malignancy (1%) [213].

Once a perforation occurs, saliva, retained gastric contents, bile and acid may enter the mediastinum and result in mediastinitis. As the midoesophagus lies adjacent to the right pleura and the distal oesophagus is next to the left pleura, perforations at these locations usually directly lead to collections in the respective pleural cavity.

History

A history of endoscopy in a patient with neck and/or chest pain in combination with fever is suggestive of an iatrogenic oesophageal perforation with possible mediastinal involvement. On the other hand, in patients with spontaneous perforation diagnosis may be more difficult because the clinical presentation is highly dependent upon the size and location of the injury and the time after occurrence of the injury. Although in the early phase after spontaneous perforation, symptoms are often unspecific (e.g. fever, chest pain, past or ongoing vomiting, tachycardia, tachypnoea and dyspnoea) symptoms/signs of sepsis develop in the later course of the disease.

Patients with spontaneous rupture (i.e. Boerhaave's syndrome) often have a history of alcoholism and/or gastric or duodenal ulcer.

Regardless of the aetiology, an oesophageal perforation is a surgical emergency, because leakage of oesophageal or gastric contents into the mediastinum usually rapidly leads to sepsis, multiorgan failure and death. Delay in diagnosis has a high impact on overall mortality, especially when the diagnostic delay is >24 h after perforation [51]. The rarity of the diagnosis and the variability in clinical presentation are the main reasons for diagnostic–therapeutic delays. This is especially true for spontaneous perforations where the clinical suspicion is low. In patients with oesophageal perforation, the cornerstones of treatment are rapid diagnosis, appropriate haemodynamic monitoring and support, antibiotic therapy, restoration of luminal integrity and control of extraluminal contamination.

Diagnosis

Cervicothoracicabdominal contrast-enhanced CT-scan with additional oral contrast (water-soluble) is the diagnostic tool of choice—showing not only the extent of the oesophageal injury but also the extent of infection, including any mediastinal involvement. Additional oesophagoscopy might be necessary to assess the exact extent of the perforation as well as to help with the decision-making for the optimal treatment. When performing oesophagoscopy in a patient with suspected oesophageal perforation, air insufflation should be strictly avoided because this may cause further dissection of the perforation.

Management principles. The patient is made nil by mouth and should undergo aggressive fluid resuscitation along with IV broad-spectrum antibiotics covering aerobic and anaerobic bacteria. Antifungal coverage is only advisable in selected cases (e.g. patients in an immunosuppressive state or patients who already were under broad-spectrum antibiotics prior to perforation). Furthermore treatment with a proton pump inhibitor should be initiated to control acid reflux [52, 217].

In general a specialist multidisciplinary approach, considering the patients' condition on one hand and the particular characteristics and dynamics of the oesophageal perforation on the other hand, is the key to an optimal treatment [215, 218–223].

Over time a clear treatment shift towards less invasive treatment options can be observed [52, 215, 217–223].

Surgical technique. Primary repair of the perforation site is warranted whenever possible, even if the diagnosis is delayed >24 h [220], but the likelihood for breakdown of the repair is considered to increase substantially with a diagnostic delay >72 h [224]. Exceptions from primary repair include cervical perforations that cannot be visualized/accessed (see 'drainage only'), diffuse mediastinal necrosis and/or large perforations without the possibility of reapproximation, oesophageal malignancy, end-stage benign oesophageal disease (e.g. achalasia), or if the patient is clinically unstable [225–227].

For primary repair, the affected mediastinal tissue is debrided, the pleural space(s) are cleaned and the lung decorticated if necessary. Then, devitalized tissue at the perforation site is debrided and the muscular layer is incised longitudinally along the muscle

fibres superior and inferior to the perforation to expose the entire extent of the mucosal injury. If possible, the mucosa is closed separately with absorbable interrupted sutures and the muscularis layer is closed with interrupted nonabsorbable sutures. Otherwise, the defect is simply closed with full-thickness interrupted nonabsorbable sutures. The repair site should be enhanced with the use of a vascularized pedicled flap (e.g. intercostal muscle, diaphragm, omentum or gastric fundus—depending on the location of the suture line), especially when there has been a delay in diagnosis and/or substantial extraluminal contamination was present [214].

