Infected orthopedic implants

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Infected orthopedic implants present a heavy burden to patients, surgeons and the community in terms of morbidity, mortality and cost. In this mini review sources of infection are traced and so are the risk factors and incidence. The pathomechanisms are explored and the clinical presentations as well as diagnostic tools are discussed. In addition, the various treatment methods are explained.

Keywords:
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Introduction

Infection in general, and bone infection in particular, is catastrophic. In the presence of foreign bodies, implants, or artificial joints, it becomes disastrous. It may manifest as early, delayed, or late [1]. It presents a heavy burden on patients and hospitals in terms of morbidity, mortality, and associated costs. The average cost of combined medical and surgical treatment is estimated to be US $15 000 for an infected implant [2]. For joint replacement, the economic cost of this complication is up to US $50 000 per patient and 250 000 million per year [3,4].

The ability of all bacteria [5] to stick to surfaces and form biofilm, which protects bacteria from the surrounding environment, worsens the situation. The difficulty is compounded more because bacteria in biofilms are difficult to detect in routine diagnostics and are inherently tolerant to host defenses and antimicrobial therapy [6]. This is a real challenge to modern medicine.

The source of infection

This may be a direct contact with the wound or airborne contamination: this often leads to early infection, within 3 months of operation, or delayed infection, within 1 year [7]. It may be a bloodborne contamination during or after operation: this is the common cause of late infection [7]. The third source is the spread of a superficial wound infection into deeper tissues [7].

The interaction between the timing of bacterial seedling of the wound or implant, the virulence, and number of microorganisms versus the immunological response of the patient will determine whether a short-term purulent infection presents within a few weeks of operation or a long-term delayed or late infection develops months or years later [1].

Risk factors

Susceptibility to infection is multifactorial:

(1) The personality of the injury includes open or closed fracture, multiple injuries, degree of soft tissue injury, energy of the fracture, and degree of vascular injury [8].
(2) Quality of the operation and facilities include the surgeon, surgical technique, debridement of dead muscles, contaminant removal, lavage, postoperative care and hospital cleanliness [8], type of surgery (implant or nonimplant), and duration of surgery [9]. After plating of a broken bone, devascularized areas may occur at the interface between the plate and the bone and between the plate and soft tissue, even after preservation of the periosteum: these necrotic areas predispose to infection and nonunion [10]. Similarly intramedullary nailing, reamed or not, may lead to necrosis of the central part of the bone cortex, thus jeopardizing union and promoting infection [11].
(3) The nature of the device, which includes biocompatibility of material or materials used; promotion or inhibition of tissue adhesion and/or bacterial growth; surface properties; design; number of possible dead spaces; function, temporary or permanent; and adjacent beside moving tissues, such as tendons [8]. The attachment surfaces have got special relevance. They vary in their ability to support biofilm development owing to different substratum characteristics, such as surface charge [12]. Also porous surfaces with rough surface

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microtopography entrap more bacteria compared with those with smooth surface [13].

(4) Patient characteristics: patient's age and duration of preoperative hospitalization proportionately increase incidence of infection [14]. Other factors such as diabetes mellitus; hyperglycemia, independent of diabetes mellitus resulting from normal physiological response to injury [15]; anemia; immunosuppression; concurrent urinary tract infection; renal failure and hemodialysis; malnutrition; obesity; and hypertension add significantly to the incidence of infection [14]. In addition, the presence of a foreign body per se has been shown to significantly increase susceptibility to infection. For example, the minimal infecting dose of *Staphylococcus aureus* causing an abscess in guinea pigs was more than 100 000-fold lower near subcutaneous devices than in skin without implant [16].

Incidence

This depends on the surgical site and the procedure; in some reports, it varies from negligible to 29% [17]. Transcutaneous fracture fixation pins have a 2–30% chance of infection [18] and may reach up to 50% [19]. Bone supplementation can be as high as 13% [20], and spinal infections are in the range of 2–5% [21]. For prosthetic replacement, and depending on the center, infection varies from 1.5 to 2.5% for primary replacements and up to 20% for revisions [22]. In developing countries, the situation is more difficult [14]. In internal fixation of closed fractures, infection may occur in 1–2%, whereas this may exceed to 30–40% after fixation of open fractures [23,24]. In cases of devastating trauma despite aggressive antibiotic prophylaxis and delay of hardware placement, infection occurs frequently [25]; an incidence of 33% was reported in some series [26]. On average, ~5% of initially inserted internal fixation devices become infected [2]; in some reports, it was 16.7% [9].

