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Surgical site and vascular infections: treatment and prophylaxis

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Summary Vascular infections typically include those of surgical sites, prosthetic grafts, and vascular ulcers, including some diabetic foot ulcers. Each of these infections represents a serious health concern, particularly among individuals with comorbid conditions who are at an increased risk of morbidity and mortality. Surgical site infections occur primarily as a result of contamination by skin organisms during surgery, whereas prosthetic graft infections result typically from a progressive wound infection. Diabetic foot ulcers and infections are especially complicated and difficult to treat. They occur in individuals with systemic illness that has compromising effects on the nervous, vascular, musculoskeletal, and immunologic systems. Vascular infections, like those elsewhere in the body, reflect an imbalance between the host and bacteria. Efforts to limit or prevent the likelihood of patients developing these infections centre on reducing the bacterial inoculum by means of asepsis and antisepsis. As well as size of the bacterial inoculum, the bacterial properties of pathogenicity and resulting virulence are also significant. The most frequent pathogenic bacteria encountered in surgical patients are Gram-positive cocci (e.g. *Staphylococcus aureus* and streptococci). Strains with multiple antibiotic resistance (e.g. meticillin-resistant *S. aureus* [MRSA], *S. epidermidis*, and vancomycin-resistant enterococci [VRE]) can cause significant surgical site infection problems. Local resistance patterns and surveillance efforts are essential to ensure appropriate empiric antibiotic selection for prophylaxis or treatment.

Introduction

Despite the advent of antimicrobial therapy, infectious diseases continue to emerge and reemerge as antimicrobial resistance among bacteria increases. A study by Pinner et al.[1] showed the alarming trend that, between 1980 and 1992, mortality in the USA as a result of infectious diseases increased by 58%. This study further showed that age-adjusted mortality increased by 39% and that mortality in men exceeded that in women by almost five times[1]. Although vascular infections are relatively infrequent, they are associated with high morbidity and mortality[2]. For example, prosthetic graft infections can be both limb- and life-threatening[2]. Co-morbid conditions that increase the risk of vascular infection include, but are not limited to, diabetes, ischaemic leg ulcers, and smoking[2]. Treatment of these infections and those caused by biofilm-producing bacteria represent a significant clinical challenge. Antibiotic therapy has decreased the mortality associated with vascular infections; however, a successful therapeutic outcome depends on not only the location and extent of the infection, but also the type of organism and its sensitivity to the selected antibiotics[2].

Antimicrobial resistance among bacteria is an increasing threat. Clinically important drug-resistant bacteria that commonly cause healthcare-associated infections include meticillin-resistant *Staphylococcus aureus* (MRSA) and meticillin-resistant coagulase-negative staphylococci (CNS, eg *S. epidermidis* and others); vancomycin-resistant enterococci (VRE), and multidrug-resistant Gram-negative rods, including strains of *Pseudomonas aeruginosa*,

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Table 1
Surgery- and patient-related risk factors for surgical site infection

Surgery-related risk factors	Patient-related risk factors
Delayed surgery	Advanced age
Long surgical procedure	Chronic renal insufficiency
Presence of a groin incision	Diabetes mellitus
Postoperative seroma, lymphocele, or haematoma	Distal skin necrosis or gangrene
'Re-do' surgery	Female gender
Undermining skin edges	Malnutrition
Use of prosthetic graft material	Obesity
	Preoperative use of aspirin
	Rest pain

Stenotrophomonas maltophilia, and *Acinetobacter* spp. which may be resistant to most available antimicrobials. CNS, *Enterococcus* spp., *P. aeruginosa* and *S. aureus* have all been isolated from biofilms on prosthetic valves and central venous catheters [3]. In addition, strains of *S. aureus* and CNS with reduced susceptibility to vancomycin and other glycopeptide antibiotics have recently been reported [4,5]. Vancomycin resistance among enterococci is of particular importance, as among intensive care unit patients with nosocomial infections, the percentage of enterococcal isolates resistant to vancomycin has increased from 0.5% in 1989 to 25.2% in 1999 [6,7].

Recognition of the risk factors that precipitate these infections, minimisation of those risk factors, together with early recognition and prompt treatment of the infections, are essential. Here, we discuss the three most commonly encountered vascular infections: those of surgical sites, prosthetic grafts, and diabetic foot infections, with an emphasis on empiric antimicrobial options for the prevention or treatment of such infections in an era of ever increasing antimicrobial resistance.

