Prosthetic infections and high-risk surgical populations

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Abstract

Surgical site infection is one of the most common healthcare-associated infections in the UK, leading to high patient mortality, morbidity and healthcare costs. The presence of a prosthetic material further complicates treatment. Prosthetic-related infections most commonly arise from opportunist skin flora, *Staphylococcus epidermis* and *Staphylococcus aureus*, and are challenging to diagnose and treat due to biofilm formation. Current management is tailored antibiotic regimes and debridement, however in resistant cases, prosthetic removal is required. New technology into biofilm-resistant prosthetic surfaces hopes to reduce the incidence of infection. As advances in surgical care continue, surgery in patients with immunodeficiency becomes more common. This cohort have an increased risk of infection, therefore patient optimization and multidisciplinary approach to care is vital to prevent infection.

Keywords Biofilm; Infection; Orthopaedics; Prosthesis; Surgery; Vascular

Introduction

Surgical site infection (SSI) is one of the most common healthcare associated infections. It complicates 5% of all surgical procedures, leading to longer hospital stays, significant patient mortality and morbidity as well as high healthcare costs. With advances in surgical practice, more high-risk patients are undergoing surgical procedures.[1]

Prosthetic devices are artificial materials implanted within the body to replace missing part(s) after surgical intervention. Prosthetic devices predispose patients to infection by supporting biofilms that allow multiplication of pathogenic bacteria that are highly resistant to antibiotics. The incidence of prosthetic-related infection varies between prosthesis, patient demographics and perhaps the surveillance and reporting methodology. The incidence of infection in vascular grafts between 0.5% and 6%,[2] 0.5% and 2.2% in cardiac devices[3] and 1% and 3.7% in knee arthroplasty.[4]

Definition

Surgical site infection is an infection that becomes apparent within 30 days of the operation, most commonly between 5 and 10 days; however, prosthetic infections can present many months later. There are three levels of surgical site infection, as defined by the Centre of Disease Control:

- Superficial incisional: infection of the skin and subcutaneous tissues. Patients present with a hot, erythematous and tender wound.
- Deep incisional: infection of the fascia and muscle layers. Patients present with fever, abscess, purulent discharge and breakdown of wound edges.
- Organ or space infection: infections of peritoneal and joint spaces. This also presents with abscess and purulent discharge.

Risk factors for prosthetic infections[1,2]

There are a number of documented risk factors for prosthetic infection. These can be separated into the following categories:

- wound characteristics: contaminated/dirty wound, haematoma, burns
- location of surgery: bowel surgery, groin surgery, avascular surfaces
- operation: prolonged procedure, compromized sterile technique, emergency, re-do operation and post operative complications such as SSI and lymphocele
- patient factors: American Society of Anaesthesiology (ASA) grade 3, 4 or 5, obesity, smoking, age, medication (steroids, chemotherapy, immunosuppressants), radiotherapy, malnutrition (albumin <30 mg/dl), comorbidities (diabetes, immunocompromised), bacteraemia.

Pathogenesis of biofilm formation

During the introduction of a prosthesis into the surgical site a cascade of interactions between the prosthesis, host immunity, coagulation cascade and bacteria occur. The development of prosthetic infections is secondary to the formation of biofilm. Biofilm is a dynamic colony of bacteria on a scaffold of extracellular proteins tightly adhered to a biotic or abiotic surface. In the case of prosthetic infections bacteria is mostly opportunistic skin flora, which enter the wound during the operation. Less commonly, haematogenous spread may lead to prosthetic infection.