As the anatomical structures of the neck typically confine extraluminal contamination to a limited space, cervical perforations are typically more easily treated than perforations of the thoracic or intra-abdominal oesophagus. The cervical oesophagus is best approached via a left cervical incision and can be managed by drainage and primary repair. If the cervical perforation cannot be visualized, simple drainage is often sufficient to allow healing of the perforation, in the absence of any distal obstruction [53].

Thoracic perforation—special considerations

The level of the perforation of the thoracic oesophagus and the site of pleural contamination determines the surgical approach to controlling the leak and repairing the perforation. A midoesophageal perforation is usually approached through a right thoracotomy, whereas a distal oesophageal perforation is approached through a left thoracotomy.

During thoracotomy an intercostal muscle flap as a potential buttress of a primary repair can already be prepared. Pulmonary decortication is performed if exudate and debris are present to facilitate adequate lung expansion. A nasogastric tube is guided past the site of repair and into the stomach, taking care to avoid damaging the repair site. A jejunostomy feeding tube can be inserted by a minilaparotomy procedure at the time of the oesophageal repair. This is particularly important if significant extraluminal contamination is present (in anticipation of a prolonged intensive care unit admission) or in patients who already suffer from malnutrition.

Postoperative management

Patients should be kept nil by mouth for an adequate period (i.e. at least 5 days). Jejunal tube feedings should be started 48–72 h postoperative in stable patients without evidence of an ileus. Broad-spectrum antibiotics are continued for 7–10 days depending on the patients' condition. A contrast oesophagogram should be obtained around postoperative day 7, if the patient is clinically stable. If there is no evidence of an oesophageal leak or postoperative ileus, the nasogastric tube can be removed and oral feedings initiated. Drains remain in place until patients are tolerating oral feedings without any clinical evidence of a leak.

Alternatives to primary surgical repair

Whenever nonoperative management is advocated, patients need to be under close surveillance in order to detect any signs of clinical deterioration (e.g. fever, tachycardia) indicating that the patient might require surgical intervention to control extraluminal contamination and to restore luminal integrity.

Nonoperative management. Nonoperative management in terms of medical treatment only is generally only possible in small iatrogenic or rarely in traumatic injuries, which are often diagnosed at the time of occurrence or shortly thereafter and are associated with only minimal extraluminal contamination. The cornerstone of nonoperative management is careful patient selection, wherewith an almost 100% survival rate can be achieved. Iatrogenic cervical perforations are most commonly suitable for nonoperative management due to the anatomical confinement of the oesophagus by the surrounding structures.

In patients with more extensive, but still contained leakage, a more aggressive management including endoscopic intervention with or without percutaneous or even surgical drainage might be necessary [53].

Endoscopic stent placement

Oesophageal endoscopic covered stents can be useful for the management of an oesophageal perforation in selected patients [53, 229]. However, precise stent placement can only restore luminal integrity and prevent further extraluminal soilage. Control and drainage of the extraluminal contamination are crucial for effective management of the oesophageal perforation. In a retrospective review of 191 patients by Freeman et al. the main independent risk factors for stent failure were location of the injury in the proximal cervical oesophagus or injuries traversing the gastro-oesophageal junction (no distal 'anchoring' because the distal end of the stent lies in the stomach) and length of injury longer than 6 cm [230]. The most common complication is stent migration (especially when used in close proximity to the gastro-oesophageal junction) and stent obstruction.

When comparing plastic and metallic stents, stent migration rates with the need for reintervention are significantly higher with plastic stents, whereas metallic stents (especially partially covered stents) show a significantly higher incidence of tissue ingrowth and postoperative strictures [53].

The basic principles of oesophageal stent implantation are as follows:

1. Endoscopy to localize the perforation and measure the length of the injury;
2. If a percutaneous endoscopic gastrostomy tube placement is considered, this should be performed prior to stenting (with minimal insufflation), in order to prevent accidental stent dislocation;
3. A covered stent, measuring at least 4 cm longer than the size of the injury (allowing a proximal and distal overlap of at least 2 cm), is placed under fluoroscopic and endoscopic control;
4. Debridement of the mediastinum and drainage of extraluminal contamination;
5. Postoperative contrast oesophagography to assess efficacy of stenting (correct placement and no/only minimal leakage).

