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Infectious Complications of Cardiac Surgery: A Clinical Review

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INFECTIOUS COMPLICATIONS after cardiac surgery occur in 5% to 21% of cases.[1,2] Major infectious complications increase postoperative mortality by more than 5 times and prolong recovery.[2,3] Forty-seven percent of these patients require more than 14 days in the hospital compared with 5.9% ($p < 0.0001$) of patients without a major infection.[3] As a result, infectious complications substantially increase the cost of care.[4] However, infectious complications can be reduced with many simple interventions, starting with risk factor modification at the first anesthetic preoperative screening visit right through to postoperative risk factor vigilance in the intensive care unit (ICU).

The most common sites of infection are the respiratory tract (45.7%-57.8%), the surgical site (27.7%), and catheters or devices (20.5%-25.2%).[2] This review describes the incidence, impact, treatment, and prevention of infections occurring perioperatively or within the first 12 months of surgery, focusing on interventions in which the anesthesiologist and intensivist play a key role, as well as those infections in which optimum management has been controversial.

LITERATURE REVIEW METHODS

Relevant published literature was identified using PubMed and MEDLINE searches. Queries were performed by combining the search terms "infection" and "infectious" complications with the specific topics of interest. Imposed search limitations included English language and years 1990 to the current date. Additional articles were identified from reference lists in the studies that were reviewed and from appropriate society guidelines and corresponding web sites.

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SURGICAL SITE INFECTIONS

Surgical site infections (SSIs) after cardiac surgery can present with a wide range of severity. Superficial sternal wound infections (SSWIs) complicate 0.5% to 8% of cardiac surgery cases and involve the skin, subcutaneous tissue, and pectoralis fascia.[5,6] Deep sternal wound infections (DSWIs) involve the sternal bone, the substernal space, and the mediastinum[7] but are less common than SSWIs, with an incidence ranging between 0.4% and 2%.[3,7-10] However, they are the most important and potentially lethal SSI, doubling mortality when present,[11] and the actual incidence may be 50% to 80% higher when postdischarge surveillance is undertaken.[5]

DSWIs usually present with systemic signs of infection or local signs, such as chest pain and wound discharge.[7] Computed tomography scanning is very sensitive in the diagnosis of DSWIs but lacks specificity within 21 days of surgery (39% *v* 85% after 21 days).[12] This poor specificity may be overcome using single-photon emission computed tomography scanning with technetium-99m hexamethylpropyleneamine oxime, which also discriminates between a superficial and deep infection.[13] However, single-photon emission computed tomography scanning is not used routinely in clinical practice. Blood cultures also may be useful. The isolation of *Staphylococcus aureus* from blood is associated with DSWIs in more than three quarters of patients.[14] This organism is the most common cause of DSWIs, which, combined with other gram-positive organisms, account for approximately 80%.[15]

The ideal management of DSWIs is controversial[16] for 2 main reasons: Not all surgeons report equivalent success with a given technique and a DSWI is a heterogenous condition requiring individualized management. Three factors affect the surgical approach: The time of the presentation, the number of risk factors, and whether previous techniques have been tried and failed.[7] The traditional approach is wound debridement, primary closure, and continuous irrigation for several days. Although some centers report poor outcomes with this approach, others continue to use it with or without minor modifications and report excellent results (ie, a 95%-98% cure rate).[17,18] After debridement, many centers refer for reconstructive procedures. These include pectoralis major, omental, or bipedicled pectoralis-rectus abdominis flaps. Long-term outcomes can be excellent (ie, a 90%-93% cure rate).[19-21]

A strategy that is becoming more popular is vacuum-assisted closure (VAC). Initial debridement is performed with the removal of sternal wires, and a VAC system is applied. The next stage is performed a few days later either by closure with a tissue flap or by sternal rewiring. Although there are isolated reports of right ventricular rupture after the application of VAC, these are exceptionally rare. The technique appears safe, well tolerated by patients, and a good way of allowing antibiotics to take complete effect before wound closure.[22,23] In a recent series, in-hospital mortality was significantly lower in patients treated with VAC and delayed sternal rewiring (5.8% *v* 24.5%, $p = 0.005$) than patients treated "conventionally" (debridement and irrigation or debridement and tissue flaps).[24] The mortality benefit was still apparent at 5 years.[25] Without comparative, prospective trials, it is impossible to recommend one approach over the other.