The microbiological profile

Staphylococci, both coagulase positive and coagulase negative (epidermis), constitute the majority of the offending organisms; in some reports, they comprise 99% [27], 70–90% [28], 80% [1], and two-thirds of the cases [27]. Polymicrobial infection was reported in 22.5% of the cases [29]; this was the cause of 68% of early infections [27]. In ~16% of the cases, cultures did not grow pathogens, mostly owing to the use of empirical antibiotics before hospital admission [14]. Generally, early infections were characterized by a predominance of virulent pathogens, notably *S. aureus* and hemolytic streptococci. Coagulase-negative staphylococci are predominantly an important cause of early infections; however, their diagnosis is often delayed because of their less pronounced tendency to produce tissue necrosis or a florid host response [27].

Pathogenesis

The presence of an implant within the body is known to increase susceptibility to infection [16,30], activating the host defenses, and stimulating the host's immune system [31]. Impaired host defense mechanisms associated with traumatic conditions involving vascular injuries and locally declining pH and oxygen tension negatively affect antibiotic diffusion and penetration into deep compartments [32].

The fate of a biomaterial surface may be considered as 'race for the surface' involving the extracellular matrix (ECM) proteins, host cells (fibroblasts, osteoblasts, and endothelial cells), and bacteria [33]. Once fracture fixation devices (or prostheses) have been implanted, they acquire a conditioning film of ECM proteins [34].The ECM is a biologically active layer composed of a complex mixture of macromolecules, such as fibronectin, fibrinogen, albumin, vitronectin, and collagen [30]. Host cell adhesion, migration, proliferation, and differentiation are all influenced by the composition and structural organization of the surrounding ECM [35]. The interaction between host cells and the ECM is mediated by specific receptors such as integrins, which are composed of α and β subunits and link many ECM proteins to the eukaryotic cellular cytoskeleton [35].

However, the ECM not only serves as a substrate for host cells but also for colonization of bacteria [30]. If host cells, such as fibroblasts, arrive first at the biomaterial surface and secure bonds are established, bacteria are confronted with a living integrated cellular surface [30] which possesses functional host defense mechanisms that can resist bacterial adhesion and colonization [33]. Unluckily, it has been found that bacteria, for example, *S. aureus*, express many surface adhesins that promote attachment to plasma and ECM proteins of host cells or those adsorbed onto metal or polymer surfaces [36]. Additionally, nonspecific factors such as surface tension, hydrophobicity, and electrostatic forces play a role in this respect [37].

Different studies have shown that most bacteria, 99.9% [30] if not all [5], grow in a matrix-enclosed biofilm, which is highly hydrated, attached to surfaces in all nutrient-sufficient aquatic ecosystems and that these

sessile bacterial cells differ profoundly from their planktonic (floating=swimming) counterparts [38,39]. The tendency of bacteria to preferentially attach to solid surfaces, where nutrients are more concentrated [38], is a fundamental survival feature that evolved over millions of years to deal with tremendous fluctuations in environmental conditions [5]. Another survival feature is that depletion of metabolic substances and/or waste product accumulation in biofilms force microbes to enter into a slow or nongrowing (stationary) state, rendering them up to 1000 times more resistant to most antimicrobial agents than their planktonic counterparts [40].The slow-growing bacterial subpopulation was designated as the small colony variants, the dwarf colony or G variants [41]. This behavior was described with different species of Staphylococci as well as other species of other genera. The phenotypic trait of slow growth leads to the development of microcolonies, usually defined as being ~10-fold smaller than the normal colonies. They have the ability to persist intracellularly, thus protected from antibiotics and host defenses. The relation between these bacteria and recurrent infection is well recognized [41].

Biofilm formation

A biofilm is defined as a 'structural community of bacterial cells enclosed in a self-produced polymeric matrix formed by extracellular polymeric substances (EPS), and adherent to an inert or living surface' [42]. These bacteria exhibit an altered phenotype different from the planktonic bacteria regarding gene transcription [40], and interacting with each other [43]. This observation of biofilm formation was described many years ago [38,39] but was brought into wide attention only recently.

The basic ingredients of a bacterial biofilm are microbes, glycocalyx, and surface, and virtually any surface is a fair game for bacterial colonization and film formation [5].

Bacterial exopolysaccharides are the main components of the biofilm glycocalyx, which has been named the slime layer. In most species, the glycocalyx is predominantly anionic and creates an efficient scavenging system for trapping and concentrating nutrients from the surrounding environment [44,45]. It thus provides a certain degree of protection for its inhabitants against certain environmental threats including biocides, antibiotics, antibodies, surfactants, bacteriophages, and foraging predators such as free living amoebae and white blood cells [44,45]. In fact, the glycocalyx creates a three-dimensional force field that surrounds, anchors, and protects surface bound bacteria [5].

When a biofilm is composed of heterogeneous species, which is the usual, the metabolic byproducts of one organism might serve to support the growth of another, whereas the adhesion of one species might provide ligands allowing the attachment of others [45,46].