Endoscopic vacuum-assisted closure system

Negative pressure wound therapy is a well-established treatment method for superficial wounds that in recent years also has become more and more popular for the treatment of oesophageal anastomotic leakage [231, 232]. The vacuum system is introduced endoscopically either into the paraoesophageal cavity or, in case of a small orifice, at the level of the oesophageal leakage and

connected to a portable pump. The negative pressure therapy continuously removes wound secretion as well as interstitial oedema and improves microcirculation, resulting in an accelerated formation of granulation tissue and thus closure of the infected internal wound. Experience with this novel method is growing fast and its application shows promising results also for the treatment of oesophageal perforation [54]. In case of larger oesophageal defects, endoscopic VAC (E-VAC) can furthermore be combined with oesophageal stenting if necessary [231].

Importantly, vacuum therapy in general has to be accompanied by proper cleansing and drainage of the extraluminal contamination.

Drainage only

Surgical drainage as the sole operative management is reserved for perforations of the cervical oesophagus when the perforation site cannot be completely visualized and when there is no distal obstruction. Furthermore drainage only can be an option for small, contained perforations of the thoracic oesophagus in stable patients. Drainage placement can either be performed CT-guided or during thoracoscopy/thoracotomy for lavage of the hemithorax.

Oesophagectomy. Primary repair is not advisable if there is perforated ulcerative cancer or a perforation proximal to untreated achalasia, an undilatable stricture or malignancy. In these cases oesophagectomy with primary reconstruction can be performed in highly selected and clinically stable patients with only minimal contamination, otherwise diversion is often more advisable [233].

Diversion. Diversion should be considered in unstable patients and/or if repair is not possible due to the size of the defect and the friability of the surrounding tissue. This is particularly true in the presence of a necrotic gastric tube after oesophagectomy. Diversion includes debridement and drainage of extraluminal contamination, left-sided externalization of the cervical oesophagus (i.e. cervical oesophagostomy), resection of the affected part of the oesophagus, gastrostomy tube and/or positioning of a jejunostomy feeding tube and finally the closure of the diaphragmatic hiatus.

If the patient is haemodynamically unstable and critically ill, adequate drainage and a diversion without an oesophageal resection can be performed until the patient is stabilized in order to allow definitive operative management.

Reconstruction of the oesophagus is typically performed after full recovery, around 6–12 months after the perforation. Restoration of alimentary tract continuity often requires a retrosternal colon interposition [234].

Outcome. The most common cause of death is sepsis leading to multiorgan failure. The main variables associated with mortality are location and aetiology of the perforation on one hand, and delay in diagnosis on the other hand. Concerning aetiology, mortality rates are described to be 15% for spontaneous perforation (where diagnosis is frequently delayed), 13% for iatrogenic and 2% if secondary to foreign bodies. When differentiating between the location sites of the perforation, mortality rates are reported as follows: 6% in cervical (tissue planes limit spread of contamination) and 11% in thoracic perforations [55].

Concerning diagnostic delay a recent meta-analysis of 75 studies showed that overall mortality rates for diagnosis within 24 h is significantly lower compared with a >24 h delay (7.4% vs 20.3%) [55].

Summary of recommendations for diagnosis and treatment of oesophageal perforation.

- 'Cervicothoracoabdominal CT-scan' with IV and oral contrast is the diagnostic tool of choice and is preferentially performed prior to 'oesophagoscopy' (without air insufflation) (Class I, Level of Evidence C).
- 'Rapid diagnosis and treatment with a multidisciplinary approach' should be initiated in order to avoid high complication and mortality rates (Class IIa, Level of Evidence C).
- 'The two main principles of treatment' include control of oesophageal leakage and drainage/debridement of extraluminal contamination:
  - 'Primary repair' of the oesophageal perforation is recommended whenever possible within the first 72 h after perforation (Class I, Level of Evidence C).
  - 'Nonoperative, medical treatment' should be reserved for clinically stable patients with only small contained perforations (no drainage into pleura or peritoneum) and without evidence of systemic inflammation (Class IIa, Level of Evidence C).
  - 'Drainage alone' should be used for perforations of the cervical oesophagus which cannot be visualized, but only in the absence of any distal obstruction (Class IIb, Level of Evidence C).
  - 'Oesophageal stenting in combination with pleural/mediastinal drainage' maybe be considered in haemodynamically stable cases with a contained leakage from the oesophagus in the early course after perforation (<24 h).
    - Stable patients with early uncontained leakage may profit from stenting in combination with thoracoscopy for pleural lavage and drain placement
    - Stenting may replace or bridge to definitive surgery in patients with extensive comorbidities and the inability to tolerate more extensive surgery (Class IIb, Level of Evidence C).
  - Endoscopic vacuum-assisted closure system

E-VAC might be helpful in selected patients not only for small but also for larger perforations in the absence of malignancy, if extraluminal contamination is controlled (either drained, surgically controlled or contained leakage) (Class IIb, Level of Evidence C).

