# Device-Related Infections


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**Abstract** Device-related infection is responsible for a quarter of all health care-associated infections and can even compromise device function. These infections are caused by the colonization of microorganisms during the implantation processes. Unfortunately, the treatment option for device-related infection is limited. To make the situation worse, some of these organisms form biofilms that cover the device surface notably weakening the effectiveness of antimicrobial treatments. This chapter summarizes our current understanding of the pathogenesis of device-related infection. It also discusses our knowledge of the processes governing the formation, regulation, and resistance of biofilms. Finally, we introduce several new methods developed for diagnosing and treating biofilm infections on medical devices.

**Keywords** Medical device · Infection · Extracellular polymeric substances · Biofilm · Protein · Biomaterials · Fibrinogen · Implants · Hydrophobic · Quorum sensing · Surface-active compounds · Diagnosis

## Introduction

Medical devices have transformed health care significantly improving the lives of patients. The incorporation of medical devices for treatment have restored mobility, regulated or restored body functions, and permitted easy and relatively painless drug delivery. Examples of these devices include: cardiac implants (pacemakers, vascular grafts, cardiac valves, etc.); central and peripheral vascular catheters; endotracheal tubes; contact lenses; tissue fillers/breast implants; orthopedic and prosthetic implants; and urinary catheters [1]. Unfortunately, implanting devices can result in the introduction of normally benign flora or pathogenic organisms resulting in infection and compromising device function. This represents a significant burden on the health care system and causes significant morbidity and mortality.

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Device-related infections account for 25.6% of all health care-associated infections in the USA [2] and a 6.4% prevalence in England with 1,000,000 reported per year [3]. The routes of infection include surgical implantation procedures, placement of devices in extended contact with mucous membranes and hematogenous seeding [4, 5]. Causative organisms include Gram-positive bacteria such as *Staphylococcus aureus* (*S. aureus*), *Staphylococcus epidermidis* (*S. epidermidis*), Coagulase-negative *Staphylococci (CoNS), Streptococcal* species, *Enterococcus faecalis (E. faecalis)*, and Enterococcal species. *S. aureus* and S. *epidermidis* are known to make up the majority of prosthetic implant infections [2, 3]. Commonly isolated Gram-negative species include *Pseudomonas aeruginosa* (*P. aeruginosa*), *Escherichia coli (E. coli), Proteus miriabilis (P. miriabilis)*, and *Klebsiella pneumoniae (K. pneumoniae)* [1, 3, 6]. In addition to bacteria, yeasts, especially the Candida species, can play a role in these infections [6].

Further complicating device infection is the formation of biofilms by the infecting organisms. A biofilm is a highly organized aggregate of bacteria (or yeast) attached to a surface or each other that secretes hydrated extracellular polymeric substances (EPS). The EPS is composed of polysaccharides, extracellular DNA, and proteins. Biofilms are known to exhibit community behavior, communicating and regulating gene expression in the biofilm by quorum sensing molecules. The biofilm aggregate represents a defense against hostile environments (chemotherapy, immune response, and predation) enabling the survival of the microorganisms in the biofilm [7–14]. Biofilm formation on devices occurs in several steps: attachment to conditioned implant surfaces, microcolony formation, maturation and dispersal [2, 6, 8, 10, 11, 15–18]. A graphical summary of these traits is shown in Fig. 1.