The formation and establishment of biofilm has been suggested to occur in four stages[5]:

1. Adhesion: within seconds of prosthetic implant, introduction peptide bonds form between the bacterial cell wall and prosthetic surface, aided by surface binding proteins 1 and 2. Simultaneously the coagulation cascade lays down layers of fibrinogen, into which bacteria may bind, mediated by protein autolysin. The bacteria form micro colonies and

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secret extracellular polymeric substances (EPS) (polysaccharides, nucleic acids and proteins), forming a membrane, which is rich in bacteria and debris from inflammation.
2. Accumulation: bacteria thrive in the nutrient rich membrane, reproducing and form strong bonds via intracellular adhesion proteins, coded for by *icaDBC*, creating a complex 3D structure. The tight adhesions decrease chemotaxis and opsonization of neutrophils and protect bacteria from antibiotics.
3. Maturation: bacteria continues to reproduce and mutate, increasing resistance to environmental factors, mediated by eDNA.
4. Detachment (dispersal): the dynamic 3D biofilm environment allows bacteria to detach and seed new colones.

Biofilms autoregulate themselves by altruistic suicide and flatricide to control population size. The population consists of two cell types, persister and non-persister cells, which increases virulence and antibiotic resistance of the biofilm.[6] Persister cells have low reproductive rates and high resistance to antibiotics. Non-persister cells include killable cells, which are rapidly eliminated by antibiotics, and tolerate-but-killable cells, which require higher levels of antibiotic for eradication.

The persistence of biofilms leads to a chronic inflammatory state and peri-prosthetic tissue destruction.

Microbiology

The most common bacteria affecting prosthetic infections are Gram-positive staphylococci, followed by Gram-negative bacilli and *Candida*.[6,7] The pathogenicity of the microbe is guided by the virulence of the genes expressed in that strain.[5] Early presentation is associated with more virulent species, such as *Staphylococcus aureus* and Gram-negative bacilli, whereas late presentations are associated with coagulase negative staphylococci and *Propionbacterium ances*.

Staphlococcus epidermis and *S. aureus* are the most common cause of prosthetic-related infections, but with increased patient comorbidities, emergency operations and revision surgery, multidrug-resistant *S. aureus* (MRSA), polymicrobial infections (7%) and *Candida spp.* (2%) are becoming more prevalent. *Pseudomonas aeruginosa* is one of the most common Gram-negative infection affecting 10% of vascular graft infections and is associated with bleeding and anastomotic disruption[2,8]

Prevention

The prevention of surgical site infection is an expanding area of research with many proposed interventions to limit the risk of surgical site infections. The current recommendations for minimizing risk of surgical site infection are shown in Box 1.

Clinical presentation

Surgical site infections may present months after the initial operation in those with prosthetic implants. Acute infections, occurring within 30 days, present with pain, fever, cellulitis and feature bacteraemia and leucocytosis. There may also be an underlying abscess or sinus formation. Infections presenting between 1 and 3 months give a similar clinical presentation. Prosthesis infected with less virulent species often present with non specific symptoms and a high index of suspicion for infection should be maintained with recent implant surgery.

Recommendations to prevent surgical site infections[1]

Preoperative

Screening and decolonization of MRSA in carriers

Enhanced nutritional support

Prophylactic antibiotics before clean surgery with prosthesis or implant, clean contaminated surgery and contaminated surgery

Consider single dose of antibiotic prophylaxis before starting anaesthesia, give antibiotic earlier when a tourniquet is planned

Do not shave hair — use clippers if hair removal required

Intraoperative

Prepare skin immediately before incision with an antiseptic solution

Antiseptic solutions left for adequate time:

- Betadine® requires skin contact for at least 2 min
- Chloraprep® must completely evaporate before placing drapes

Pre-oxygenation with 80% inspired O_2 during and post procedure if possible

Careful control of blood glucose

Adequate fluid balance and hydration

Ensuring patient body temperature is at least 36.5°C

Antimicrobial coated suture material (triclosan)

Postoperative

Cover incisions with interactive dressing at the end of operation

Box 1

Orthopaedic

Infection rates varying been prosthetic joint sites, with relatively low rates in hip and shoulder replacement, compared to elbow replacement. Early symptoms include erythema, pain, swelling, cellulitis, sinus or persistent wound drainage, whereas chronic symptoms include chronic pain and prosthesis loosing, without systemic symptoms. In 10—20% undergoing revision for prosthesis loosening, infection was found to be the cause.[9] Presence of a discharging sinus over a prosthetic joint can be pathognomonic for a periprosthetic infection.