- 'Oesophagectomy' may be proposed in the presence of oesophageal malignancy or in case of irrepairable extensive oesophageal damage (Class IIb, Level of Evidence C).
- 'Diversion' may be an option when all of the above-mentioned treatment possibilities have been exhausted; especially when patients present with clinical instability and cannot tolerate an extensive operative procedure, or in cases of extensive oesophageal damage not amenable to primary repair (Class IIb, Level of Evidence C).

Chronic fibrosing mediastinitis

Introduction. Chronic fibrosing mediastinitis or 'sclerosing mediastinitis' is a more indolent form of mediastinitis and usually occurs as a complication of granulomatous infections, most commonly due to *Histoplasma capsulatum* or even more rarely *Mycobacterium tuberculosis* [235]. *Histoplasma capsulatum* is a dimorphic fungus that is commonly found in soil that contains large amounts of bird or bat droppings. It is not only prevalent in the USA (especially in the Ohio and Mississippi River valleys) but also in parts of Central and South America, Africa, Asia and Australia. In Europe the disease is exceptionally rare. An infection with *H. capsulatum* is sub-clinical in the vast majority of patients and begins as an asymptomatic pulmonary infection, which then disseminates to the mediastinal lymph nodes. The involved mediastinal lymph nodes can enlarge and coalesce into an inflamed caseous mass (i.e. mediastinal granuloma) or can lead to a sclerosing process (i.e. fibrosing mediastinitis). Although mediastinal granuloma is discovered either incidentally or because it compresses mediastinal structures such as the SVC, airways or the oesophagus, fibrosing mediastinitis mainly leads to a progressive obstruction of the airways and great vessels (especially the SVC).

Fibrosing mediastinitis is believed to result from leakage of fungal antigens from lymph nodes into the mediastinal space, leading to an immunogenic reaction followed by an exuberant fibrotic response [235]. It is a slowly progressive disease with a variable natural history. The mean interval between the development of symptoms and death is reported to be <6 years in most reported series, and death most frequently results from cor pulmonale or relentless respiratory compromise due to recurrent infection, bronchial obstruction or haemoptysis [56, 236]. Nevertheless it has to be noted, that the outcome reported in the literature may be worse than in reality, because it is most likely associated with the preferential reporting of more severe cases in the medical literature.

History. The signs and symptoms of fibrosing mediastinitis depend upon which structures of the mediastinum are involved and the degree to which those structures are compromised. Typical complications result from compromise of the airways, heart and great vessels, or oesophagus. Airway compression can lead to postobstructive pneumonia or atelectasis, most commonly occurring in the right upper lobe [237]. Heart and great vessel involvement can cause pulmonary artery and/or pulmonary vein obstruction, constrictive pericarditis, or SVC syndrome. SVC obstruction due to fibrosing mediastinitis typically develops slowly over a period of years, allowing the formation of an extensive collateral circulation that may be adequate to prevent both stasis and elevated pressure in the tributaries of the SVC [56, 238]. SVC obstruction is less common than tracheobronchial narrowing [56, 239]. Oesophageal compression can lead to dysphagia and/or odynophagia. Haemoptysis may also occur in fibrosing mediastinitis as a consequence of fibrous tissue invasion of a bronchus, postobstructive necrotizing pneumonia or obstruction of pulmonary venous return.

Diagnosis. Chest CT-scan may show an infiltrative process in the mediastinum and can exclude malignancy. Typical findings are calcifications within a mediastinal process in combination with calcified lymph nodes and splenic calcifications [56, 240, 241]. Other findings are vascular occlusion with collateral blood flow around obstructed vessels, thickened interlobular septa and tracheobronchial narrowing [239, 241]. Biopsies may be hazardous in the presence of dense fibrosis and calcification with a high risk of bleeding from enlarged collateral vessels. Serologic studies are of limited benefit because they frequently fail to establish the diagnosis.