The management of DSWIs is complex, and prevention by risk factor modification offers the most effective intervention. A host of independent risk factors have been identified for sternal site infections (Table 1).[22,26-30] Of these, cardiogenic shock, long perfusion times, and intra-aortic counterpulsation devices are the most strongly associated with infection. However, obesity, diabetes, smoking, blood transfusions, and cardiac failure also have been identified as important risk factors because of their frequency and the fact that they can be

modified by thorough preoperative screening and the initiation of preventative measures (see prevention section).[3]

ACCESS AND MONITORING DEVICE INFECTIONS

The rate of central venous catheter (CVC)-associated bloodstream infection in cardiothoracic ICUs has been decreasing in recent years. Between 2004 and 2009, the average rate of infection in cardiac ICUs in the United States dropped from 2.7 to 1.4 per 1,000 catheter days.[31,32] Despite this, CVC-associated bloodstream infection still accounted for 4.7% of all infections in the ICU.[33] When present, a CVC-associated bloodstream infection increases the risk of an SSI by 5.2 times in cardiac surgery patients.[34] In these patients, the organism most frequently isolated is coagulase-negative *Staphylococcus* followed by gram-negative bacteria and then *S aureus*.[35]

The risk of developing a CVC-associated bloodstream infection is influenced by several factors. For example, changing a CVC over a guidewire increases the likelihood of infection by >4 times (odds ratio [OR] = 4.59, $p < 0.0001$),[36] and CVCs with multiple lumens are associated with a higher risk of infection (OR = 2.15; 95% confidence interval [CI], 1.00-4.66).[37] It is worthwhile highlighting that the site of device placement (eg, internal jugular, subclavian, or femoral) has no significant effect on the development of infection.[36,38] However, current guidelines emphasize avoiding the femoral site based on earlier studies.[39-41] Routine replacement of CVCs is not recommended[42] and reduces the likelihood that a CVC will be exchanged over a guidewire. Even CVC dressings only need changing every 7 days provided chlorhexidine-impregnated sponges are used and they remain unsoiled.[43] These dressings are cost-effective and reduce the number of catheter-related bloodstream infections (1.4 *v* 0.6 per 1,000 catheter days).[44]

As evidence accumulates to direct the best practice, implementation becomes an overwhelming challenge. In the past decade, a great deal of success has been achieved by using simple comprehensive bundles. Bundles of best practice have been particularly successful in preventing CVC-associated bloodstream infections (Table 2). Indeed, in 1 study, the rate was reduced to 0,[45] and equally impressive results were seen in a state-wide initiative in Michigan (Keystone ICU Project) in which a median rate of 2.7 infections per 1,000 catheter-days decreased to 0.[46] Bundles encourage providers to follow simple steps to ensure that CVCs are placed and managed under optimal conditions. However, successful implementation requires a comprehensive program described as the 4-Es approach (Table 3).[47] Bundles do not completely abolish the risk of infection, and a suspected CVC-associated bloodstream infection still requires prompt CVC removal as well as the initiation of antimicrobial therapy for 1 to 2 weeks. Failure to remove an infected CVC increases the chance of treatment failure by 6-fold (OR = 6.6; 95% CI, 1.8-23.8; $p = 0.004$).[48]

Arterial catheters are colonized with similar organisms to CVCs,[49] but related infections occur less frequently (1.7 [1.2-2.3] *v* 2.7 [2.6-2.9] per 1,000 device days).[50] Overall, 16% of arterial catheters show bacterial colonization. Therefore, replacing arterial catheters as well as the CVC should be considered in any patient with a bloodstream infection.[47]

The incidence of bacteriuria in patients with urine catheters is 3% to 8% per day, with duration of catheterization being the most important risk factor. Bacteriuria does not necessarily represent a urinary traction infection (UTI). In asymptomatic patients, catheter-associated (CA) UTIs only occur when there are more than 100,000 colony-forming units per milliliter of at least 1 bacterial species without another explanation.[51] In patients with symptoms or signs, a CA-UTI is diagnosed with a single organism colony count of greater than 10,000 per milliliter. The incidence of CA-UTI is reduced most effectively by early catheter removal. A recent study showed that a nurse-led reminder system reduced CA-UTI

rates by more than 50%.[52] Overall, the most effective method to limit the incidence of central venous, arterial, or urinary catheter-related infection is device removal as early as possible.