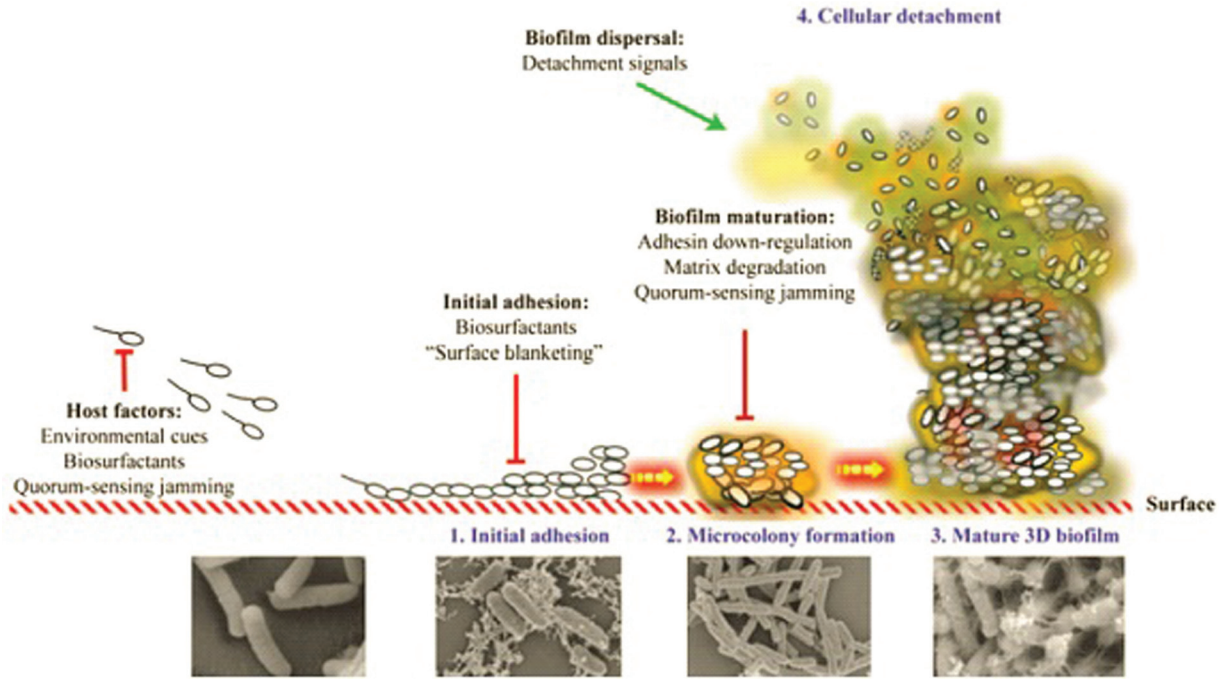
The process of bacterial adhesion to a surface, living or abiotic, is dictated by a number of variables, including the species of bacteria, surface composition, environmental factors, and essential gene products [5]. Adhesion of bacteria to abiotic surfaces is generally mediated by nonspecific interactions (e.g. hydrophobic), whereas adhesion to living or devitalized tissue is done by specific molecular (lactin, ligand, or adhesion) docking mechanisms [44].

Biofilm formation is completed through several stages (Fig. 1):

(1) Surface conditioning: surfaces on which bacteria will settle are conditioned by adsorption of organic and inorganic nutrients such as glycoprotein mucin that influence subsequent bacterial attachment [40,48]. This process describes the interaction of the substratum with its environment [33]. Once a surface has been conditioned, its properties are permanently altered, so that the affinity of an organism for a native or a conditioned surface can be quite different [5].
(2) Primary bacterial adhesion or docking: this is the meeting between a conditioned surface and planktonic microorganisms. This stage is dictated by a number of physiochemical variables and is reversible. At first, the microorganisms must be brought into close approximation to the surface (either randomly or directed by chemotaxis or by mobility). In clinical practice, types of surfaces prone to biofilm formation are numerous and include wounds, teeth, the gastrointestinal tract, and indwelling medical devices including orthopedic implants, prosthetic heart valves, central venous catheters, contact lenses, intra-uterine loops, dental units, water lines, dialysis equipment, urinary catheters, and endoscopes [5,40]. In addition, some diseases are known to invite biofilm formation such as native valve endocarditis, otitis media, chronic bacterial prostatitis, cystic fibrosis, and periodontitis [40].

    Once this is attained, the final determination of adhesion depends on the net sum of attractive or repulsive forces generated between the two surfaces, which are many and varied [46]. Electrostatic interactions tend to favor repulsion

Figure 1



Stages of biofilm formation and dissolution [47].

because most bacteria are negatively charged, whereas hydrophobic interactions favor primary adhesion [44]. An additional reason for bacterial adhesion is nutrients in an aqueous environment tend to concentrate near a solid surface [38].