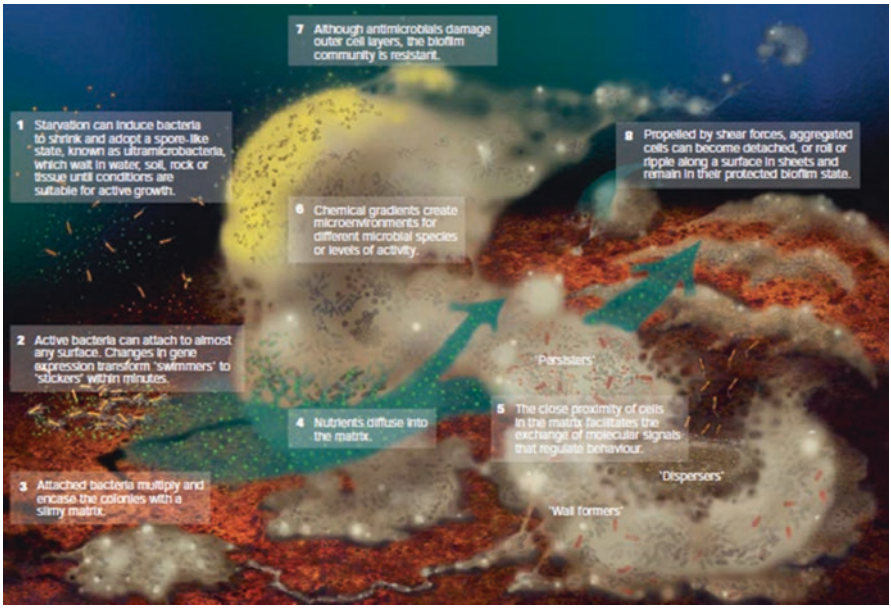


**Fig. 1** A summary of the complexity of biofilms illustrating the colonial and organized nature of this type of infection. Reprinted with permission from Springer Nature, Nature Reviews Microbiology, Hall-Stoodley et al. (2004) [11] Copyright 2004

## Implant Surface Conditioning

Immediately after implantation, medical devices are rapidly coated with host proteins, specifically plasma proteins that condition the surfaces of the implants. A majority of the implant devices attract hydrophobic proteins like albumin, immunoglobulin IgG, and fibrinogen. Once in contact with these surfaces, the proteins can either maintain a configuration similar to the configuration in the liquid phase or, due to conditions in the local environment, unfold and denature exposing occult epitopes to the immune system enhancing inflammation at the implant site [19]. An example of this is the binding and conformational change of the serum protein fibrinogen. In Tang et al. [20], it was demonstrated that fibrinogen underwent a time-dependent conformational change, exposing the occult sequences P1 and P2. These epitopes enhanced the recruitment of phagocytic cells to the implant, increasing levels of inflammatory cytokines, suggesting that these two epitopes are linked to fibrotic reactions [20]. In this background of inflammation and surface coating, bacteria have developed a means to exploit and bind to these host proteins that coat implanted materials. Figure 2 shows an image of *S. aureus* biofilm that has formed on a host-conditioned catheter segment.

## Bacterial Adhesion to Surfaces

Bacterial adhesion is a two-step process with a primary adhesion step ("docking") and a secondary adhesion step ("locking") [16]. The first stage of adhesion is random with the organism arriving at the surface by chance. This process occurs by physiochemical interactions (hydrophobic, electrostatic, van der Waals forces, temperature, and hydrodynamic forces). These interactions are reversible and can be altered by environmental conditions and depend on the net sum of attractive and repulsive forces over a critical proximity to the surface [16]. Overall, electrostatic interactions favor repulsion based on bacterial and surface-negative charges, while hydrophobic interactions drive primary adhesion [16, 21]. The secondary adhesion

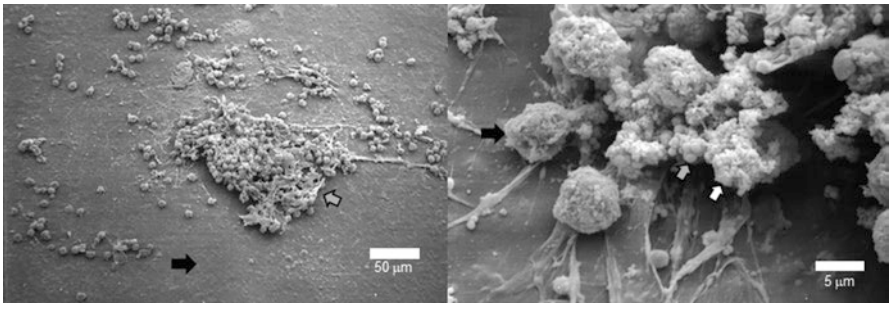


**Fig. 2** SEM images of *Staphylococcus aureus* biofilms on the surface of Teflon-coated catheters established in a mouse model of biofilm infection. The panel on the left shows the biofilm (gray arrow) adhered to the catheter surface (black arrow). The right-hand image shows the individual staphylococci (gray arrow), matrix (white arrow), and host immune cells (black arrow)

or "Locking" is facilitated by receptor–ligand reactions between the bacteria and the surface. This step of adhesion is permanent unless disrupted by mechanical and physical means. Once this secondary binding is complete, the process of biofilm formation begins [2, 8, 16]. Figure 2 shows a scanning electron microscopy (SEM) established biofilm on a Teflon-coated catheter segment.