PNEUMONIA

Recent studies report that ventilator-acquired pneumonia (VAP) occurs in 5.5% to 8.0% of patients undergoing major cardiac surgery.[53-55] In patients requiring more than 48 hours of mechanical ventilation, this figure approaches 50%.[54] VAP after cardiac surgery is associated with longer ICU stays (25.5 *v* 3 days), a longer length of hospitalization (40.7 ± 35.1 *v* 16.1 ± 30.1 days, $p < 0.0001$), higher mortality (50%-55%), and, ultimately, an increased cost.[53,55,56]

VAP is suspected if radiology tests show a new pulmonary infiltrate in the presence of 2 of the following: Leukocytosis, leukopenia, purulent respiratory secretions, fever, or hypothermia. Suspecting pneumonia based on these criteria is a sufficient reason to start antibiotic therapy once the appropriate cultures are obtained. The best culture specimen is controversial. Large studies comparing fiberoptic-guided bronchoalveolar lavage with simple endotracheal specimens have shown conflicting results.[57,58] In current practice, 75% of VAPs are diagnosed by endotracheal specimen collection,[59] and European guidelines suggest local expertise and resources should dictate the method chosen.[60]

VAP usually is bacterial in origin. *Pseudomonas aeruginosa* and *S aureus* are the most commonly identified. The remaining cases are accounted for mostly by gram-negative bacteria with Enterobacteriaceae (eg, *Klebsiella* spp, *Enterobacter*, *Serratia* spp, and so on) and *Acinetobacter baumannii* commonly being isolated.[1,53,54,59,61] The initial empiric treatment should target common pathogens and account for the onset of infection in relation to hospital admission.[60] Late- onset VAP, developing after more than 5 days in the hospital, is more likely to involve multi–drug-resistant organisms.[62] Patients with recent antibiotic or health facility exposure should be considered to have late-onset VAP even if they develop signs within 5 days. The recommended initial treatment provides broad-spectrum coverage because failure to select an effective agent increases mortality.[63] Once culture results are available, therapy should be adjusted accordingly and methicillin-resistant *S aureus* (MRSA) treatment discontinued if *S aureus* is not identified.[60] Treatment duration should not exceed 8 complete days of treatment because longer courses provide no additional benefit and increase the chance of recurrent infection with a resistant organism. The exceptions are nonfermenting gram-negative organisms, in particular *P aeruginosa*, in which a 15-day treatment is associated with less recurrence.[61] However, mortality and unfavorable outcomes were not reduced by continuing therapy for 15 days. In addition, the immunocompromised population has not been studied so it is unclear if limiting treatment to 7 to 8 days applies to these patients.[64] Implementing preventative measures in the form of a bundle can significantly reduce the incidence of VAP.[65] These strategies, which are summarized in Table 4, are likely to become important quality indicators in the near future.

PREVENTION

Antibiotic Prophylaxis

It is beyond doubt that perioperative antibiotic prophylaxis improves surgical outcomes by preventing SSIs,[66] and it is a core measure in the Joint Commission's Surgical Care Improvement Project in the United States. Cardiac surgery is no exception,[67] yet 3 controversial questions remain: Which antibiotic, when should it be administered, and for how long?

Suitable antibiotic choices require gram-positive activity because these organisms account for 80% of SSIs.[15] Most placebo-controlled trials showed superiority with cephalosporins.[68] The cephalosporin of choice, which is recommended by the Society of Thoracic Surgeons, is cefazolin. It is cheap and has better gram-positive activity than later generations of cephalosporins.[69] Recently, a large meta-analysis concluded that second- or third-generation cephalosporins should be used.[70] However, this conclusion was not based on lower SSI rates, which were the same as those for first-generation cephalosporins, but rather on lower postoperative VAP rates and all-cause mortality. More rigorous verification is needed before changes to practice patterns can be recommended.

In patient populations with a high incidence of MRSA, vancomycin may be a more appropriate choice. One study found that changing to vancomycin prophylaxis after the emergence of MRSA eradicated perioperative infections caused by this organism.[71] In 2008, it was reported that when the hospital MRSA infection rate reached 60%, changing to vancomycin decreased the monthly SSI rate by 2.1 cases per 100 surgical procedures (p = 0.032, overall SSI rate = 6.8/100 surgeries).[72] Vancomycin should be considered, either on its own or in combination with cefazolin, in populations with a high prevalence of MRSA colonization. However, the MRSA rate that corresponds to a high prevalence is unclear. Certainly 60% should be considered high prevalence, but the optimal cutoff point is likely to be lower.

The antibiotic should be administered to achieve peak tissue levels at the time of skin incision. Cefazolin reaches peak plasma concentrations within 20 minutes and peak interstitial levels within 60 minutes.[73] Therefore, cefazolin should be dosed as a bolus 20 to 30 minutes before incision. Vancomycin has an optimal dosing window of 16 to 60 minutes before skin incision.[74] Because vancomycin needs to be administered slowly to avoid red-man syndrome, it should be started 60 minutes before incision.

