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Multi-Disciplinary Antimicrobial Strategies for Improving Orthopaedic Implants to Prevent Prosthetic Joint Infections in Hip and Knee

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Abstract

Like any foreign object, orthopaedic implants are susceptible to infection when introduced into the human body. Without additional preventative measures, the absolute number of annual prosthetic joint infections will continue to rise, and may exceed the capacity of health care systems in the near future. Bacteria are difficult to eradicate from synovial joints due to their exceptionally diverse taxonomy, complex mechanistic attachment capabilities, and tendency to evolve antibiotic resistance. When a primary orthopaedic implant fails from prosthetic joint infection, surgeons are generally challenged by limited options for intervention. In this review, we highlight the etiology and taxonomic groupings of bacteria known to cause prosthetic joint infections, and examine their key mechanisms of attachment. We propose that antimicrobial strategies should focus on the most harmful bacteria taxa within the context of occurrence, taxonomic diversity, adhesion mechanisms, and implant design. Patient-specific identification of organisms that cause prosthetic joint infections will permit assessment of their biological vulnerabilities. The latter can be targeted using a range of antimicrobial techniques that exploit different colonization mechanisms including implant surface attachment, biofilm formation, and/or hematogenous recruitment. We anticipate that customized strategies for each patient, joint, and prosthetic component will be most effective

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AUTHORS' CONTRIBUTIONS

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at reducing prosthetic joint infections, including those caused by antibiotic-resistant and polymicrobial bacteria.

Keywords

infection; joint; arthroplasty; implant; individualized medicine

Currently, prosthetic joint infections (PJI) account for at least 16% of total joint revisions in the hip and knee,[1,2] yet roughly 30% of joint revisions are thought to be caused by aseptic loosening.[3–5] Due to the likelihood of undiagnosed PJIs,[2,6–8] the exact number of PJI-related revisions is unclear. Importantly, however, known PJI-related revisions are more costly and time consuming than others, and increase the probability of poor prognosis (e.g., limb salvage operations or PJI recurrence).[9–11] Therefore, recognizing the unique biological characteristics of relevant microbial organisms and their infection-causing mechanisms are of utmost importance for both preventing and treating PJIs.

A promising strategy for counteracting the negative effects of bacterial invasion and PJI is a multifaceted approach involving physical, chemical, and biological counter measures tested at multiple spatial scales both ex vivo and in vivo. The increasing occurrence of antibiotic resistance has raised awareness that each bacterial taxon may need a specifically catered formula for diagnosis, treatment, and long-term eradication. Further complicating this issue is the potential for concerted attacks by multiple types of bacteria (i.e., polymicrobial infections). More patients and the continued over-prescription of antibiotics can accelerate the rapid evolution of antibiotic-resistant bacteria and increase the potential for PJI complications with limited treatment solutions. In this review, we examine the taxa most responsible for orthopaedic PJIs, explore key mechanisms of implant PJI, and propose novel strategies to reduce the risk of PJI.

Etiology of Prosthetic Joint Infections

The etiologies of PJI in the hip and knee are similar: *Staphylococcus* is the most prevalent causative agent, accounting for more than half of all cases (Table 1). Surprisingly, *S. aureus* is widely known to be very pathogenic,[12] but only causes about half of *Staphylococcus*-related PJIs. Others are caused by coagulase-negative *Staphylococcus* (CoNS), which includes several species: *S. haemolyticus, S. capitis*, and *S. hominis*, and most commonly *S. epidermidis*.[13] A key mechanism of action for *Staphylococcus*-related PJIs is the formation of biofilms.

In addition to *Staphylococcus*, many PJI-causing bacteria can form biofilms, which are particularly resistant to treatments[14] because they often require genus-specific modes of eradication.[15] Although biofilm structures vary, multiple species can coexist within one biofilm, which facilitates conjugation and could confer antibiotic resistance.[16,17] Adding to this complexity, the extracellular polymeric substance of biofilms is largely composed of polysaccharides that encapsulate bacterial colonies,[18] filter antimicrobial chemicals, prevent antibiotic perfusion, and limit pharmaceutical efficacy.[19] Further, within a biofilm, bacteria can communicate via quorum sensing, which has been shown to regulate the expression of

genes involved in virulence and dispersal.[19] Quorum sensing, which controls gene expression in response to fluctuations in the density of microbial populations, has also been observed to promote DNA transformation.[20] The latter not only elevates the potential for antibiotic resistance, but also provides a mechanism for the rapid evolution of harmful polymicrobial communities.