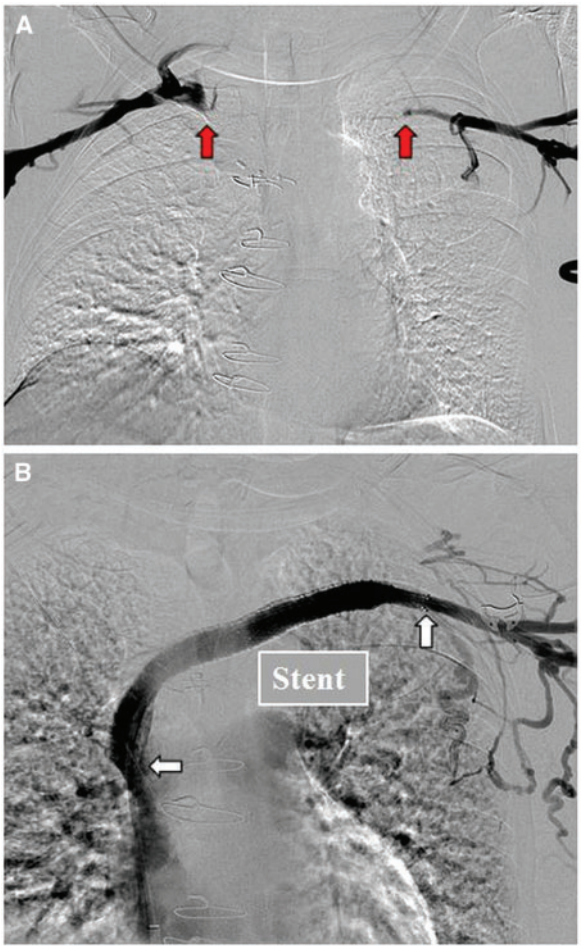

Figure 3: (**A**) Phlebography showing complete obliteration of the SVC with complete bilateral subclavian vein occlusion (arrows) in a 60-year-old female patient suffering from chronic fibrosing mediastinitis. (**B**) After percutaneous transluminal stent implantation into the brachiocephalic vein with unobstructed flow from the left subclavian vein into the SVC (arrows mark the ends of the stent). SVC: superior vena cava.

Management. There is no curative therapy for fibrosing mediastinitis and antifungal agents are generally ineffective, although several case reports have suggested a potential benefit [56, 239, 240, 242]. Glucocorticoids also do not appear to be generally beneficial, although controlled trials have not been performed [56, 243]. A possible exception is autoimmune fibrosing mediastinitis, which often presents in a rather diffuse than localized pattern, and has been shown to respond more favourably to glucocorticoid therapy, although these cases are difficult to identify [236].

Surgery can be performed in highly selected cases to relieve airway, vascular and/or oesophageal obstruction, as well as managing tracheo-oesophageal fistula [238, 243]. However, extensive fibrosis, calcification and collateral vascularization may limit the benefits of surgery and are associated with substantial morbidity and mortality [56, 238, 243].

Airway and vascular stents have been used to treat airway obstruction and SVC obstruction, respectively [244–247], but it seems that there is a frequent need for reintervention in these patients (Fig. 3).

The same is true for oesophageal dilatation, which usually has to be performed repeatedly. In case of an already fully occluded SVC, bypass surgery to the SVC has been successfully performed for symptomatic patients with SVC obstruction [57].

Summary of recommendations for chronic fibrosing mediastinitis.

- Diagnosis is made by 'Chest CT', which may show an infiltrative process in the mediastinum with calcifications and calcified mediastinal lymph nodes
- (Class IIa, Level of Evidence C).
- Biopsy specimens may show signs of Histoplasmosis infection or only mature collagen formations. Biopsy may be omitted if the patient has a typical clinical and radiological presentation, because of a significant risk of bleeding (Class IIb, Level of Evidence C).
- Antifungal drugs and glucocorticoids are ineffective (Class III, Level of Evidence C).
- Surgery may be considered to palliate symptoms by relieving obstruction of the airways, great vessels or oesophagus (Class IIb, Level of Evidence C).
- Stent placement either endoscopically (oesophagus, airway) or percutaneously (vascular) may be an alternative to surgery for highly selected patients (Class IIb, Level of Evidence C).

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