Prophylaxis should not be continued beyond 48 hours. In 1 large study involving more than 2,500 cardiac surgery patients, continuing antibiotic prophylaxis beyond 48 hours resulted in a higher risk of colonization with multi–drug-resistant organisms (OR = 1.6; CI, 1.1-2.6) without reducing the risk of SSIs (OR = 1.2; CI, 0.8-1.6).[75] Two meta-analysis studies combining the last 40 years of trials also have concluded that antibiotic prophylaxis beyond 48 hours is not associated with a clinical benefit.[70,76]

It is unclear whether antibiotics should be continued for 24 hours, 48 hours, or beyond the intraoperative period at all. For general surgery, the consensus is that antibiotics should not be continued beyond the first 24 hours unless the operative site is contaminated,[76] and recent guidelines recommend not continuing beyond the intraoperative period.[77] However, in cardiac patients, a single-center, randomized, controlled trial using cefazolin showed a benefit in the 24-hour arm versus the intraoperative-only arm (3.6% *v* 8.3% infections, respectively; p = 0.004).[78] Given this controversy and the absence of evidence showing harm by continuing antibiotic prophylaxis for 48 hours, current guidelines recommend continuing antibiotic prophylaxis for a maximum of 48 hours after cardiac surgery.[79] This recommendation was reinforced by a recent large meta-anaylsis.[70]

Preoperative Nasal Mupirocin

Nasal mupirocin has been used preoperatively in an attempt to eliminate staphylococcal nasal colonization. A study in 1995 showed that nasal carriage of *S aureus* is associated with an increased risk of SSIs (OR = 9.6; CI, 3.9-23.7).[80] A more recent study found that the *S aureus* SSI rate was reduced (1.68%-0.37%) when a preoperative mupirocin treatment protocol was initiated.[81] Furthermore, 3 sequential cohort studies and the 2007 Society of Thoracic Surgeons guidelines suggested a benefit when using mupirocin.[69] However, a

double-blind, placebo-controlled, randomized trial in cardiac surgical patients showed no benefit.[82] Selectively treating *S aureus* nasal carriers may amplify the benefit of this therapy. Recent studies using rapid real-time polymerase chain reaction tests to identify *S aureus* nasal carriers have shown that, among surgical patients, carriers who are randomized to combined treatment with both nasal mupirocin and chlorhexidine body washes have a significantly lower risk of deep SSI compared with those not treated (relative risk = 0.21; 95% CI, 0.07-0.62).[83] Although the number needed to treat to prevent 1 infection is high (28.5), screening and treating carriers in institutions with a high incidence of SSI may be recommended.[84]

Preoperative Skin Antisepsis

Until recently, there were no robust studies examining the best agent for preoperative skin cleansing. However, in 2010, a randomized controlled trial involving 849 patients showed that Chlorapreп (Cardinal Health, Dublin, OH) (2% chlorhexidegluconate/70% isopropyl alcohol) was superior to 10% povidone-iodine for the prevention of SSIs (9.5% *v* 16.1% SSI rate, $p = 0.004$).[85]

Intraoperative Topical Agents

Several intraoperative, topical strategies have been investigated to prevent SSIs, although commonly used interventions such as iodine wash, have not been studied in a controlled fashion.[86] The implantation of a gentamicin-impregnated collagen sponge recently has been shown to reduce the rate of SSI when compared with a collagen sponge control in a randomized trial (OR = 0.15; 95% CI, 0.02-0.69).[87] The use of platelet-rich plasma (PRP) and platelet-poor plasma (PPP) is an intervention anesthesiologists may need to assist with, since preparation requires centrifuging 50 to 60 mL of the patient's own blood. PRP is applied to the chest incision site before closure and, theoretically, delivers important cytokines directly to the incision site promoting healing, whereas the application of PPP to each layer during closure provides clotting components, which reduces bleeding. In 1 large retrospective study looking at more than 1,000 patients, the application of PRP and PPP significantly reduced the incidence of sternal SSIs (0.18% *v* 1.98%, $p < 0.01$).[88]