Surgical site infections

It is estimated that more than 27 million surgical procedures are performed annually in the USA, and as the population ages, this number is likely to increase [8]. Despite refined surgical techniques, environmental changes in the operating room, and the use of preventive antibiotics, infection at the surgical site continues to be a major source of morbidity following operative procedures [9]. In addition, surgical site infection prolongs hospitalisation and increases many other costs that could have been avoided if infection had not occurred [9]. Surgical site infections are the most commonly encountered nosocomial infections in surgical patients. They occur in up to 20% of all patients who are admitted to the hospital for skin and soft tissue infection [10]. There are a number of predisposing factors that put these patients at a higher risk for surgical site infections, including diabetes, smoking, obesity, and malnutrition [11]. Table 1 shows the common surgery- and patient-related risk factors for surgical site infection following surgery.

The Centers for Disease Control and Prevention (CDC) and the National Nosocomial Infections Surveillance (NNIS) group undertook a formal, logistic regression analysis in which they evaluated all of the potential risk factors for surgical site infection. They found three factors that were strongly linked with incidence of surgical site infection: an American Society of Anesthesiology score of greater than or equal to 2; having a contaminated or dirty wound; length of operation time being greater than the 75th percentile for the operation being performed [12]. In addition, a new factor has emerged: being colonised with *S. aureus* prior to surgery. Colonisation with this organism has been shown to have a significant association with MRSA surgical site infection [11].

In 1999, the CDC published guidelines designed to help prevent surgical site infections [11]. These guidelines highlight the need for antimicrobial prophylaxis, operating room ventilation, normothermia, and glucose control as standard prophylactic strategies. Whether supplemental oxygen should be given perioperatively remains controversial. A study published in 2000 saw a 50% reduction in surgical site infections in patients undergoing colorectal cancer surgery if they were given 80% oxygen compared to patients given 30% oxygen during, and for 2 hours after, surgery [13]. This study prompted many hospitals to adopt this approach as the standard of care. In 2004, however, the study was reproduced in a general surgical patient population, and although the study design was the same, these investigators saw no difference in the incidence of surgical site infection [14].

It is clear that the mainstay of surgical site infection prophylaxis is antimicrobial prophylaxis. Numerous studies have demonstrated reductions in the rate of surgical site infection in patients undergoing surgery when an antibiotic was administered preoperatively [15-20]. Stone and coworkers [20] demonstrated that multiple doses given preoperatively in biliary and gastrointestinal surgery are no better than a single preoperative dose, and that antibiotics initiated postoperatively have the same rate of surgical site infection as placebo. In another study, the same authors showed that a regimen of five postoperative days of preventive antibiotics after preoperative administration was no better than the perioperative administration alone [19]. From these and other studies, specific criteria for the use of preventive antibiotics in surgery have subsequently been developed [15]. Prolongation of antibiotic administration beyond the immediate perioperative period

does not appear to improve results. In fact, prolonged postoperative administration of preventive antibiotics increases antibiotic-associated morbidity (e.g. *Clostridium difficile* enterocolitis), increases the resistance of nosocomial bacteria [21], and increases costs [22].

The leading causes of surgical site infections are *S. aureus* and streptococci. *S. aureus* is particularly troubling as the vast majority of strains isolated in the USA today have meticillin resistance. Data from the CDC for 2004 indicate that, in the hospital setting, 59.5% of all *S. aureus* infections are now meticillin-resistant [12]. Recent studies indicate that MRSA surgical site infection is associated with higher mortality, greater length of stay, and greater cost compared with meticillin-sensitive *S. aureus* (MSSA) infection [23].

The rising rate of MRSA in the surgical patient population provoked a change to the 1999 guidelines. In 2004, the Surgical Infection Prevention Group published an updated version of the guidelines that addresses MRSA surgical site infection [24]. One study in particular prompted this change [25]. The study looked at 885 cardiac surgical patients who were randomised to either cefazolin or vancomycin. While there was no difference in the rate of surgical site infections, there was a difference in the microbiology. When patients developed surgical site infections, those who received cefazolin developed MRSA infections, whereas the group that was treated with vancomycin developed MSSA infections [25]. Table 2 lists the antibiotics currently approved for the treatment of MRSA infections. Clearly, administration of an antibiotic with the appropriate spectrum of activity is critical to preventing surgical site infection.