Vascular

The most common location of vascular graft infections is the groin. In addition to the above symptoms, vascular graft infections can also present with graft occlusion with distal ischaemia, peripheral septic emboli, pseudoaneurysm, anastomotic rupture with haemorrhage, erosion through wounds/adjacent structures and poor tissue incorporation of the graft.

Specific presentations of intra-cavity graft infections include erosion into the gastrointestinal tract resulting enterococci/anaerobic bacteraemia and bleeding. Intra thoracic graft erosion can result in infective endocarditis, septic emboli and thoracic aortic aneurysm/dissection.[2,8,10]

Cardiac

Cardiac infections are classified into pocket and deep infections. Pocked infections surround the device pocket or subcutaneous leads, whereas deep infections affect the endocardium causing infective endocarditis and septic emboli. Cardiac surgical site infections can also present with mediastinitis due to sternal wound breakdown (Figure 1). Staphylococci and Gram-positive bacteria account for 68–93% of infections, Gram-negative species 18% and 15% are culture negative.[3]

Mesh

Mesh is commonly used in general surgery for hernia repair and in pelvic procedures. Infection presents with erythematous wounds, fever, purulent discharge and abscess. Late presentations include chronic pain, non-healing wounds, recurrent defects and enterocutaneous fistula formation.[11]

Diagnosis

Currently there is no gold standard for diagnosis of prosthetic-related infections. Biochemical markers of inflammation, specimen cultures and imaging all play a role in diagnosing infection and guiding treatment. Most culprit organisms are normal skin flora so diagnostic relevance of culture samples is difficult. For joint infections, the literature suggests preoperative sampling of synovial fluid and avoidance of skin swabs help increase diagnostic accuracy.

Microbial diagnosis

Classic microscopy and culture of tissue and blood samples is used. It is a relatively inexpensive and widely available technique to identify microorganisms and test for antibiotic sensitivity. The process is, however, lengthy and labour intensive. The results rely on representative samples, which are often difficult to acquire in prosthesis, and results may be biased by clinical antibiotic use. The literature suggests using sonication of explanted devices to detach biofilm, multiple intra operative samples and culture over 14 days to improve accuracy.

Non-culture methods include gene amplification methods, for example multiplex polymerase chain reaction (PCR) and fluorescence in situ hybridization (FISH). These methods do not rely on growth of bacteria, are not biased by antibiotics, are able to detect multiple species and can differentiate contaminate from pathogen as well as guide antibiotic choice. However, multiplex PCR and FISH are expensive and require specific expertise and equipment.[10]

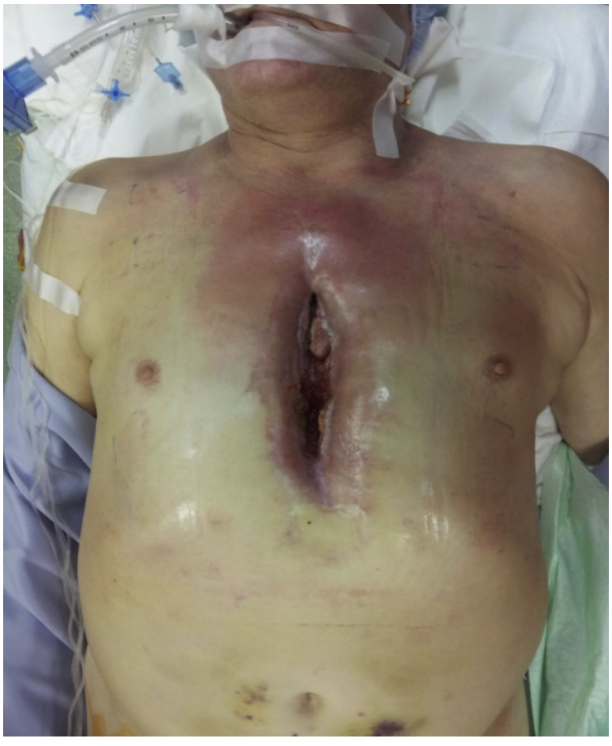

Figure 1 Median sternotomy wound infection.