Glucose Control

Diabetes is an independent risk factor for the development of SSIs in perioperative cardiac surgical patients. In 2001, van den Berghe et al[89] demonstrated the importance of tight glucose control (80-110 mg/dL) in critically ill surgical patients, showing a substantial reduction in mortality when compared with the usual care at the time (4.6 *v* 8.0, $p < 0.04$). The benefit was more pronounced in patients staying in the ICU longer than 5 days. However, more than a decade later, there still is uncertainty over what the ideal target glucose should be, primarily because subsequent studies have not reproduced this benefit and, in some cases, they showed increased morbidity resulting in early stoppage because of adverse events in tight control groups.[90-92] The Normoglycemia in Intensive Care Evaluation-Survival Using Glucose Algorithm Regulation study (NICE-SUGAR) study helped clarify the situation in general critical illness; tight glucose (81-108 mg/dL) compared with more liberal control (<180 mg/dL) was associated with a higher mortality (27.5% *v* 24.9%, $p = 0.02$).[93] Interestingly, the mortality difference could not be explained by hypoglycemia alone, and it is likely that glucose variance (as well as hypoglycemia) was an important factor in determining the observed increase in mortality.[94,95] Patients on a tight control regimen are more likely to experience large swings in blood sugars (eg, because of overtreatment of hypoglycemia). Therefore, it would appear that targeting a blood sugar of <180 mg/dL is superior to both tight control and no control.

It is likely that the benefits of glucose control extend to cardiac surgical patients because most of the large glucose control studies have included cardiothoracic surgery patients and because poor glucose control is associated with a higher risk of SSWIs and DSWIs.[22,26-29] Specific studies in this population have shown that glycemic control reduces DSWI rates[96] and that moderate control (120-180 mg/dL) has similar outcomes to tight control but with fewer hypoglycemic events.[97] Insulin targets in cardiac surgical patients are complicated by evidence that high-dose insulin combined with a glucose infusion improves left ventricular function[98] although such a strategy is likely to increase glucose variance in most practice settings, possibly resulting in higher overall morbidity.

CONCLUSIONS

There are many opportunities for infection to develop in cardiac surgical patients, and interventions to combat this require a multidisciplinary approach, often starting with risk factor modification in the preoperative anesthetic evaluation and continuing through to interventions in the postoperative ICU setting. Many simple measures can reduce postoperative infections and have become important quality indicators. Nurse-led reminder systems, care bundles, admission order sets, and discharge protocols appear to be particularly effective at meeting quality targets.

Certain treatment options for proven infection are gathering momentum. In particular, debridement followed by the placement of a wound VAC is becoming a popular and effective strategy for DSWIs. In the future, technologies, such as rapid polymerase chain reaction detection methods for MRSA, may help direct perioperative prophylaxis. Future research efforts focusing on the development of novel antimicrobial agents, combined with rational treatment and preventive strategies, will ensure that clinicians continue to have the necessary tools to combat infection throughout the 21st century and beyond.

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Table 1

Risk Factors for SSIs After Cardiac Surgery[22,26-29]

Preoperative Risk Factors	Intra- and Postoperative Risk Factors
• Obesity	• Pedicled internal thoracic artery
• Stroke	• Postoperative hemorrhage
• Heart failure	• Emergency surgery
• Diabetes	• Steroids
• Advanced age	• Prolonged mechanical ventilation
• Atrial fibrillation	• Use of intra-aortic counterpulsation devices
• Smoking	
• Peripheral vascular disease	• Redo surgery
• Renal failure	• Blood transfusion
• Cardiogenic shock	• Postoperative hemorrhage
• Myocardial infarction	• Closure performed by an assistant
	• Tracheostomy *
	• Prolonged perfusion times

* According to recent studies, early tracheostomy does not increase the risk of DSWIs.[30]

Table 2

Interventions to Reduce CVC-Associated BSI[45]

Clean hands before touching patient or handling line
Clean skin with chlorhexidine
Use full-barrier precautions during CVC insertion (large sterile drape, mask, hat, sterile gown, and sterile gloves)
Avoid femoral site if possible
Remove unnecessary catheters

Abbreviations: BSI, bloodstream infection; CVC, central venous catheter.

Adapted from Pronovost et al.[46]

Table 3

Ensure All Patients Receive Bundle Intervention by Implementing the 4-Es Approach Targeting Key Stakeholders[46]

Engage
• Explain why interventions are important
Educate
• Share the evidence
Execute
• Design intervention, targeting barriers, focusing on standardization with independent check and system for learning from mistakes
Evaluate
• Regularly assess implementation of measure and analyze unintended consequences

Table 4

Measures Proven to Reduce the Incidence of Ventilator-Acquired Pneumonia From Muscedere et al[65]

Physical strategies
• Oral route of intubation when possible
• New ventilator circuits for each patient – only change when soiled or damaged
• Change heat and moisture exchanger with each patient and every 5-7 days
• Use closed endotracheal suctioning system
Positional strategies
• Elevate head of bed to 45° or as close to this as possible
Pharmacologic strategies
• Oral antiseptic with chlorhexidine