Binding to abiotic surfaces by bacteria is driven by nonspecific means such as electrostatic, hydrophobic and hydrophilic interactions mentioned above but different mechanisms come into play on conditioned surfaces [2, 8, 16, 21, 22]. In the case of device-related infections, the bacteria encounter surfaces that are preconditioned by host proteins. Bacteria have developed a wide array of adhesion that can exploit collagen, fibronectin, fibrinogen, and lectin and can express a variety of surface-active compounds (SACs) to aid in attachment [16, 21, 23]. *S. epidermidis* has been demonstrated to have competitive binding for fibronectin with heparin [22] and the ability of *S. aureus* to bind to a variety of epitopes including fibrinogen, collagen, and bone sialoprotein is well documented [23–26]. There is evidence that suggests *E. coli* and *Pseudomonas aeruginosa* can alter their surface hydrophobicity by the secretion of SACs [21]. *Pseudomonas aeruginosa* expresses PA-IL and PA-IIL which recognize host glycans [27]. Other bacteria cell surface features that initiate or aid in binding include flagella, lipopolysaccharides (LPS), fimbrae, mycolic acids and lipopolysaccharides [8]. Additionally, their context and environmental conditions can result in distinct adhesion coming into play to aid with surface attachment. The El Tor strain of *Vibrio cholera* when in contact with borosilicate uses a mannose-sensitive hemagglutinin not associated with pathogenicity to bind to these surfaces. In contrast with this, when the bacteria comes in contact to chitin, a virulence-associated toxin-coregulated pilus is used to attach and begin biofilm formation [28]. Another feature of some of these adhesions is that they are transcriptionally regulated and are expressed either during the planktonic or sessile phases of life. Polysaccharide intercellular adhesion (PIA) expressed by *S. epidermidis* is an example of these transcriptionally regulated inhibitors. Interruption of the icxADBC operon controlling the expression of PIA results in impaired adherence mutants, while expression in a deficient strain enables attachment to surfaces [16, 29–31]. The binding of organisms to surfaces can also promote the adhesion of other organisms to the surface and each other [32]. For example, Leung et al. demonstrated in an in vitro biofilm model that colonization of biliary stents by *E. coli* enhances the binding of *Enterococcus* [32].

## Biofilm Formation

After adhesion to the surface, bacteria form microcolonies composed of single and multiple species of bacteria, alter their phenotypes to a sessile existence, and begin to express EPS. The maturing biofilm develops stratified structures with nutrient channels and differing zones of metabolic rates and genomic expression giving rise to a situation analogous to tissues in higher organisms [15, 33]. As the high densities

of cells limit the rate of growth and nutrients [15], biofilms display altruistic and cooperative properties [34]. In multispecies biofilms, different species can utilize alternative catabolic pathways and feed off the metabolites of other species [34, 35]. The resulting microenvironments with the developing biofilm result in different growth responses and gene expression by the bacteria ultimately resulting in structurally complex mature biofilms [33]. Environmental stresses placed on the forming biofilm can speed the development of the biofilm. In both *S. aureus* and *S. epidermidis*, the main polysaccharide in the matrix is PIA, which is expressed via the icxADBC operon. In response to environmental stresses such as antibiotic treatment, osmolarity, alcohols, low oxygen, low nutrients, and heat lead to increased expression of PIA and more rapid matrix development [2, 29, 30]. The rate of liquid flow and sheer stress also can result in modifications to the amount of the matrix produced depending on the vascularization and location in the body. Increased levels of PIA are present in *S. epidermidis* catheter infections compared to other lower shear environments [2]. After maturation, complex signaling within biofilms can result in the dispersal of planktonic bacteria and can occur actively or passively [11, 15, 17]. Passive dispersal of biofilms occurs because of abrasion, fluid shear (erosion and sloughing), predator grazing, and medical intervention [15, 17, 33]. Active dispersal is initiated by the biofilms in response to environmental or signaling cues. These cues include changes in nutrient levels, quorum sensing molecules, chemical signals, and cyclic dimeric guanosine monophosphate (GMP) [17]. Active biofilm dispersion allows the bacteria to colonize other surfaces and serves as a survival mechanism [15, 17, 33].

## Quorum Sensing and Biofilm Regulation

Bacteria regulate physical processes and cooperative efforts via small molecule autoinducers that are expressed at a basal level during growth in a process known as quorum sensing (QS) [8, 11, 18, 36, 37]. These molecules allow coordination of a response in a population-dependent manner by the activation or repression of gene expression. The localized QS molecules are directly related to the population density and only induce behavior in locally high concentrations of bacteria [18, 36, 38]. Currently, there are three classes of QS molecules with example systems and functions showing in Table 1. For a more comprehensive review of these systems, see references (18, 36–39).