Among PJIs, polymicrobial infections occur in approximately, 7–17% of cases overall (Table 1) and are often most difficult to treat. Strikingly, though, Benito et al.[15] reported a fivefold increase in the yearly occurrence of polymicrobial infections from 7.1 to 41.7% over a period of 6 years from 2004 to 2010, and an equally alarming increase in the yearly proportion of infections caused by gram-negative bacteria (21.4–66.7% over the same period). Of these, Enterobacteriaceae are challenging because they resist a wide range of antibiotics.[21,22] making staged eradications less effective (Table 1). PJIs can occur at different times throughout the lifetime of an implant, and therefore, mitigation strategies need to consider temporality: Early (<3 m), delayed (3m-2y), and late (>3y).[23] Early PJIs occur as a result of direct perioperative inoculation (either at the time of surgery or within 2–4 days of surgery), and according to the results presented by Benito et al.[15] includes all polymicrobial infections. Delayed PJIs can be caused by perioperative inoculation of a less virulent bacterium, or a blood-borne (hematogenous) source. Late onset PJIs are more commonly caused by a remote infection (possibly due to an unrelated injury) that leads to hematogenous seeding of the implant surface or joint space by harmful bacteria.[23] Remarkably, the species or strain(s) involved in a PJI may vary by time since surgery. For example, early and late PJIs are typically caused by virulent species (e.g., *S. aureus*), while delayed onset PJIs are caused by less virulent species that take longer to manifest (e.g., CoNS).[23] Regardless of the timing of a PJI, treatment options generally follow the same algorithm, which results in the removal of an otherwise functional prosthesis.[14]

Some revisions labeled as “aseptic loosening” may instead be caused by undiagnosed, low-grade PJIs.[2] Limited diagnostic techniques contribute to widely varying estimates of aseptic loosening rates;[6] some reports state PJI as the cause of failure in 4–13% of revisions originally diagnosed as aseptic loosening,[7,24] and patterns as high as 72% have been presented for this data mislabeling scenario.[25] PCR methods can detect DNA from CoNS, *Streptococcus*, *Salmonella*, *Propionibacterium*, and *Enterococcus* species in “aseptic loosening” implants.[7] Nevertheless, PCR can be prone to detecting false positives and is unlikely to accurately characterize polymicrobial PJIs.[7] Other factors that could obfuscate a PJI include: biofilms, intracellular infections of peri-implant tissue, or phenotypic reductions of bacterial colony size in situ.[2] Whether undetected PJIs of an implant are primarily responsible for loosening remains the subject of considerable debate,[2] yet the need for preventing bacterial adhesion to orthopaedic implants is crucial for reducing all PJI-related complications.

Bacterial Adhesion to Orthopaedic Implants

According to some researchers, nearly 60% of PJIs occur during implantation procedures by known sources of pathogenic bacteria such as the patient’s skin or a contaminated surgical suite.[26] Suboptimal surgical attire can also have generalizable effects on the prevalence of

surgical wound infections.[27] PJIs begin with bacterial adherence to the implant surface, making necessary an accurate understanding of the specific adhesion mechanisms employed by PJI-causing bacteria to prevent their establishment. Hip and knee implant surfaces are heterogeneous, with each modular component specifically designed to suit a particular function within a joint. For example, the femoral stem and acetabular cup of a hip implant are designed to promote osseointegration, and have therefore been subject to modifications in surface topography and chemistry. In contrast, the necks, liners and femoral heads of implants have a smooth composition designed to reduce friction between intercalating components.

