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EDITORIAL

Deep sternal wound infection after cardiac surgery: Evidences and controversies

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Abstract

Despite many advances in prevention and perioperative

care, deep sternal wound infection (DSWI) remains a pressing concern in cardiac surgery, with a still relevant incidence and with a considerable impact on in-hospital mortality and also on mid- and long-term survival. The permanent high impact of this complication is partially related to the increasing proportion of patients at high-risk for infection, as well as to the many patient and surgical risk factors involved in the pathogenesis of DSWI. The prophylactic antibiotic therapy is one of the most important tools in the prevention of DSWI. However, the choice of antibiotic, the dose, the duration, the adequate levels in serum and tissue, and the timing of antimicrobial prophylaxis are still controversial. The treatment of DSWI ranges from surgical revision with primary closure to surgical revision with open dressings or closed irrigation, from reconstruction with soft tissue flaps to negative pressure wound therapy (NPWT). However, to date, there have been no accepted recommendations regarding the best management of DSWI. Emerging evidence in the literature has validated the efficacy and safety of NPWT either as a single-line therapy, or as a "bridge" prior to final surgical closure. In conclusion, the careful control of patient and surgical risk factors - when possible, the proper antimicrobial prophylaxis, and the choice of validated techniques of treatment could contribute to keep DSWIs at a minimal rate.

Key words: Risk factors; Sternotomy; Wound healing; Wound infection; Postoperative care

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Core tip: Intensivists and cardiothoracic surgeons are commonly worried about surgical site infections due to increasing length of stay, costs, and mortality. In particular, deep sternal wound infection (DSWI) is a worrying complication after cardiac surgery, with a still relevant incidence. Unfortunately, DSWI appearance is related to a wide number of both patient and surgical factors. This review may be useful for guiding

physicians to the knowledge of main risk factors and the choice of the appropriate management of DSWIs with the aim of reducing the rate of this potentially devastating complication in cardiac surgery patients.

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INTRODUCTION

Deep sternal wound infection (DSWI) is one of the most complex and potentially devastating complications following median sternotomy in cardiac surgery with a significant impact on both patient prognosis and hospital budgets^[1-5]. Despite many advances in prevention, it still remains significant and ranges between 0.5% and 6.8%^[6-10], with in-hospital mortality rates between 7% and 35%^[2,3,7,9,11-13]. Moreover, mid- and long-term survival is significantly reduced in patients that have experienced DSWI. By the end of the first year, Filsoufi *et al*^[6] found a 15% absolute survival difference between patients without DSWI and those who had developed this complication. In a 10-year follow-up study after coronary artery bypass grafting, the adjusted survival rate was 39% for patients who developed DSWI compared with 70% in patients who did not^[14]. Excess costs arise primarily owing to additional antibiotic treatments and surgical procedures, as well as increased hospital length of stay^[13,15].

The management of DSWI has progressed through long-lasting clinical experience. Commonly adopted strategies of treatment include surgical revision with primary closure, surgical revision with open dressings or closed irrigation, reconstruction with soft tissue flaps, and application of negative pressure wound therapy (NPWT)^[16-18]. However, at the moment, there has been no general consensus regarding the appropriate management of DSWI.

DEFINITION

According to Centers for Disease Control and Prevention (CDC) guidelines, the definition of a DSWI requires positive culture results of surgical sites or drainage from the mediastinal area or evidence of infection during surgical re-exploration or fever, sternal instability, and positive blood culture results^[19].

RISK FACTORS

Patient and surgical factors contribute to the risk of DSWI after cardiothoracic surgery. Patient factors include age^[20-22], female sex^[20,22,23], obesity^[2,4,20,21,24-28], diabetes

mellitus or hyperglycemia during the perioperative period^[2,20,21,24,26-29], smoking tobacco^[2,4,28-30], recent treatment with antibiotics^[31], *Staphylococcus aureus* nasal carriage^[32,33], skin infection anywhere on the body^[31], chronic obstructive pulmonary disease^[25,27], heart failure^[2,34], kidney dysfunction^[27,34], peripheral vascular disease^[2,26], and emergent or urgent surgery^[28,35].

The reason for the increased risk of DSWI in obese patients can be related to the poor perfusion of subcutaneous adipose layers with low levels of prophylactic antibiotics in this tissue. Gummert *et al*^[24] found a 1.5-times increased adjusted risk of DSWI after cardiac surgery in patients with body mass index > 30 kg/m². Filsoufi *et al*^[6] reported that obesity was associated with a more than 2-fold increased risk of DSWI.