Table 2
Antimicrobial therapeutic options for the treatment of MRSA infections

Agent	Comment(s)
Oral agents	
TMP/SMX	Highly susceptible; not active vs streptococci
Rifampin	Rapid resistance when used alone
Clindamycin	>90% susceptible GI side effects Inducible clindamycin resistance
Tetracyclines	85–90% susceptible
Linezolid	Highly active
IV agents	
Vancomycin	"Gold standard" for MRSA
Clindamycin	>90% susceptible GI side effects Inducible clindamycin resistance
Linezolid	Highly active
Daptomycin	Used for skin and soft tissue infections; poor activity in pneumonia
Tigecycline	Used for complicated skin and soft tissue infections and intra-abdominal infections
Dalbavancin	Once weekly dosing

Prosthetic graft infections

Infections developing in prosthetic vascular graft material are generally rare events, occurring at rates between 0% and 3.1%. However, graft infections when they do occur are a severe complication of vascular surgery and are associated with significant morbidity (systemic illness and major limb amputation) and mortality [26–29].

Most graft infections occur in the groin [27], and, as with other lower-extremity graft infections, usually occur in the early postoperative period, typically as a result of a progressive surgical site infection [29]. Comorbid risk factors associated with graft infections include the presence of ischaemic leg ulcers, diabetes, smoking, infected lymph nodes, and transient bacteraemia from a purulent draining wound or sinus, an abscess, a lymphocele, skin necrosis, pain, septic emboli with petechia, a pulsatile mass, fever, or graft thrombosis [27,29–32]. Surgery-related factors that increase the risk of graft infection include the type of graft material involved, graft construction, improperly sterilised materials, break in sterile technique, implantation site, improper administration of antibiotics, endogenous flora, concomitantly performed surgical procedure, emergency operations, reoperation at the site of infection, and prolonged operating room time [33]. Antonios and colleagues [34] recently published the first risk-factor analysis that included statistical evaluation in a case-controlled study of prosthetic vascular graft infection, and found groin incision, wound complication, and wound infection to be significantly associated with the development of vascular graft infection [34].

Historically, the most common pathogen found in early-onset infections were coagulase-positive staphylococci, such as *S. aureus*, and in late-onset infections coagulase-negative staphylococci such as *S. epidermidis* were most common. More recently, mixed pathogens have predominated as causative organisms in these infections [27,29]. *S. aureus* and *S. epidermidis*, together with *Escherichia coli*, currently make up 75% of early and late graft infections [35]. *Proteus* spp. and *P. aeruginosa* have also been found [35]. MRSA was reported to be the most common organism isolated in vascular graft infections; Earnshaw [36] reported MRSA graft infections being associated with a significant increase in the risk of amputation and prolonged duration of hospitality.

Despite the use of systemic antibiotic prophylaxis, vascular graft infections still occur. To address this problem, antibiotic- and antimicrobial-impregnated grafts have been developed and used in experimental and clinical studies to assess their preventative effectiveness. For example, Giacometti and colleagues [37] have used a rat model to show the effectiveness of quinupristin–dalfopristin-soaked grafts, as well as grafts impregnated with the peptides ranalexin and buforin II, in the prevention of vascular prosthetic graft infections. Similarly, Yasim and coworkers [38] found vancomycin-, teicoplanin- and 40% fusidic acid-soaked grafts to be effective in preventing primary prosthetic vascular graft infection in rats, and Lehnhardt et al. [39] also used an animal model to show that local and systemic antibiotic prophylaxis improves protection against graft infection. Another in vitro study [40] reported that daptomycin and linezolid exhibited more

potent antimicrobial activity against device-adherent staphylococci compared with gentamicin or vancomycin. In clinical studies, rifampin-impregnated Dacron grafts have been used for the prevention of vascular graft infection [38].

All types of prosthetic vascular grafts are susceptible in varying degrees to infection via direct contamination during implantation or bacteraemia after operation. Dacron and ePTFE are the most frequently used materials. ePTFE is relatively nonporous compared with Dacron and is more hydrophobic than Dacron. This may explain why it is less likely to form bonds with those bacteria whose cell walls have hydrophobic properties. Turgut et al. [41] found that *S. epidermidis*, *S. aureus* and *E. coli* have greater affinity to Dacron grafts when compared with ePTFE; they conclude that this finding may be of clinical importance and might influence the surgeon's choice when selecting a graft.

The gold standard for treatment of an infected prosthetic graft remains explantation of the graft and subsequent reperfusion by placing a new graft, most commonly via an extra-anatomic uninfected route [42] and less commonly via *in situ* grafting using an autogenous (vein) conduit. Antimicrobial therapy is a vital adjunct to surgical management; in some cases it may be the only option if the patient is not fit for further operative intervention.