**Table 1** The three classes of quorum sensing molecules used by bacteria

| Bacteria | Signaling molecule | Example system | Function |
|---|---|---|---|
| Gram-negative | Acyl Homoserine Lactones | *LuxI/LuxR* | Bioluminescence |
| Gram-positive | Small peptides | *Agr* | Virulence factors |
| Both Gram-negative and Gram-positive | AI-2 | *LuxS* | Interspecies communication |

The AI-2 signaling molecules are unique in that they allow for cross-species communication

QS molecules are known to play a role in biofilm formation and regulate societal traits such as competence, sporulation, virulence factors, structural formations, dispersion, antimicrobial expression, fratricide, bioluminescence, and symbiosis [18, 39]. QS molecules are reported to be involved in altruistic cooperative group benefits even when confronted with other bacteria that would exploit this altruism. An example would be a trade-off in growth rates where slow rates with a high yield are ultimately better for the population than a fast growth rate with low yield. The higher yields suggest a more efficient use of resources even at the expense of individual bacteria [18, 34]. The modulation of virulence factors by QS molecules implicates them in the biofilm formation and infection processes. Multiple species of bacteria do not express virulence factors until a critical concentration of bacteria is reached allowing them to collectively avoid the host immune system [39–42]. While QS systems can be extremely precise, there is also a certain degree of leakiness in these communication systems allowing cross talk between species [36]. In cystic fibrosis infections, *P. aeruginosa* can upregulate virulence factors in response to intercepting AI-2 signals from nonpathogenic oropharyngeal flora [41]. Another cystic fibrosis pathogen, *Burkholderia cepacia*, can intercept *P. aeruginosa* QS signals and upregulate its virulence factors to establish infection [37, 41]. Species cross talk between *Haemophilus influenzae* and *Moraxella catarrhalis* can help establish chronic infections and resistance in polymicrobial otitis media [43].

## The EPS Matrix

The essential part of the biofilm is the production of an EPS matrix which comprises roughly 90% of the biomass of the biofilms [44]. The EPS represents both a habitat and a fortress for the bacteria encased within. The organization of the matrix depends on the structural components within the matrix and the metabolic activity occurring within the biofilm [10]. The largest component of the matrix is water comprising up to 97% of the matrix with the remaining bulk of the materials being composed of soluble components like polysaccharides, proteins, and eDNA. Insoluble matrix components include amyloids, cellulose, pili, flagella, and fimbriae [9]. The physical distances between microcolonies during the initial formation result in voids that ultimately become pore and channels which facilitate nutrient and liquid transport within the biofilm [9, 10]. The formation of the matrix results in emergent properties that help the biofilms survive in the environment. The matrix provides localized gradients allowing for different populations of bacteria to survive various niches and utilize different metabolic pathways for survival. The material of the matrix also functions to absorb resources from the surrounding environment. The matrix also serves to sequester secreted enzymes resulting in a de facto external digestive system. This environment enables social behavior between bacterial species, both cooperative and competitive [10, 18, 35]. Since the matrix is a semisolid gel, the matrix can also form a skin and retain water protecting the biofilm from dehydration. Its gel-like nature also allows the migration of bacteria in the

biofilm and in some cases can represent population efforts that parallel the division of labor [9, 10]. A key advantage of matrix formation is tolerance and resistance from chemotherapy, host defenses, and predation by *Protista* [45].