The basic process in this stage is the production of EPS by the bacterial cells owing to stimulation of membrane-bound sensory proteins, which allows for the development of cell-to-cell bridges, which in turn cement bacterial cells to the surface [40,49]. Bacteria–bacteria adhesion results in multiple layers of bacteria [50], thus leading to huge increase in the microbial mass [6]. The most important host proteins promoting *S. aureus* adhesion to implanted devices are fibronectin, fibrinogen, fibrin, and collagen [51]. It was also found that several components in *S. aureus* can specifically recognize different host ECM proteins [32,36,51], and thus augment bacterial colonization; the latter was accentuated by defects in the local neutrophil function [16] and inadequate cytokine levels [52].

(3) Secondary bacterial adhesion or locking: this is the anchoring between bacteria and the surface by specific adhesins [53]. In some texts, this is referred to as colonization [19]. This is achieved through a very complicated process by the end of which bacteria become firmly attached to the surface, and this is an irreversible stage, especially in the absence of physical or chemical intervention [5]. The attached bacteria grow and divide, forming microcolonies that are considered the basic organizational units of a biofilm [38,42]. Entrapment of other planktonic cells in the EPS also occurs [54], adding to the mass of the biofilm. The colonization of a surface by one bacterium, that is, primary colonizers, is often followed by the attachment of others, secondary colonizers, to the same surface [19].

(4) Biofilm maturation: In this stage, the overall density and complexity of the biofilm increase as surface-bound organisms replicate (or die) and the extracellular components generated by the attached bacteria interact with the organic and inorganic molecules nearby to create the glycocalyx. To this may be added host-derived inflammatory response, proteins, or matrix proteins, in case of infected implants [5]. The completed biofilm has a complex architecture, consisting of bacteria in EPS-enclosed microcolonies interspersed with less dense regions of the matrix that include highly permeable water channels carrying nutrients and waste products [55].

Generally, all biofilms are fully hydrated, open structures composed of 73–98% noncellular material including water channels and exopoly-saccharides [5]. The growth potential of any biofilm is limited by the availability of nutrients in the immediate vicinity, the perfusion of these

nutrients to cells within the biofilm, and removal of the waste [5]. A commensal relationship may exist among members of mixed biofilm communities regarding nutrient use [56]. In addition, bacteria within a biofilm perceive and respond to one another by cell-to-cell signaling or quorum-sensing [57]. These quorum-sensing molecules are released in response to nutrient limitation, accumulation of toxic byproducts, and possibly other factors [57,58]. Other important factors include an optimum hydrodynamic flow across the biofilm, internal pH, oxygen perfusion, carbon source, and osmolarity [44]. Many virulence factors are needed for biofilm development and maturation. These include flagella, which tether and adhere bacteria to epithelial cells [59]; pilli, which allow for gliding mobility of some bacteria, and this acts as a mechanism for dissemination of bacteria to new surfaces [60]; lipopolysaccharides, which help adhesion of some bacteria to silica and other surfaces [61]; alignate, which anchors some bacteria to different surfaces [62]; the quorum-sensing autoinducers (related to homoserine – lactone), which repress human responses [59]; and the production of exotoxin A [59].

The biofilm architecture varies wildly depending on the type of bacteria [63]; this might be owing to the expression of lateral flagella stimulated by surface contact. It might look like an underwater coral reef with pyramidal or mushroom-shaped projections extending away from the surface and channels and caverns running through (Fig. 1) [5]. When the biofilm reaches a critical mass and dynamic equilibrium is reached, the outer-most layer of growth begins to generate planktonic organisms; these are now free to escape the biofilm and colonize other surfaces [5]. On the contrary, cells nearest the surface become quiescent or die because of lack of nutrients, decreased pH and PO_2, or accumulation of toxic metabolic byproducts [64].

(5) Detachment: detachment of a formed biofilm, also known as dispersion or dissolution, is an active process that is highly regulated by the attached cell population [56]. In this process, biofilm bacteria disseminate into other areas for further colonization [19]. There are many suggestions to explain this change; most of them are related to the behavior of the invading microorganisms [49,56,65]. Generally, it is believed that turbulent shear forces may be responsible for detachment of clumps of biofilm cells and subsequent transfer to other surfaces for attachment. This type of detachment only seems to be accurate for biofilms that are grown under laminar shear forces and are more likely to detach when shear forces become more turbulent [66]. Available evidence suggests that the primary development, maturation, and breakdown of a biofilm might be regulated at the level of population density-dependent gene expression controlled by cell-to-cell signaling molecules such as acylated homoserine lactones [62]. Once fully mature, a biofilm generates altered patterns of bacterial growth, physiological cooperation, and metabolic efficiency, all of which provide a form of functional commensal co-ordination that mimics primitive eukaryotic tissue [44,67].