The British Society for Antimicrobial Chemotherapy (BSAC) Steering Group on the treatment of hospital infections recommends treatment with cefuroxime and metronidazole, with or without amoxicillin, as appropriate empiric therapy for early-onset prosthetic vascular graft infections [43]. For penicillin-allergic patients, ciprofloxacin and clindamycin are suggested as alternative agents. Given that *S. aureus* is the most frequently isolated organism in early infection, and that meticillin resistance is increasingly common, it has been suggested that empiric treatment of early-onset infection should include a glycopeptide where MRSA is prevalent [44]. For late-onset infections, the BSAC guidelines recommend that antibiotic treatment be deferred until the infective aetiology has been confirmed, except in the very ill patient. Accordingly, there is little guidance as to the appropriate management of a patient in whom graft infection is suspected, but not confirmed, but who cannot tolerate surgery to remove the infected graft or to obtain appropriate specimens [45]. Indeed, it is not uncommon for a surgeon to be faced with a patient whose fitness for surgery is questionable due to the presence of multiple risk factors unrelated to the graft. Such patients are more likely to experience post-operative problems in the long to medium term. A multi-disciplinary group to provide expert consensus and guidance in the management of such patients is warranted.

Diabetic foot infections

Diabetic foot infections can be non-limb-threatening or limb-threatening [46]. Non-limb-threatening infections include superficial infections without systemic toxicity, minimal cellulitis extending less than 2 cm from the portal of entry, and ulceration not extending fully through the skin and lacking significant ischaemia. Limb-threatening infections include more extensive cellulitis, lymphangitis, ulcers penetrating through skin into subcutaneous tissues, and prominent ischaemia [46].

As with other vascular infections, *S. aureus* is the most common pathogen isolated in non-limb-threatening infections [47]. Facultative streptococci are the second most common cause of these infections. Limb-threatening infections tend to be polymicrobial. Again, *S. aureus* is a major pathogen, as are group B streptococci, *Enterococcus* spp., and facultative Gram-negative bacilli. Anaerobic Gram-positive cocci, *Peptostreptococcus* spp. and *Bacteroides* spp. may also be present [47].

Antimicrobial treatment for a non-limb-threatening infection is usually selected to address staphylococci and streptococci [47]. Mild infections can be treated at home with oral clindamycin, cephalexin, amoxicillin/clavulanate, or dicloxacillin. Superficial diabetic ulcers that are complicated by cellulitis generally require parenteral antibiotics, such as intravenous cefazolin or nafcillin [47]. Initial antimicrobial treatment of limb-threatening infections requires broad-spectrum antibiotics because of the polymicrobial nature of these infections. A variety of antibiotic regimens are advocated for initial empiric therapy of diabetic foot infections [47,48]. The combination of dindamycin and cefepime or a fluoroquinolone has often been used, as has cefoxitin or ampicillin/sulbactam. Combination therapy with clindamycin and levofloxacin offers broad coverage and is also a common empiric therapy for diabetic foot infections [47,48]. Once culture and sensitivity results are obtained, the initial antibiotic can be modified as necessary.

If, despite adequate wound care and culture-directed antibiotics, a non-healing infected diabetic foot ulcer worsens, surgery is required to debride infected tissue and achieve a healed wound to restore the functional status of the limb. Stabilising the vascular and orthopaedic components of diabetic foot ulcers is necessary to impede the progression of the ulcer-infection–amputation scenario. Diabetes is the leading cause of amputation in the USA. In 2002, 82,000 lower-extremity amputations were performed on diabetic patients [49]. For many patients, their diabetes is complicated by comorbid conditions, particularly involving kidneys and liver. The most common indications for amputation are gangrene or infection in a non-healing ulcer [50]. Morbidity and mortality rates are high following amputation. The National Institutes of Health reported that the mortality rate 1 year after amputation is between 11% and 41%, the 3-year post-amputation mortality rate is 20–50%, and the 5-year rate is 39–68% [51].

Summary

The optimal treatment for vascular infections is prevention. When these infections do occur they become potentially limb- and life-threatening complications. Gram-positive aerobes are the organisms most frequently identified in patients who develop vascular infections, with *S. aureus* being the most common. MRSA has emerged as a leading cause of postoperative infection in vascular surgery patients. It is associated with substantial

morbidity, increased length of hospital stay, and higher incidences of amputation and graft removal. Greater emphasis on preoperative screening protocols for MRSA colonisation should be considered, as well as aggressive infection control measures, alteration of preoperative prophylactic antimicrobial use in MRSA-colonised patients, and meticulous postoperative surveillance for MRSA infection. Antimicrobial treatment should include empiric coverage for MRSA in institutions where MRSA is endemic. New antimicrobial options that could be considered include linezolid, daptomycin, tigecycline, and the investigational drug dalbavancin.

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Conflict of Interest statement

Professor Shervanthi Homer-Vanniasinkam has served on various industry-supported Advisory Boards.

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