## Biofilm Resistance

One of the prime advantages of the EPS matrix is the protection from antimicrobials, the immune system, and predators. In some cases, it has been noted that to affect biofilms sometimes up to 1000-fold or more, antibiotics are required to kill the planktonic form of the same bacteria [46]. Biofilm resistance is a multifactorial process involving the biology, chemistry, and physics of the biofilm [12]. The factors that have been associated with the increase in antibiotic resistance are gradients (oxygen, nutrients, slowed agent diffusion, etc.) stress responses, gene expression (resistance factors), dormancy, and tolerance [3, 7, 8, 10–13, 15, 47, 48]. Gradients present in the biofilm can result from the diffusion of agents into the biofilm resulting in sublethal concentrations of antibiotics selecting for resistance. Gradients in nutrients and oxygen lead to zones of decreased metabolism and dormant bacteria [10, 48]. The slowing metabolism of these phenotypes can affect antimicrobials that require active cellular metabolism for efficacy [49–51]. The enzyme sequestering effects of the matrix can lead to antimicrobial deactivation and the matrix components can complex with antimicrobials leading to chelation and precipitation of these agents [10]. Close proximity of bacteria in a biofilm facilitate horizontal gene transfer of resistance mechanisms, especially under conditions of environmental stress [2, 7, 52]. In addition, preexisting drug resistance could be present in biofilms. One of the most commonly used agents to treat biofilm infections is the ansamycin antibiotic rifampicin. While highly efficacious, this RNA synthesis targeting agent requires a single mutation in the *rpoB* gene to confer resistance. In vitro resistance determination studies have found that the frequency of mutation conferring rifampin resistance is between $10^{-7}$ and $10^{-8}$ [53–55]. Base on this frequency, if the biofilm being treated has a population of $10^9$ cfu, then by random chance there are approximately 10–100 bacteria that have the mutation conferring rifampicin resistance. Thus, monotherapy treatment with antibiotics will result in enrichment of the mutant population and addressing this requires extended therapy with drug cocktails to avoid this enrichment [56–58]. A final source of biofilm resistance is the subpopulation of persister cells that develop in biofilms. This cell phenotype can survive high levels of antibacterials while lacking any specific resistance mechanisms [7, 47, 59]. These dormant cells can survive blocking the activity of antibacterials by depriving them of targets through metabolic inactivity and remain dormant [47]. Eventually when environmental conditions permit, these cells will emerge from dormancy and proliferate. The exact mechanisms of persister formation are unknown but current theories center on toxin and antitoxin systems (TA) [47, 60]. The five classes of TA systems are composed of a stable protein toxin that disrupts an essential metabolic function and a labile antitoxin which is coded in an operon (see Table 2).

**Table 2** The five toxin–antitoxin systems with their regulatory elements and mechanisms of actions [61]

| Type | Regulatory element | Mechanism of action |
|---|---|---|
| I | sRNA | Binding to toxin mRNA preventing ribosome binding |
| II | Protein | DNA binding that suppresses toxin transcription |
| III | RNA–protein complex | Toxin function inhibited by interaction with pseudoknots antitoxin RNA |
| IV | Protein | Blocking of toxin target site on cytoskeletal proteins |
| V | Endoribonuclease | Cleavage of toxin mRNA |

All of these systems are believed to play an active role in the generation of persister populations in biofilms

This arrangement results in tight co-transcription and translation [60, 61]. One of the key drivers of persister formation is environmental stress, especially antibiotic treatment. It is believed that the TA system activity is modulated by the (p)ppGpp signaling nucleotide and that persister cells can spontaneously form in bacterial populations [61].

Biofilms are also highly resistant to clearance by the immune system. When a device is implanted, especially internal implants, the procedure can result in localized acute and chronic inflammation which can lead to a foreign body reaction. The implantation results in localized acute and chronic inflammation plus a foreign body reaction to the implant [2, 19, 20]. Ultimately a fibrous capsule forms around the implant resulting in a zone of suppressed immune response know as a *locus minoris resistentiae* which can increase the chance of infection and biofilm formation [2, 62, 63]. Studies have also uncovered that biomaterial implants can also alter immune cell responses. The implanted biomaterial can activate the complement system, platelets, and neutrophils. Chronic inflammatory responses may lead to neutrophil exhaustion, depletion of oxidative species and "frustrated phagocytosis" while other demonstrate that leukocytes can react and then penetrate the biofilm [2]. Studies performed in animal models with *S. aureus* suggest that the immune response may skew from the traditional pro-inflammatory response to a pro-fibrotic response. The *S. aureus* biofilm was able to alter macrophage responses toward an anti-inflammatory response with significant reductions in IL-1β, TNF-α, CXCL2, and CCL2 expression [2, 14]. In addition to dampening the inflammation, *S. aureus* biofilms have been shown to change macrophage responses to the M2 phenotype and immune suppressive T cell response by increased expression of *Arg1* [64, 65]. *S. aureus* can also induce dysfunction and death in macrophages via various toxins, including Leukocidin [64]. *Pseudomonas aeruginosa* biofilms have been found to suppress neutrophils disrupting the response and reducing neutrophil oxidation potential [66].