Biofilm resistance to antimicrobials

Biofilmbacteria are far more resistant to antimicrobials than are organisms in suspension [5].

Suggestions to explain this behavior are as follows:

(1) The biofilm has been described as a molecular filter or shelter niche for bacteria. The fact that nutrient concentrations are higher at surface – interfaces – provides a favorable growth potential for bacteria [68].
(2) The biofilm glycocalyx prevents the perfusion and penetration of biocides to cellular targets [69] possibly because of charge interaction between EPS and the antimicrobials and/or by exclusion of the antimicrobials owing to their size [70] or by reacting with or neutralizing antimicrobials [71].
(3) The dormant growth pattern of biofilm bacterial population renders organisms in different to antibiotic activity [72]. In this case, resistance is not based on specific resistance determinants such as mutation of existing genes or by acquisition of foreign resistance determinants, but on changes in bacterial metabolism on attachment [5,73] or through changes in their membrane transport systems or bacterial surface-associated molecules which bind to or inactivate antimicrobials [65]. In this context, the formation of small colony variants is important; they reside within cells, have reduced metabolism, cause recurrent infection, and their low membrane potential makes them resistant to all antimicrobials [74].
(4) The microenvironment of the biofilm adversely affects the activity of the antimicrobials; factors including pH, PCO_2, PO_2, and divalent cation concentration will provide undesirable effects at the deepest layers of the biofilm, where acidic and anaerobic conditions prevail [75], which compromise the effect of most antimicrobials [75].

(5) The production by bacteria of certain enzymes such as catalase or β-lactamase and also the production of certain plasmids [19] contribute to bacterial resistance to antibiotics and disinfectants.
(6) Surface topography: bacteria in biofilm on rough surfaces and those with crevices become more resistant to antimicrobials than those on smooth surfaces [76] possibly owing to inaccessibility.
(7) Bacteria in biofilms can turn on stress response genes and switch to more tolerant phenotypes upon environmental stresses. Prolonged starvation induces loss of culturability under standard conditions whereas the cells remain metabolically active and structurally intact [6].
(8) The role of 'persisters' is important. Experiments show that most bacterial cells in biofilms are effectively eliminated by low concentrations of antibiotics, which is not much different from what is observed with planktonic cells. However, after an initial 3–4-log drop, a further increase in the antibiotic concentration has no effect on killing of bacteria. As a result, a small fraction of persister cells emerge and is ultimately responsible for the very high level of resistance of the biofilm bacteria [77]. Unluckily, biofilms were found to produce more persisters than other bacterial population. Surprisingly, persisters survive and are actually preserved by the presence of an antibiotic that inhibits their growth [78]. In other words, the antibiotic helps persisters persevere [79] especially in the presence of deficient immune system [78,79]. It was postulated that each antibiotic can kill only a certain percentage of the targeted bacteria. The remaining bacteria, that is, the persisters, breed antibiotic-resistant offsprings. This, in fact, is a long-term disaster, as the concerned antibiotic is no longer effective, and search for new one becomes obligatory [80].

Visualization of bacteria in biofilms

Bacteria in biofilms are difficult to detect in routine diagnostics [6], and this adds to the difficulty in diagnosis and treatment. Many methods have been tried, but certainty is difficult to achieve:

(1) Conventional plate counting. The removal of attached bacterial cells from affected surfaces for examination is abrasive to attached cells and may result in injury to bacterial cells, which could in turn result in viable but not culturable bacteria [6]. Therefore, a resuscitation step is needed to allow for cell recovery [81]. Many methods have been described to achieve this target; however, all these methods allow for enumeration of bacteria attached to surfaces by colony counts and do not reveal the in-situ structure of the biofilm [19].
(2) Direct viable counting and use of different metabolic indicators [82]. The results of these techniques are not always certain.
(3) Confocal scanning laser microscopy. This is a three-dimensional noninvasive inspection and computer reconstruction of mature biofilms without appreciable distortion of architectures [83]. This method was used to study bacterial associations with surfaces *in situ* [84], and thus, the structure of mixed biofilms may be elucidated [19].
(4) Scanning electron microscopy is commonly used to observe the morphology of bacterial biofilm on surfaces [19].
(5) Atomic force microscopy is capable of imaging surfaces at nanometer resolutions [85]. By this method, biofilm can be observed *in situ*, so also other cell–cell features.
(6) Light microscopy with computer enhancement and transmission electron microscopy, together with scanning electron microscopy, have limitations, either owing to issues of resolution or by the creation of artifacts caused by dehydration or processing techniques [5].
(7) Recently, the use of bioluminescence imaging and fluorescence reflectance imaging to monitor implanted bacterial cells has added much to our knowledge (vide infra).