Imaging

Imaging of suspected prosthetic wound infections is useful to delineate the pathology and plan for surgical interventions. The choice of imaging modality must be tailored patient co-morbidities, location of the prosthesis and type of prosthesis.

Ultrasound (US): has the benefit of being radiation free, but is highly user dependant. In cardiac device and implant infection US echocardiogram is the first line investigations to visualization vegetations on the valves. Transoesophageal US is more sensitive (90–96%) than transthoracic US.[3]

In extracavity vascular graft infections, US is useful to visualize peri-prosthetic collections/fluid and pseudoaneurysms.[2,8]

X-rays: are of limited use due to lack of sensitivity and specificity; however, serial X-rays are used in orthopaedic prosthetic infections to provide a baseline for comparison and may reveal evidence of joint loosing or osteomyelitis. X-Ray findings suggestive of infection are transcortical sinus tract, prosthesis loosing and bone resorption.[9]

A chest X-ray should be carried out in patients with suspected cardiac implant infections.[3]

Computed tomography (CT) and magnetic resonance imaging (MRI): CT scans are able to obtain a large amount of anatomic information quickly and accurately. CT and MRI have 95% specificity and 55% sensitivity. The lower sensitivity is due to appearances of normal post operative changes, which become pathological if persistent after 6–8 weeks. The downside of CT scanning is exposure to high doses of radiation and nephrotoxic contrast and artefact from metallic implants, decreasing image quality.

CT scanning is the first-line imaging investigations for suspected vascular graft infections. Findings of perigraft fluid or gas, perigraft stranding in tissue planes, focal bowel wall thickening and pseudoaneurysm are all suggestive of infection (Figure 2).[10]

CT scanning should also be considered in cardiac devices and implant infections where US echocardiogram is negative.[3]

MRI produces similar anatomic assessment, however, can only be used in those with MRI-safe metallic implants. Metallic implants also lead to artefact, which may render images uninterruptable. Cardiac pacemakers are contraindicated. MRI is also less tolerable to patients due to long scanning times, more expensive than CT and gadolinium contrast can cause systemic fibrosis in those with renal impairment.[10]

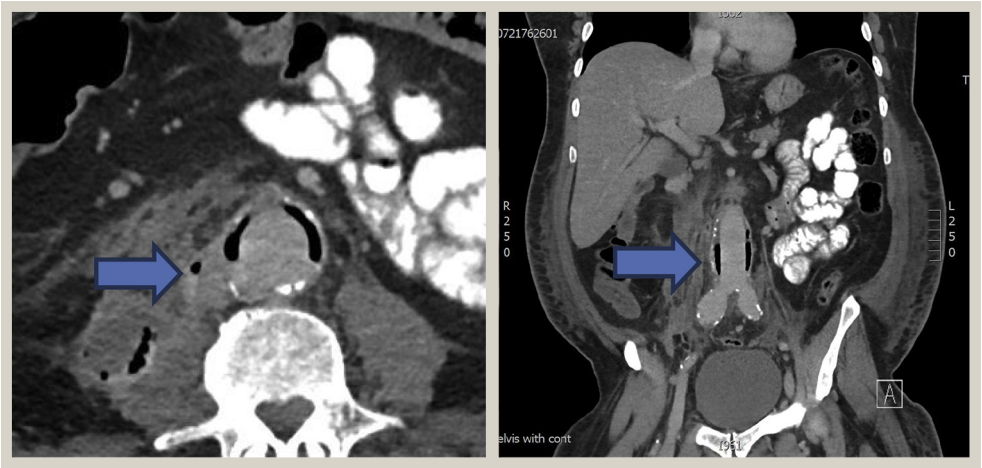

Figure 2 CT showing infected aortic graft infection (blue arrow).