Convincing evidence has emerged that the control of blood glucose levels during surgery and the immediate postoperative period with frequent monitoring and protocols for continuous intravenous administration insulin can decrease DSWI rate^[36,37]. Researchers at the Mayo Clinic concluded that a 20 mg/dL (1.11 mmol/L) increase in the mean intraoperative blood glucose level correlated with an increase of more than 30% in adverse outcomes^[38]. A large prospective study of diabetic patients undergoing cardiac surgery demonstrated that hyperglycemia was an independent risk factor for death, length of hospital stay, and infection rates, and found that a continuous insulin infusion reduced these risks^[39].

Smoking tobacco can impair the tissue microcirculation and increase the risk of DSWI. Møller *et al*^[40] showed that preoperative cessation of smoking 6-8 wk prior to operation significantly reduced the infection rate in a prospective randomized trial in orthopedic prosthesis surgery. Actually, the CDC guidelines recommend smoking cessation at least 30 d prior to surgery^[19].

The patient's carriage of *Staphylococcus aureus* on skin and nares has been identified as an important risk factor for DSWI^[32,33]. The Society of Thoracic Surgeons practice guidelines upon antimicrobial prophylaxis recommend routine 5-d mupirocin 2% nasal administration for all patients undergoing cardiac surgery in the absence of a documented negative testing for staphylococcal colonization^[41]. However, concerns still remain about the extensive use of mupirocin because of lack of efficacy, risk of widespread high-level resistance, and costs^[42-44]. A systematic review of the literature and meta-analysis by Kallen *et al*^[45] demonstrated a 45% reduction in surgical site infections (SSIs) caused by *Staphylococcus aureus* with the use of preoperative mupirocin among cardiac surgery patients known to be colonized with *Staphylococcus aureus*. Of note, the only prospective, randomized, and double-blinded trial of mupirocin in cardiac surgery patients did not show benefit: No patients with poststernotomy mediastinitis caused by methicillin-resistant *Staphylococcus aureus* (MRSA) had identical isolates in preoperative and surgical-site cultures^[46].

Surgical risk factors include prolonged duration of aortic cross clamp, cardiopulmonary bypass perfusion or overall surgery^[22,26], use of internal mammary artery (IMA) grafts-especially bilaterally^[2,24,25,27,30], inadvertent paramedian sternotomy^[47], use of bone wax, extensive use of electrocauterization^[27], surgical procedures requiring prosthesis implant, use of intra-aortic balloon pump or ventricular assist device^[23,27], postoperative bleeding^[10], blood transfusions, re-exploration for bleeding^[6,23,24,48,49], re-operation, postoperative respiratory failure with prolonged mechanical ventilation^[2,6], and prolonged stay in intensive care unit (ICU)^[4,24,26].

Controversial opinions still remain on the IMA harvest technique. The skeletonization harvest technique is already known to severely reduce the incidence of DSWI - particularly in diabetic and obese patients - because of the better preservation of collateral sternal blood flow and internal thoracic veins^[50]. However, many cardiothoracic surgeons are reluctant to application this technique as it can easily lead to graft conduit damage^[51]. Evidences also suggest the need for dosing adjustment following IMA harvesting as this significantly diminishes antibiotic penetration into the presternal tissue^[52].

Level of concern has varied regarding to the risk of DSWI due to use of bone wax. Animal studies showed an increased risk of *Staphylococcus aureus* infections^[53]; however, a prospective, randomized trial of 400 patients found no detrimental effects^[54].

Finally, adherence to basic principles of care contributes to reduce the risk of DSWI. These mainly include reduced preoperative hospital stay, increased perioperative oxygenation, preoperative showering using antiseptic solution, hair removal over the operating site using scissors or a depilatory cream instead of shaving, and scrubbing of the operation site with a proper antiseptic solution and letting it dry^[6,19,31,55]. Chlorhexidine-, alcohol- or povidone-iodine-based solutions can be used; indeed, the CDC guidelines do not recommend one antiseptic solution over the others^[19].

PATHOGENS

Recent reports focused on a growing number of DSWIs caused by methicillin-resistant Gram-positive pathogens^[56]. *Staphylococcus epidermidis* is one of the most common agents in poststernotomy mediastinitis when foreign materials such as prosthetic heart valve are implanted; moreover, approximately 75% of the *Staphylococcus epidermidis* strains are methicillin-resistant^[57]. The other major pathogen in poststernotomy mediastinitis is *Staphylococcus aureus*. The latter microorganism has been increasingly associated with colonization of the patients' nares. National Nosocomial Infections Surveillance System reports that the rate of MRSA has risen from 30% in 1989 to 60% in 2005 in ICU patients with nosocomial infections and MRSA was the causative microorganism in a third of the patients with DSWI^[58].