Any prosthetic component is susceptible to microbial colonization, which can lead to full-onset PJI. One study, for example, found no significant difference in the preference of bacteria between knee and hip implant components,[28] possibly due to the heterogeneous adhesion abilities of different species of bacteria. Others found that acetabular cups and polyethylene liners were most commonly infected.[29,30] Although these studies demonstrated that all components of knee and hip implants can become infected, they did not address the divergent behaviors among multiple species of bacteria. This is due, at least in part, to the fact that multiple components can become infected simultaneously or asynchronously, which can be difficult to measure in vivo. Further complicating this issue is the observation that different species of bacteria may better infect specific implant components creating a heterogeneous surface mosaic of infected sites. This is evidenced by an apparent strong preference of *S. epidermidis* for polyethylene liners,[30] which is likely due to an adhesion mechanism that increases substrate suitability.

Causative agents of PJI have a diverse arsenal of adherence mechanisms. For adherence to an inert surface, non-specific adhesion is governed primarily by molecular chemistry (e.g., van der Waals, Lewis acid/base, electrostatic, and hydrophobic forces).[31–34] Some researchers postulate that non-specific adhesion between a microbe and its substrate can only be explained by the combined interaction of both weak (van der Waals) and stronger (electrostatic) forces.[32,34,35] Lewis acid/base forces, caused by the coupling between electron-accepting and -donating molecules, drive the potential for adherence. Therefore, on a Lewis acidic surface that has electron-accepting potential, bacteria can more readily donate electron-pairs. This was observed in three species of rod-shaped bacteria, whereby the species with highest electron-donating capacity had greatest attachment success.[32] Similarly, the charge differential (electrostatic force) between a bacterium and surface can heavily influence adhesion potential.[33] Thewes et al.[31] suggested that hydrophobic interactions are the most important predictor of unspecific *Staphylococcus* adhesion. Using single cell force spectroscopy, an attraction between hydrophobic surface and bacteria was measurable to a distance of 50 nm, while hydrophilic surfaces resulted in only weak bacterial adhesion. These results suggest that the cell wall-bound proteins of *Staphylococcus* have high affinities for hydrophobic surfaces,[31] but the responsible proteins have yet to be identified within this context. Variables such as surface proteins and overall cell wall charge vary greatly by bacterial taxon.[36] A greater understanding of such surface proteins (and other key structural constituents) are important to consider when examining specific binding profiles, and identifying strategies for preventing bacterial adhesion to orthopaedic implants.

Pili (aka. fimbriae) are cell-bound elongated structures with many functions, such as an adhesin for gram-negative bacteria.[19,37] Type I and Type IV pili are each critically important for the abiotic surface adherence of *Escherichia coli*[38,39] and *Pseudomonas aeruginosa*,[40] respectively. Most essential though is the role of curli fibers in *E. coli* adherence.[41,42] Of note, certain laboratory strains of *E. coli* could not adhere to abiotic surfaces, but continuous culture led to mutants that could adhere.[43] In this way, curli become a requirement for *E. coli* adhesion to abiotic surfaces.[44] More recently, Mauclaire et al.[45] proposed curli-mediated adhesion as the reason *E. coli* formed more extensive biofilms than *S. aureus*. The presence of curli may allow *E. coli* to overcome repulsive charge differentials between cell and surface to facilitate adhesion.[46] Anatomical structures of bacteria, such as pili and curli, which have evolved to improve their survival and reproduction, are not only important for understanding cell behavior, but also for focused attempts at preventing their adhesion to prosthetic biomaterials in clinical orthopaedic settings.

Curiously, the main causative agents of PJI: *S. aureus* and *S. epidermidis* do not have anatomic protrusions for mechanistic attachment. Instead, the cell wall enzyme *AltE* increases hydrophobicity of *S. epidermidis*, while *S. aureus* has teichoic acids that influence cell charge and accommodate adhesion.[47,48] *Staphylococcus* cell wall-anchored proteins also serve an important role in abiotic adherence,[49] which commonly feature positively charged amino acid residues, hydrophobic extracellular domains, and functional adhesins that result from exposed ligand-binding domains.[12] Chemical interactions (outlined above) are the primary forces modulating key proteins under abiotic conditions, making necessary ex vivo experimentation and implant optimization within this context to understand virulence factors that should be manipulated to attenuate PJIs.