^{18}F-Fludoxyglucose positron emission tomography/computed tomography.

Where CT is uncertain, radio-nucleotide scans can increase diagnostic accuracy in prosthetic infection. In vascular graft infections, FDG-PET/CT has 0% sensitivity, although a lower specificity due to tissue healing post implant. FDG-PET/CT scans are also used when there is diagnostic uncertainty in cardiac implants infections.[2,3,8]

Management

The management of prosthetic infections should be via a patient-centred approach with involvement of the multidisciplinary team. Initial management is based on clinical presentation. In acutely unwell patients, at least two broad-spectrum antibiotics should be commenced, after discussion with the local infectious diseases/microbiology specialist. The antibiotics should be rationalized once laboratory sensitivity results are available. In clinically well patients, sampling of the infected prosthesis should be undertaken first. Over the past decade antibiotic resistance has become increasingly prevalent, especially in MRSA β-lactam. Antibiotics also have little effect on biofilms.

Surgical management with early debridement is key to remove haematomas, devitalized tissues and sinus tracts. Multiple debridements may be necessary. Incision and drainage should be performed for abscesses and consideration must be given to whether to remove and potentially replace an infected prosthesis. In some patients multiple operations may not be feasible, in which case long term antibiotics and amputation or palliation may need to be considered.

Orthopaedic

Surgical intervention is the gold standard of orthopaedic prosthetic infections. Options range from debridement with retention of prosthesis, one or two stage exchange, resection arthroplasty, joint arthrodesis and limb amputations.[9] When infection presents within 4 weeks of the procedure, early open debridement with copious irrigation with antibiotic containing solution is indicated, along with antibiotics. The choice of antibiotic, route of administration and length of treatment is dependant on the organism. Guidance must be sought from the local infectious diseases/microbiology specialist. High failure rates are associated with MRSA infections, Gram-negative organisms, sinus tracts and presentation 2 weeks after initial procedure.[9]

In chronic infections, or infections via haematogenous spread, exchange arthroplasty is the gold standard intervention. This is undertaken via a one or two-step approach dependant on patient fitness. The new implant is secured with antibiotic loaded cement (vancomycin or tobramycin) and antibiotic impregnated bone allographs may also be used. The one-step approach is favoured as it offers lower patient mortality and better cost effectiveness. Procedures are followed with intravenous antibiotics then oral antibiotics. Joint arthrodesis and amputation are indicated when all other interventions fail. Joint arthrodesis being reserved for ambulatory patients.[9]

Vascular

Management of extra cavity graft infections is guided by the Samson criteria (Table 1).

The management of intra-abdominal vascular graft infections consists of 6 weeks of intravenous antibiotics followed by 3–6 months of oral antibiotics. Surgical options include in situ reconstruction or extra-anatomical bypass and graft excision in those with extensive infection or MRSA.[2,8]

Cardiac

Non-complicated cardiac implant infections are managed with 10–14 days of antibiotics and removal of the device. When cardiac prosthetic infections are associated with infective endocarditis, 6 weeks of intravenous antibiotics and removal of the device is required. Infections of prosthetic heart valves have a mortality rate of 30% and replacement is indicted when medical therapy has failed or complications develop.