The clinical importance

In addition to the inherent resistance of bacterial biofilms, *S. aureus* capsular material (surface-associated proteins) promotes osteoclast formation and thus plays a role in bone resorption in osteomyelitis [86]. In addition, bacterial remnants and subclinical biofilms residing on prostheses surfaces promote implant loosening by opsonizing otherwise relatively inert wear particles. This is caused by interaction between microbial pathogen-associated molecular patterns and toll-like receptors, a part of the innate immune system of the patient; this may be a novel mechanism of aseptic loosening of endoprostheses [87]. Biofilms may, however, fulfill protective and functional roles in some aspects of life. In industry, mixed species biofilms are useful in bioremediation processes of human and manufacturing wastes [88]. Unfortunately, they may cause economic problems such as corrosion of some metals [56] and

shortening of the product shelf-life of food products and predispose to foodborne illness [19].

Diagnosis

A major issue in the management of infected implants is the relative difficulty in making an early diagnosis. Delay in institution of effective medical and/or surgical treatment has an important effect on the chance of saving the prosthesis and limb function. It has been found that no single routinely used test is sufficiently accurate to diagnose this type of infection.

In addition, there is no worldwide acceptance of definition of surgical wound or surgical site infection (SSIs), and at least 41 different definitions have been mentioned [89]. There is no single symptom common to all definitions, but the most common criterion of infection was purulent discharge [89]. The most widely recognized definition for SSIs is that described by Horan *et al.* [90] and adopted by the Center for Disease Control [89]. According to this definition, SSIs are classified into superficial, deep incisional SSIs, and organ-space SSIs. The ASEPSIS system [91] was meant to assess wounds following cardio-thoracic surgery. It is a quantitative scoring method that provides a numerical score related to the severity of wound infection. The Southampton scale was designed for postoperative assessment of hernia wounds, with wounds being categorized to present complications and their extent [92]. Both systems, however, were developed for use following specific types of surgery, and this may limit their usefulness.

Generally, diagnosis is based on clinical signs, laboratory and microbiological tests, and histopathology and imaging studies.

Clinical signs

In early stages of infection, there is persistent local pain, erythema, edema, wound healing disturbances, hematoma, and fever. In delayed or late infection, there is persistent and increasing pain, implant loosening, and a sinus tract may develop.

Laboratory investigations

Inflammatory markers [C-reactive protein (CRP), erythrocyte sedimentation rate, and white cell count] are neither sufficiently sensitive nor specific, as they are high for up to 2 weeks after surgery [93]. Repeated measurements are more informative than a single one. The CRP returns to normal after 3 weeks postoperatively, and a secondary increase of CRP after an initial postoperative decline is highly suggestive of infection [10]. CRP is also reliable in differentiating between septic and aseptic loosening [1]. The erythrocyte sedimentation rate peaks at the seventh day and returns to normal 3–6 months after arthroplasty [10,93]. Procalcitonin levels (>0.3 ng/ml) are very specific (98%) but have a low sensitivity (33%) [94]. Blood cultures should be performed, though their results are often negative owing to intake of antimicrobials [95]. Antistreptolysin O titer may help in diagnosis of β hemolytic group A, C, and G streptococci [96].

Microbiological

Laboratory tests for culture and sensitivity of invading microorganisms necessitate the use of pure cultures grown on nutritionally rich media and in planktonic state; this never reflects what is going on in diseased tissues, and results obtained are biased [5]. There is a strong need for testing organisms isolated from infected implants in the growth mode that is most likely encountered *in situ*, as the results differ profoundly from those of the planktonic growth [10]. Aspiration of fluid collection and culturing is important; however, false negative results may occur owing to prior intake of antibiotics [95]. Swabs should be avoided because of low sensitivity [10]; injury of bacterial cells may occur, and in this case, special culturing techniques are needed [10]. The use of sonication techniques to dislodge the microorganisms from explanted devices may increase the sensitivity of the culture [97]. A major drawback of these measures is the difficulty to identify bacterial species because of their variations in phenotypic appearance and biochemical reaction [98]. Cultures of a superficial wound often present bacterial skin colonization [95]. The use of PCR assays may be helpful for rapid and sensitive diagnosis, although controversial results have been reported [99].

Histopathology

This could add important information in this respect [95].