The immune response is activated in PJI, which does not clear the infection, but is deleterious in the joint environment. One reason for this pattern is that toxins secreted by *S. aureus* and other pathogens may diminish the immune response. It has been well-established that *S. aureus* biofilms can impair immune responses in recipients of implants, at least in part by preventing the destruction of microbes by macrophages. Phenotypic analysis of *S. aureus* isolated from musculoskeletal infections indicates differences in virulence[50] and that *S. aureus* may already reside endogenously in many patients prior to PJI occurrence.[51] Therefore, there is considerable interest in the development of vaccines that could specifically neutralize the virulence of common PJI-causing bacteria, such as *S. aureus*, to mitigate joint infection rates.[52] Recent studies have elucidated potential mechanisms in *S. aureus* biofilms that alter macrophage activity through microbial toxins that disrupt immune responses.[53] Accurate identification and characterization of PJI-causing bacteria, including additional insights into virulence factors, will ultimately improve patient-specific treatment strategies.

Among many virulence factors (e.g., evasion or suppression of the host immune response) employed by PJI-causing bacteria, adhesins allow for their survival and persistence within the joint by facilitating attachment to prosthetic materials.[54] Once a prosthesis is implanted, autogenous host fluids are quickly adsorbed,[12,36,49,55,56] which generates a conditioning film (e.g., albumin, fibronectin, fibrinogen, laminin).[18] However, bacteria have other virulence factors that effectively regulate adhesion to conditioning films.[36,49,55] For

example, *S. aureus* and *S. epidermidis* adhesins specifically bind to microbial surface component recognizing adhesive matrix molecules (MSCRAMMs); a class of molecules with similar protein structures and ligand binding mechanisms.[49,57] Although named for attachment to the host extracellular matrix, their functions also include binding to conditioning films[49,57] via fibronectin binding proteins, collagen adhesins, clumping factors, and bone sialoprotein binding protein.[58–63] Importantly, virulence factors can interfere with host cell activity, accelerate or delay PJI formation, and make treatment strategies susceptible to failure or misdiagnosis.[54,64]

Protein adsorption onto biomaterials may further facilitate bacterial binding in a positive feedback fashion, because denaturation exposes additional binding sites.[36] The presence of specific MSCRAMMs varies among species and strains, as seen in a study involving more than 200 PJI-related isolates of *S. aureus*.[55] Fibronectin binding proteins appear crucial for *S. aureus* implant adherence as one study reported that all isolates carried at least one form of fibronectin binding protein.[65] This observation was supported by Arciola et al.,[66] who showed an even higher prevalence of fibronectin binding proteins among *S. aureus* isolated from PJIs of the hip and knee.[66] Fibronectin binding is not exclusive to *Staphylococcus*, because curli also have this ability.[41,67–69] Notably, glycoproteins present in the bloodstream can also be used by mannose-binding fimbria (e.g., *E. coli* and *P. aeruginosa* possess these structures) can also bind to conditioning films.[41,70] As outlined, virulent bacteria have multiple strategies for adhering to biomaterials, such as orthopaedic implants, and therefore require a multifaceted approach to preventing their attachment and progression into a PJI.

Current Methods for Preventing PJI

Recent efforts to reduce prosthetic joint infections include increased surgical suite sterility, and improved antibiotic prophylaxis.[71,72] Prophylactic antibiotics used in hip and knee reconstructions target gram-positive PJIs,[71] which may selectively favor gram-negative PJIs. Irrigating wounds with a broad-range antimicrobial, such as Betadine, are effective at reducing PJI rates,[73,74] and widely used due to cost efficiency and availability.[73] However, further strategies to diminish the evolutionary capacity of bacteria need to be investigated and delivered to the exact site of PJI establishment. In particular, the implant itself should counteract PJI induction. Biomaterial manufacturing techniques have promoted research into optimizing topographies for osseointegration,[75] but such modifications could also promote bacterial colonization. By combining approaches that negate bacterial attachment and/or kill bacteria upon contact, antimicrobial orthopaedic implants have emerged (Table 2).