## Diagnosis of Biofilm Infections on Medical Devices

Diagnosis of infections on biofilm-infected devices is commonly determined using traditional microbial growth means. For orthopedic devices, the device itself is sampled with three to six biopsies of the surrounding tissues [67]. Sonication of the

devices or samples to remove the adherent bacteria has proven to be superior to identifying delayed and late infections compared to a tissue sample, histology, and synovial culture [2, 3, 46, 68, 69]. In most cases, removal of the device or sampling of the surface and associate materials (respiratory secretions, urine samples, etc.) are used to confirm the presence of a biofilm [67]. These conventional methods are not without drawback. The main challenge is that it is difficult to survey the presence of small colony variants in biofilms on different regions of medical implants. To overcome such limitations, several new methods have been investigated in recent years. For example, indirect methods of diagnosis have been successfully used to confirm implant infection including immunoglobulin assays, the inflammatory marker C-reactive protein, and histopathological evaluation of samples [70]. Other diagnostic methods include PCR (which can also screen for drug resistance markers) [3, 70], next-generation sequencing, fluorescent in situ hybridization (FISH), Matrix-Assisted Laser Desorption/Ionization Time-of-Flight Mass Spectrometry (MALDI-TOF) mass spectroscopy, and assay of α-defensin levels in the synovial fluid [2, 67].

Of recent interest has been the incorporation of nuclear medicine in visualization of infected implanted devices and foci of infection. These methods have included computerized tomography (CT) magnetic resonance imaging (MRI), ultrasound, and radionucleotide methods such as Single Photon Emission Computed Tomography (SPECT) and Positron Emission Tomography (PET). Current applications include combinations of both screening modalities to generate anatomical information via CT scanning with the labeling data from either SPECT or PET (SPECT/CT or PET/CT) [71–73]. CT imaging utilizes X-rays to generate three-dimensional slices of the target while SPECT incorporates the gamma ray emissions from a radioisotope to show specific areas of interest via the radiolabel's interactions with the target (see Fig. 3). PET looks for the localization of specific radioisotope accumulation and measures the emission of gamma photons from positron annihilations at 511 KeV which results in these photons moving in opposite directions. The impact of these photons on detectors results in a simultaneous detection event that can be used to construct a three-dimensional image of the areas where the radioisotopes have accumulated. Many of the combination systems are already available from commercial vendors and have seen use clinically [71, 72, 74–76]. SPECT/CT has been used to visualize a wide variety of infections including osteomyelitis, prosthetic joint infections, mixed infections, infectious endocarditis, and infected cardiac implant devices [72]. Currently, PET has been used to image tumors in cancer patients indirectly by using radiolabels on metabolites that have enhanced uptake in tumors or white blood cells (WBCs) migrating to the site of the tumor (see Table 3) [77–80]. While these methods have been shown to work, many rely on indirect measurements looking at a paired response to infection, such as metabolite update and infiltration of immune cells and modulators [79, 81, 82]. More direct approaches have recently been successfully attempted using tagged antibodies, antimicrobials, and molecules that are utilized by the infecting pathogens including the differentiation between Gram-positive and Gram-negative infections [75, 83–90]. While targeting by antimicrobials and immune cells is a proven approach, it must be considered that labeled agents of this type could generate a skewed or no signal based on killing of the target. An approach taken by Ordonez et al. [91] has used in silico screening to identify radiolabeled molecules that are