Mesh

Superficial infections are managed with antibiotics, incision and drainage of abscess, wound irrigation and prosthetic salvage with wide debridement. Wounds are allowed to heal by secondary intention. Deep infections require partial/complete mesh removal. The literature advocates complete mesh removal, due to high recurrence rate of infections, complicated adhesions, biofilm formation and requirement of rectus repairs in partial mesh removal.[11]

Samson classification of graft infections[2,12]

Samson Class		Antibiotic	Surgical
I	Infection to dermis	2–4 weeks oral/intravenous	–
II	Infection to subcutaneous tissues, no graft infection		Incision and drainage, wound irrigation
III	Infection of body of graft, no anastomotic site	4–6 weeks intravenous, followed by 3–6 months oral	Multiple incision and drainage/wound irrigation, followed by preservation/ reconstruction with arterial allograft/venous autograph/polyester Adequate wound coverage
VI	Infection of anastomosis, no bacteraemia or anastomotic bleeding		
V	Infection of anastomosis with septicaemia ± anastomotic bleeding	4–6 weeks intravenous, 6 months oral	Graft excision and reconstruction with adequate wound coverage (muscle flap/VAC dressing)

Table 1

Developments in infection-resistant prostheses

Current research into preventing prosthetic infections includes the development of non-adhesive surfaces and prevention of microbial growth and biofilm formation. Prosthetic surfaces containing sulfonate units high molecular weight polyethylene molecules and polydimethysiloxane have been shown to resist binding of *E. coli, S. epidermis, P. aeruginosa* and *Candida*. In orthopaedics antibiotic-impregnated bone cements has been shown to reduce the number of infections. The prevention of prosthetic infections must be multimodal, as single mechanisms of action do not maintain long-term resistance. Nanoparticles is one such technology that has been shown *in vitro* to prevent adherence, have bactericidal properties and prevent biofilm formation.[7]

Infections in high-risk populations

Diabetic foot infections

Diabetes is one of the most common chronic diseases affecting over 3.6 million people in the United Kingdom. Diabetic foot ulcers occur in 10% of patients and have poor healing rate (Figure 3).[13] This is due to disruption of the normal healing in three broad areas[14]:

1. Hyperglycaemia leads to endothelium dysfunction resulting in low nitric oxide levels leading to vasoconstriction and impaired immune and inflammatory response locally, predisposing to infection.
2. Impaired healing barriers due to deficiency in growth factors needed for inflammation and tissue regeneration. Most notably:
    a. Deficiency in endothelium growth factor (EGF), vascular endothelial growth factor (VEGF), granulocyte macrophage colony stimulating factor (GM-CSF) and interleukin (IL)-8, which regulate angiogenesis.
    b. Locally, a lack of platelet derived growth factor (PDGF), transformed growth factor (GF) beta and GM-CSF leading to impaired extracellular matrix deposition.
    c. Shortage of insulin-like growth factor (IGF 1), EGF, fibroblast growth factor (FGF), IL-6 and GM-CSF leading to reduced epithelization and ketatinocyte proliferation.
3. Local infection caused by relative immunosuppression in diabetes results in raised neutrophils, monocytes, macrophages that create granulation tissue. Leucocytes release cytotoxic, proteolytic and free radicals resulting the disorganized collagen layout in healing wounds.

Analysis of a diabetic wound shows low angiogenic factors, disordered granulation, inflammation and disordered immunity all predisposing to poor wound healing.

The most common bacterium isolated from diabetic foot wounds is meticillin-resistant *S. epidermis*, which is a common skin commensal. The isolation of this species could be due to sampling techniques.