Imaging studies

Plain radiographs have a low specificity and low sensitivity especially in early stages. However, repeated radiography may be useful [95]. In delayed and late infection, the role of plain radiographs is great. However, implant loosening may indicate either instability or infection. Similarly, widening of the fracture gap may be caused by infection or lack of blood supply to the fractured bone ends [10]. Ultrasonography may detect fluid accumulation around the implant and can be used to guide joint

aspiration and drainage procedures [10]. Computed tomography and MRI provide more specific information about normal and abnormal tissues, but a major drawback is imaging interferences near metal implants [10]. Nuclear imaging (bone scintigraphy) with the use of ^{99m}Tc has little value, as it is not specific for infection and its result remains abnormal for more than 1 year after prosthesis implantation [100]. PET and computed tomography appear to be valuable [101] and should result in far fewer false diagnoses. The use of indium-labeled-leucocyte scan is believed to be superior to the sequential technetium-gallium-white cell scan. Isotope scanning has been reported as sensitive but not specific [102]. Recently, by the use of bioluminescence imaging and fluorescence reflectance imaging, it was possible to monitor implanted bacterial cells in the superficial gluteus muscle, and also specific gene expressions in-vivo in BALB/c adult mice. It was thus possible to visualize and quantify bacterial growth, and also to monitor the infectious process throughout the course of the disease, in both the short-term and long-term relapses. As such, this animal model may be a very powerful tool for evaluating the pathophysiology of infection and the efficacy of new antibacterial drugs and implants [103].

Treatment

Prophylaxis in implant surgery includes good patient selection and eradication of any possible source of infection in the patient. In addition, the whole set involving surgery must be in an optimum situation to avoid infection. Systemic antibiotics in big doses may be useful but have definite hazards. Combination of rifampin and ciprofloxacin was favored by some authors [104].

Different locally delivery systems (of antibiotics) have been tried to optimize prophylaxis. The use of polymethylmethacrylate (PMMA) cement impregnated with antibiotics in joint replacements [105] and PMMA beads for carrying gentamicin sulfate in internal fixation [106] was found effective in different studies [107]. Owing to their higher surface-to-volume ratio, the beads are more favorable delivery vehicles [107]. Gentamicin is thermostable, and therefore, it is the best to be used in these conditions [108]; however, other antibiotics can be used. The development of bioactive glass-based materials as a delivery system is promising. Bioactive glass is osteoconductive, converts to hydroxyapatite, and heals to hard and soft tissues *in vivo*. As a result, bioactive glass-based carriers can provide the combined functions of controlled local antibiotic delivery and bone restoration. The borate-bioactive glasses have controllable degradation rates coupled with desirable properties of osteogenesis and angiogenesis [109] Other methods include collagen fleeces impregnated with antibiotics, PMMA preforms and temporary spacers, antibiotic-impregnated bone substitute material [107], or the use of antibiotic coating systems on titanium implants [110].

Coating with biodegradable poly d,l-lactide loaded with gentamicin allows initial burst release of gentamicin at high concentrations [28,111]. The use of new-generation fibrin tissue sealants to effectively deliver antibiotics to the surgical site was tried with promising results [112]. On experimental basis, the use of porous steel implants as an antibiotic-eluting device was found effective in prevention of postsurgical infection in an ovine model [113]. The use of polyurethane sleeve impregnated with antibiotics over external fixation pins to prevent pin tract infection was tried with good results [114]. Antiseptic coating using disinfectants such as chlorhexidine has been used in animals; although it has a lower potential for resistance, yet it has a toxic effect on articular cartilage [115].

Coating of prostheses and internal fixation devices with antibacterial agents is under investigation worldwide, and literature in this respect is increasingly expanding [110]. It was found that covalent coupling of vancomycin to titanium alloy prevented colonization by Gram-positive pathogens, whereas covalent coupling of titanium with tetracycline strongly retards Gram-negative colonization [116]. Also titanium with tetracycline surface supported osteoblastic cell adhesion and proliferation over a 72-h period, which offers a powerful means to protect transcutaneous implants from adhesion of Gram-negative pathogens [116]. Coatings containing nonantibiotic organic antimicrobial agents and those containing inorganic antimicrobial agents, adhesion-resistant coatings, whether by modification of physical and chemical surface properties so as to facilitate biointegration and prevent bacterial adhesion [117] or coating with antiadhesive polymers, coatings delivering nitrogen monoxide or biofunctionalization with antibacterial bioactive polymers are extensively studied at present [110]. To endow titanium-based implants with antibacterial properties, surface modifications of the implant is one of the effective strategies in this field. Possessing the unique organic structure composed of molecular and functional groups, resembling those of natural organisms, functionalized polymeric nanoarchitectures, enhances not only the antibacterial performance but also other biological functions that are difficult to accomplish on many conventional bioinert metallic implants [118].

Generally, the local application of antibiotics by whatever means is mostly used to treat existing osteomyelitis after internal fixation of fractures, but applicable ones are part of the primary procedure in joint replacement [119].