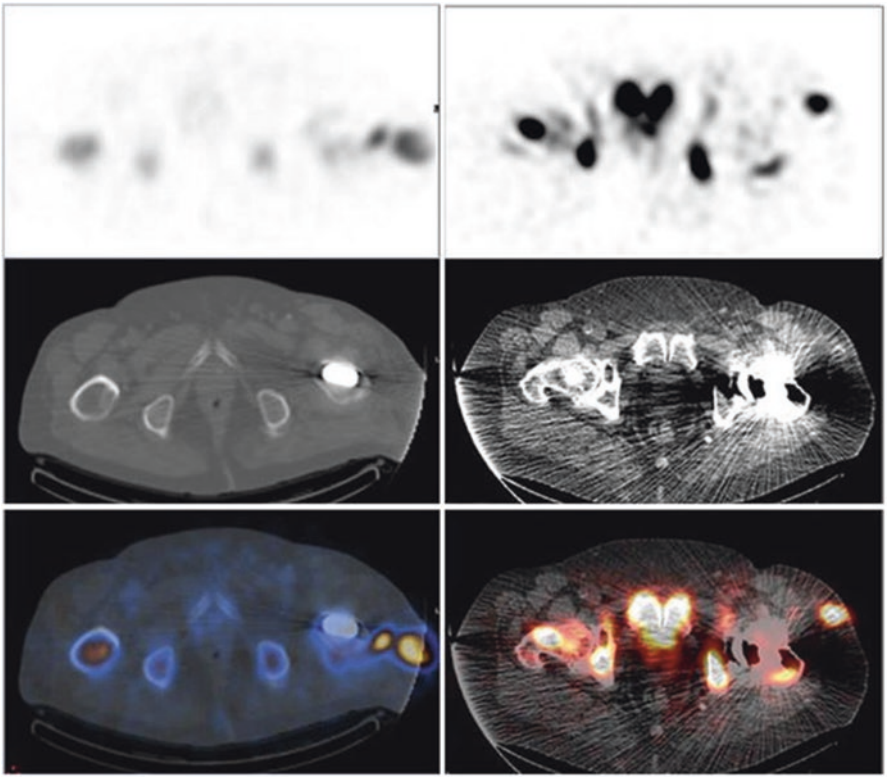

**Fig. 3** SPECT/CT images of infections in two patients with prosthetic hip infections using SPECT/CT. The upper panels show the emission while the middle panels show the CT images while the bottom panels show the superimposed images of 99mTC-HMPAO WBC uptake. Reprinted with permission from Springer Nature, Clinical and Translational Imaging, Erba and Israel [72]

**Table 3** PET radiolabels used to detect inflammation and infection

| Tracer | Abbreviation | Diagnosis | Reference |
|---|---|---|---|
| $^{18}$F-fluorodeoxyglucose (FDG) | $^{18}$F-FDG | Tuberculosis<br>*S. aureus* biofilm infection<br>Bacterial infection | Ankrah et al. [83], Neumann et al. [85], Ordonez and Jain [87], Palestro and Love [74] and Signore et al. [76] |
| $^{18}$F-labeled glutamate analogs | BAY 94-9392<br>BAY 85-8050 | Cancer | Koglin et al. [77] and Krasikova et al. [78] |
| Labeled white blood cells | $^{111}$In-WBCs<br>$^{99m}$Tc-WBC | Bacterial infection | Neumann et al. [85], Signore et al. [76] and Erba and Israel [72] |
| D-[methyl-$^{11}$C]-methionine | [$^{11}$C]-D-Met | Bacterial infection | Neumann et al. [85] |
| $^{68}$Ga-labled phage display peptides | $^{68}$Ga-A9-K-DOTA | *S. aureus* biofilm | Nielsen et al. [86] |
| [$^{18}$F]-fluoropropyl-trimethoprim | [$^{18}$F]-FPTMP | Bacterial infection | Sellmyer et al. [75] |
| 2-[$^{18}$F]-fluorodeoxysorbital | $^{18}$F-FDS | Bacterial infection | Weinstein et al. [90] |

These have been used successfully to identify tumors or infection

specifically taken up by bacteria and are not antimicrobial. There results identified ten promising leads that identified three lead candidates (Para-aminobenzoic acid or PABA, D-mannitol, and D-sorbital) that were successful in in vivo testing, specifically identifying infection sites in a murine model of myositis.

Both the SPECT and PET methods have limitations to their use that must be accounted for in the final interpretation of the results and to prevent misdiagnosis. With the indirect visualization of infection, distinctions between sterile inflammation and actual infection must be made with the approach of infection-specific tracers allowing this differentiation [75, 85, 89]. In the cases of combined systems (SPEC/CT and PET/CT) allowances must be made for the proximity of the two independent screening modalities in the physical design of the device [92] and CT measurements have to take into account photon attenuation and correction for scattering. An example of successful imaging is shown in the SPECT/CT scan in Fig. 3 from two different patients with suspected prosthetic hip infections. The top image is the emission of the tracer administered to both patients while the second image is the traditional CT scan. The final set of images is the superposition of both of the SPECT and CT images. By the combination of these results, the clinicians were able to specifically identify that the infection was limited to either the soft tissue and posterior aspect of the prothesis or the peri-prosthetic soft tissue. This fusion of the imaging technology has further allowed the identification of the cortical, corticomedullary, and subperiosteal foci of chronic osteomyelitis with a specificity value of 89% and a sensitivity of 100% [72, 93]. These results would allow for a targeted intervention if surgery and debridement would be required or allow noninvasive monitoring of efficacy of pharmaceutical treatment.