ANTIMICROBIAL PROPHYLAXIS

The advantages of proper antimicrobial prophylaxis in patients undergoing cardiac surgery have been clearly demonstrated^[19,59,60]. However, the choice of antibiotic, the dose, the duration, the adequate levels in serum and tissue, and the timing of antimicrobial prophylaxis are still controversial^[11,41,61].

The Society of Thoracic Surgeons Practice Guidelines on antimicrobial prophylaxis in cardiac surgery recommended that a cephalosporin should be given within 60 min from the skin incision and be continued for 24-72 h^[41,61]. First generation (cefazolin), second generation (cefamandole and cefuroxime), and third generation (cefotaxime) cephalosporins have been shown to be effective in reducing SSIs in cardiac surgery; however, the superiority of one class over another has not been proven^[62-64].

The frequent identification of MRSA as the cause of DSWI has brought the attention on vancomycin as the prophylactic drug of choice^[10]. Engelman *et al*^[41] stated that vancomycin is reserved mainly for patients with a history of type I allergic reaction to β -lactam agents or in the setting of the institutional presence of a "high incidence" of MRSA (class II B recommendation, level of evidence C). Vancomycin should be given with any of the following doses: 1000 mg, 1500 mg, or 15 mg/kg over 1 h, with completion within 1 h of the skin incision^[41]. The reason for the 1-h infusion is related to the risk of histamine-release phenomenon characterized by extensive erythematous rash that involves the upper chest and face ("red man syndrome") that can be triggered by a rapid infusion of vancomycin^[41,61]. Moreover, studies in the literature showed that the incidence of infection is decreased when the preoperative dose is administered within 1 h before surgical incision^[11,65]. Regarding the duration, postoperative prophylactic antibiotics are given for 48 h or less (class II A recommendation, level of evidence B)^[61].

A meta-analysis comparing cephalosporins with glycopeptides as antimicrobial prophylaxis regimens found a higher frequency of postoperative SSIs and a trend toward an increased risk of Gram-positive SSI in the glycopeptide group but a lower frequency of SSIs caused by resistant gram-positive pathogens^[66].

The relationship between timing of prophylactic antimicrobial administration and risk of infection is an additional field of debate. The 2011 American College of Cardiology/American Heart Association guidelines for cardiac surgery recommend that "Antibiotic prophylaxis should be initiated 30 to 60 min before surgery"^[9]. Key studies have demonstrated that antimicrobial prophylaxis administered too late or too early reduces the efficacy of the antimicrobial prophylaxis and increases the risk of infection^[10,11,65,67]; conversely, other reports do not clearly demonstrated the superiority of the 1-h window^[68-70].

Ideally, short courses of antimicrobial prophylaxis are preferred over longer courses to reduce costs, drug

toxicity, infection with *Clostridium difficile*, and the appearance of resistant pathogens^[11,19,61,65,71]. However, the use of cardiopulmonary bypass, the hypothermia, the length of operation, the high mortality and costs of DSWI suggest to prolonging the antimicrobial prophylaxis in cardiac surgery. A 2011 systematic review and meta-analysis of the literature significantly favored longer-term antimicrobial prophylaxis of more than 24 h in these patients^[72]. Similarly, Lador *et al.*^[73] showed that shorter duration of prophylaxis (≤ 24 h) was associated with a higher rate of DSWI, surgical intervention for any kind of SSI, and endocarditis; whereas, no difference between 48 h vs longer durations was found for all outcomes.

There is absolutely no data for continuing antimicrobial prophylaxis until chest drains are removed^[61]. Some studies highlighted the importance of weight-based antibiotic dosing in obese patients and the need for repeated doses during prolonged procedures (more than two half-lives of the drug) or in case of excessive blood loss during the procedure^[11,74]. Other investigators reported that a cefazolin bolus followed by continuous infusion improved pharmacokinetic and pharmacodynamic values, including concentrations in the cardiac muscle^[75].

MANAGEMENT

Debridement with primary closure has been the treatment of choice for a long time and, until now, it can be considered for infection localized to a small part of the sternum with little or no purulent drainage. Debridement is usually associated with the advancement of the pectoralis muscles and can be done in a single phase procedure or in a delayed closure with multiple open dressing changes followed by sternal re-wiring^[17,76-78]. The latter treatment allows improved accuracy in assessing the extent of the sternal infection and reduces the risk of recurrent infection but carries on major disadvantages: Thoracic instability, prolonged immobilization, and mechanical ventilation with increased risk of complications such as thrombosis, muscular weakness, and pneumonia^[17,76-79]. Concerns still remain about the need for obtaining negative cultures at the time of closure. Two recent studies found that the presence of positive tissue cultures did not affect the rate of recurrent infections^[80,81].