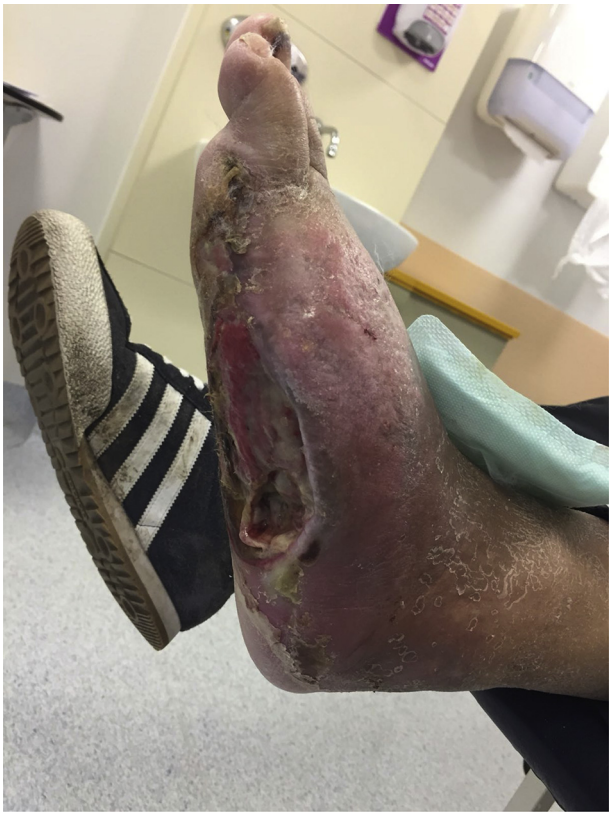

Figure 3 Infected diabetic foot ulcer.

The current management of diabetic foot wounds includes strict glycaemic control, revascularization of ischaemic wounds, debridement, off loading and wound dressings. More advanced therapies used for complex diabetic foot wounds include bio-engineered skin equivalents and larval debridement. Smoking cessation and pharmacological treatment with statins and anti-platelets must also be considered. Even with the best wound management, diabetic foot wounds are associated with protracted treatment courses, predisposing patients to developing infection. Current treatments under investigation include bone marrow derived stem cell growth factor therapy, recombination anti-platelet growth factor (becaplermin), hyperbaric oxygen therapy and extracorporeal shockwave therapy.[13]

Infections in immunocompromised patients

Patents with immunodeficiency (see Box 2) are more likely to develop complicated surgical site polymicrobial infections.

In orthopaedic procedures, guidelines advise withholding disease modifying anti-rheumatic agents (DMARDs) for 2–4 weeks before major surgery, and restarting once satisfactory wound healing to decrease the risk of surgical site infection. However, current evidence for this recommendation is lacking. Several reports suggest the risks of poor surgical outcomes when methotrexate is withheld outweigh any benefits of reduced risk of surgical site infection. However, other trials show continuation of infliximab and etanercept does significantly increase the risk and severity of surgical site infections.[12]

Causes of immunodeficiency

Chronic disease
Diabetes mellitus
Post splenectomy
Congenital immunodeficiency disorders
Anaemia
Hypothyroidism
Chronic granulomatous disease
Myelodysplastic syndromes
Cancer
Leukaemia
Lymphoma
Multiple myeloma
Therapies and drugs
Chemotherapy
Disease modifying anti-rheumatic drugs (DMARDs)
Radiotherapy
Steroids
Immunosuppression drugs, e.g. azathioprine, monoclonal antibodies
Infections
HIV/AIDS
Lifestyle
Smoking
Alcohol excess

Box 2

Transplant patients are one of the most common immunocompromised groups encountered by surgeons. In the initial stages post-transplant infection rates are low due to the minimal accumulation of immunosuppressants. From 1 to 6 months post transplant viral infections, such as cytomegalovirus and Epstein-Barr virus, occur. After 6 months 10% of patients and those with pre-existing infection, become more at risk of opportunist infections. Immunocompromised patients are often excluded from studies, but when matched to similar patients, healthy transplant patients are suggested to be at no greater risk of infection that non-transplant patients.[15]

Another consideration for patients taking immunosuppressant medication is potential interactions with antibiotics. Interaction can result in inhibition of drug metabolism, resulting in organ rejection or inhibition of antibiotic action leading to infection.[15]

Conclusion

Surgical site infections and particularly prosthetic implant infections are challenging to treat with high patient morbidity and healthcare costs. Simple actions have been shown to reduce the risk of infection and new technology continues to be developed to reduce the risk of biofilm formation and development of its complications. ◆

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