## Treatment of Biofilm Infections on Medical Devices

Treatment for device-related infections varies with the type of device and the location. In the case of peripheral devices, the easiest course is to remove the device and treat the infection with antibiotics [67]. In some cases, central venous catheters can be kept in place and treated using antimicrobial lock therapy typically with combinations of disinfectants and antibiotic at elevated levels above the minimum inhibitory concentration (MIC). With implanted devices such as prosthetic joints, the timing of the detection is critical. Infections occurring within 3 weeks of surgery can be treated with antibiotic therapy with a 70–90% success rate. For delayed or late infections, the device is usually removed to ensure that the biofilm is eradicated. The gold standard treatment is a two-stage surgical procedure where the infected device is removed, and the devitalized tissue is debrided. An antibiotic-impregnated filler is placed in the wound and at least 6 weeks of antimicrobial therapy is carried out [94]. At the completion of antibiotic therapy, the new sterile device is implanted. The success rate for the two-stage procedure is 93–100% [2, 46, 70]. Antibiotic therapy for the treatment of these infections is typically a combination therapy of rifampin, a fluoroquinolone followed by a glycopeptide [2, 70, 94, 95]. Other options in the combination therapy include daptomycin, linezolid,

tigecycline, cephalosporins and carbapenems [67], amoxicillin and trimethoprim-sulfamethoxazole [46].

Due to increasing rates of antimicrobial resistance mechanisms and the inherent resistance of biofilms, some novel approaches to dealing with biofilm infection are being explored. Therapy using bacteriophages and cocktails of bacteriophages are being used against biofilms including phages that lyse the target bacteria and phage-encoded enzymes to dissolve the EPS matrix [96]. Phages were used as successful therapeutic agents by the former Soviet Union and Eastern European countries [97]. In 2017, a personalized cocktail targeting drug resistant *Acinetobacter baumannii* successfully cleared a persistent infection in a clinical setting illustrating the utility of this therapeutic approach [98]. The incorporation of phage therapy also has been reported to enhance the efficacy of antibiotics against *S. aureus* biofilms in vitro [99]. Another novel therapeutic approach being explored is the use of antimicrobial peptides (AMPs). AMPs are small positively charged peptides secreted by virtually every type of organisms to combat pathogens [100–102]. The AMP Database as of 2019 contains a total of 3055 entries from all the kingdoms of life (Protista, Archaebacteria, Eubacteria, Plants, Fungi, and Animals) [103]. The mode of action of these ubiquitous agents is through membrane disruption and depolarization but recently evidence has been mounting that there are additional targets within bacteria such as translation, transcription, and replication that are affected by these peptides [100, 101, 104]. Currently, there are several classes of AMPs used clinically as systemic and topical agents including colistin, polymyxin B, nisin and bacitracin in addition to synthetic AMPs in development [104–106].

A challenge posed by is the modification of the environment around the wound is that it typically becomes anoxic and mildly acidic (pH 5.0). Acidic pH values can both enhance or inhibit the activity of antibiotics [107, 108]. The MICs for gentamicin against *S. aureus* increase as pH decreases while the opposite holds true for oxacillin [109]. In purulent wounds, the bactericidal activity of ciprofloxacin and imipenem is inhibited [110]. A novel approach to adapting agents to this acidic environment is the design targeted delivery systems that only activate in these mildly acidic conditions. A pH activated targeted delivery system has been tried using poly(D,L,-lactic-co-glycolic acid) (PGLA) nanoparticles that were laced with PEG to prevent nonspecific interactions. To provide specificity to the target bacteria, a poly-L-lysine was incorporated that becomes a positively charged cationic moiety by gaining electrons at an acidic pH. This technology was successfully used to deliver vancomycin to *S. aureus* in an in vitro system [110]. The targeted delivery concept has also been applied to AMPs. Modification of the Cardin and Weintraub heparin-binding sequences (AKKARA and ARKKAAKA) with histidines yielded membrane damaging antimicrobials that only were activated under acidic conditions and were active against Gram-negative, Gram-positive, and yeast [111]. A similar approach has shown in vivo efficacy against *H. pylori* infection, a causative organism in the generation of stomach ulcers. This pH responsive polypeptide AMP was designed with a random distribution of positive and negative residues which, under a physiological pH adopted a nontoxic, inactive random configuration. When exposed to acidic conditions, the AMP transitioned to the antimicrobial helical configuration [112].

## Conclusion and Summary

Device-related infection remains to be a major burden on the health care system. With the recent improved knowledge on the pathogenesis of bacterial infection, we may be able to develop new methods for the detection of bacterial activities and eradication of biofilm-encapsulated microorganisms surrounding implanted medical devices. Equally important is the need for more studies to explore the possibility of designing medical device surfaces that can reduce bacterial colonization while restoring "normal" antimicrobial responses of immune cells. It is our belief that such a biological response-oriented approach will help in the creation of next-generation medical devices with significantly improved safety and functionality.

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