An important step forward in the treatment of DSWI occurred with the introduction of continuous irrigation using closed chest catheter following revision. Further developments were achieved with antibiotic irrigation but several studies have reported high rates of failure and mortality^[82-84].

The unsatisfactory results of these different approaches increased interest in plastic procedures as alternative treatments^[6,79,84]. Bilateral pectoralis muscle flaps, as either advancement or turnover flaps, are the most usual plastic procedures in the dealing of DSWI^[16,85]. This surgical management has a quite low mortality rate but carries a series of disadvantages, including

additional surgical trauma and late flap-related morbidity such as muscular weakness, pain, and hernias^[86]. An alternative plastic procedure to pectoralis muscle flaps is the use of omentum that promotes significant angiogenesis, immunologic function, and antimicrobial activity supporting tissue-generation promotion with great capacity to occupy dead space^[6,87,88]. Usually, the use of omentum is considered in the case of complex wounds or when the defect is extremely wide with significant sternal loss. Specifically, a definite preference has been expressed for the use of omentum when the primary causative pathogen is particularly resistant, such as MRSA^[80,89] and *Candida*^[90] or when the patients suffering from diabetes mellitus^[91].

However, complications occurred in up to 18% of patients treated with this approach^[16,92].

Several recent studies, meta-analyses, and systematic reviews have validated the efficacy of NPWT in DSWI either as a single-line therapy, or as a "bridge" prior to final surgical closure^[93-97]. This wound-healing technique is based on the application of continuous or intermittent negative pressure to a wound, which results in arteriolar dilatation and, subsequently, determines wound perfusion and granulation tissue proliferation^[57,85,93]. *In vitro* and clinical studies designed to determine the effect of NPWT lent convincing evidence of efficacy and safety in term of decrease of edema, exudation, and microbial colonization as well as reduction of inflammatory cytokine release^[57,85,98-100].

In case of diagnosis of DSWI, an early application of NPWT was associated to a faster healing and an increased likelihood of survival^[18,97,101,102]. Moreover, several studies demonstrated shorter treatment duration and length of hospital stay, as well as lower costs in patients treated with NPWT^[96,98,100,103]. NPWT was also successfully applied in the case of MRSA mediastinitis and as a temporizing treatment prior to secondary closure in mediastinitis due to *Candida*^[90,104,105].

Conversely, other authors suggested that prolonged application of NPWT can result in chronic infection due to a shift in bacterial species and to an increased growth of some of them, such as *Staphylococcus aureus*^[99,106]. Different studies have focused on factors that can predict failure of NPWT. Gdalevitch *et al.*^[107] found that positive blood cultures, wound depth of ≥ 4 cm, and high degree of bony exposure and sternal instability are significant predictors of NPWT failure. Pericleous *et al.*^[108] highlighted also the importance of lung emphysema, corticosteroids, and advanced age. Finally, Gustafsson *et al.*^[109] stressed bacteremia or elevated plasma C-reactive protein levels as the most sensitive predictors of failure.

The positive effects of NPWT on complicated surgical wounds have triggered the interest in using NPWT also after closure of clean and sutured wounds to prevent SSIs in patients at high risk of developing DSWI^[110]. The surgical incision management system (Prevena™ Incision Management System, Kinetic Concepts Inc., San Antonio, TX, United States) consists of a single-use NPWT that delivers negative pressure of 75-125 mmHg (10-16.7

KPa); this system holds the incision edges together, reduces lateral tension and edema, stimulates perfusion, and protects the surgical site from external infectious sources^[110]. Grauhan *et al*^[111] showed significant reduction of SSIs in obese patients (body mass index > 30 kg/m²) with median sternotomy compared with patients treated with standard wound dressings. In general, retrospective studies and randomized controlled trials provided a substantial body of evidence that the use of this prophylactic wound dressing technique may reduce the incidence of wound infections^[112-114].

CONCLUSION

Despite several progresses in prevention and perioperative care, DSWI is still a permanent concern in cardiac surgery because of its significant rate and relevant impact on length of hospital stay, costs, and mortality. The incidence of this complication is in part due to the increased number of patients at high-risk for infection because of advanced age and rate of relevant comorbidities in the population undergoing cardiac surgery. A rigorous attention to the details of preoperative, intraoperative, and postoperative management could contribute to keep DSWIs at a minimal rate.

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