The properties of antibacterials, and in particular antibiotic coatings, must be tailored to minimize the risk of breeding or selecting resistant bacterial strains [107]; this danger cannot be excluded especially in the slow-release stage.

In the diagnosis of implant infection, there is a great need for vigilance over the possibility of infection in all situations where primary wound healing is delayed or abnormal, so that appropriate diagnostic action and therapy can be instituted as soon as possible [27]. Early treatment yields far better results than if definitive treatment is started late [120].

In addition to many predisposing factors mentioned before, it was observed that knee replacement and revision surgery have a higher risk of infection compared with hip and primary replacement surgery [121].

The goals in treating infection associated with internal fixation devices are consolidation of the fracture and prevention of chronic osteomyelitis. As such complete eradication of infection is not the primary goal as the device can be removed after consolidation of the fracture [122]. On the contrary, the goals of treatment of infection after joint replacement [prosthetic joint infection (PJI)] are to eradicate infection, prevent its recurrence, and preserve joint function [95].

Multitude of methods have been tried for the removal and prevention of bacterial biofilms on surfaces. These included the use of biocides and antibiotics, ultrasound, chelation, scraping, enzymatic digestion, high-pressure spraying, and many others [44,48,123]. All have variable and temporary success especially for infected biomedical devices [5].

Relying on antibiotic coverage in this situation is great but may be harmful. Antibiotic excesses, even of short duration, contribute to the spread of multiresistant strains [124,125] and might harm the patient, for example, antibiotic-related diarrhea in its multiple forms [27]. The prolongation of antibiotic administration beyond 24 h after surgery favors the acquisition of antibiotic resistance especially among Gram-negative pathogens [125] and may predispose for epidemics in septic orthopedic wards [126]. The situation is made more difficult by the fact that the spectrum and sensitivities of the isolated organisms vary widely in different reports [27,127,128], hence the choice of empirical antibiotic therapy before the availability of correct microbiological diagnosis is difficult. Moreover, for a good bacteriological study, a minimum of 5–6 intraoperative samples should be collected [127,129], and timely suspension of antibiotic therapy must be done to achieve reliable bacteriological results [127]. Results of swabbing a sinus are debatable [10]. In addition, opinions vary widely whether to empirically use narrow-spectrum antibiotics [126], broad-spectrum ones [38,39,127,128], or a combination [126]. In some reports, after thorough debridement and adequate drainage, the effect of the use of narrow-spectrum antibiotics was similar [126] to broad-spectrum ones. In addition, broad-spectrum coverage failed to enhance remissions or to reduce the number of surgical interventions [126]. Some authors recommended the use of glycopeptide alone [2] or in combination with carbapenem [27]. In one study [27], the use of vancomycin was advised for acute infections, whereas in chronic and hematogenous infections, this was combined with carbapenem. When culture results were obtained, vancomycin was found suitable for Gram-positive infections and carbapenem for Gram-negative infections, and for mixed infections, the two antibiotics were combined [27].

It is generally believed that the cornerstone for success of implant infection is the on-time complete drainage and debridement [126].

The nature of surgical intervention in patients with infected internal fracture fixation devices depends on the type of device, the presence or absence of bone union, and the patient's underlying condition [2]. If the implant is stable, debridement with retention of the fracture fixation device combined with long-term antibiotic treatment (which may be harmful) is reasonable [106]. Where there is dead tissue, repeated debridement is usually required, and the healing rate is encouraging [10,130]. Skin covering must be done if the bone is exposed. Direct exchange includes removing the old fixation device, and implanting a new one in the same surgical procedure was effective in some cases [10]. If resistant or difficult-to-treat microorganisms are the cause of infection, complete removal of the hardware and application of external fixator are preferable [10].

After joint replacement, infected prostheses are dealt with either by surgical removal of the implant and all

infected tissues with subsequent replacement of the joint (a single procedure or two stages) or debridement with implant retention and long-term antibiotics [120,131], putting in mind the hazards of the latter. Two-stage revision remains the most reliable method of treatment for chronic PJI, consisting of an initial debridement with hardware removal, insertion of an antibiotic-loaded cement spacer, a period of intravenous antibiotic therapy, and finally a delayed reimplantation [132].

Debridement and irrigation with retention of the prosthesis is considered to be an acceptable means at attempting joint salvage in selected cases of PJIs. It may yield good results in acute infections [122] and in those patients with no radiological evidence or symptoms of joint loosening and the presence of a functioning joint [27]. Most of those patients will have experienced symptoms of infection for a short period [27]. The risk of failure is influenced by the causative organism, the duration of symptoms, and the presence of a sinus tract. The chance of success is greatest in those patients with symptom duration of less than 2–8 days before open intervention [133]; however, the presence of a sinus increases the risk of failure [124].

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