Topographic Factors

Highly porous metal implants promote osseointegration,[76] in part, by allowing diffusion of gases and nutrients, while providing attachment sites for bone forming host cells.[77] However, pores are associated with increased surface roughness and higher surface areas, which may increase bacterial attachment.[33,76–78] Topography-oriented antibacterial attachment strategies should consider the pore size and orientation of biomaterials,[79] as well as micro- and macroporous features. For example, abiotic- and fibronectin-mediated adhesion are reduced by shear stress,[80,81] such that the macroporous structure of some implant interfaces could shield pathogens from the natural flow of host body fluids, thereby

promoting PJIs. Braem et al.[82] found that implant surface roughness improves bacterial attachment, while surface hydrophilicity hinders it. Thus, engineering hydrodynamic porous implants may help retain the benefits of both improved osseointegration and resistance to bacterial adherence.

Macroscale Features

Modifications to implant surface topography can prevent bacteria from adhering, but are difficult to customize because of bacterial adhesin diversity. Anti-adhesive techniques tested in vitro have proven effective against aerial bacteria transmission or temporary breaches of surgical suite sterility.[83] As an example, Ti naturally forms a thin titanium dioxide (TiO_2) layer when exposed to air,[84] and has an antibacterial effect from reactive oxygen species.[85] An increase in reactive oxygen species activity may also be achieved by exposing materials to UV light,[85,86] which kills both gram-positive and gram-negative bacteria. The TiO_2 layer can also be thickened through chemical or electrolytic oxidation,[87,88] allowing physical pliability of nanotopographic features and direct delivery of antibacterial agents.[89–91] When used in combination with physical and chemical modifications to macroscale surface features, changes to the nanoscale topography should have a compounded resistance to PJIs.

Nanoscale Topography

Smaller scale features are also relevant to bacterial adhesion, as smooth surfaces can provide suitable substrates for many species. Indeed, Mitik-Dineva et al.[92] experimented with glass surfaces: one with features >14 nm, and another that was 70% smoother, and showed 3× more bacterial adhesion on the smoother surface.[92] To circumvent the challenge of modifying nanoscale surface features without causing cytotoxic changes,[93] Lorenzetti et al.[94] used TiO_2 coatings to reduce bacterial adhesion by reducing available surface area.[94] Similarly, Variola et al.[90] modified Ti pores by oxidative “nanopatterning” and caused a dramatic decrease in the adhesion of both *S. aureus* and *E. coli*.[90] Such nanoscale surface modifications to metal orthopaedic implants will continue to increase options for preventing bacterial adherence, particularly when used to leverage the inherent antimicrobial properties of some metals (and metal oxides).

Intrinsic Properties of Metal

Some metal ions have intrinsic antibacterial properties. For example, Burghardt et al.[95] found that copper (Cu) ions were effective at removing planktonic *S. aureus* and biofilms, but also killed mesenchymal stem cells.[95] Alternatively, silver (Ag) has a broad range of activity that includes some antibiotic resistant bacteria.[91,96] Although effective at preventing PJI, early experiments with Ag ions also encountered cytotoxicity-related complications.[97] Of note, Ag-coated external fixation screws caused elevated levels of Ag in human serum,[97] emphasizing the importance of controlled release. While manipulating $AgNO_3$ concentrations, Zhao et al.[91] used Ti nanotubes to deliver Ag nanoparticles and kill planktonic bacteria for 30 days. To address the potential trade-off between antibacterial activity and osseointegration, sol-gel methods were used to produce a hydroxyapatite-Ag coating, which increased antibacterial activity against *S. aureus* and *S. epidermidis* without detriment to bone growth.[98] Although provocative, the inherent antimicrobial properties of

metals need to be further investigated and optimized to avoid damage to host cells and tissues.

Localized Delivery Vehicles

In response to the widespread use of antibiotic-loaded bone cement, researchers have examined this method of administering antibiotics directly to the site of implantation.[99–101] However, drug delivery is inefficient (e.g., only 20% release), temperature sensitive (exothermic reaction of curing cement), and limited to cemented implant systems.[102] In contrast, cementless porous metal implants are suited to loading with antibiotic microspheres capable of controlled drug release. Ambrose et al.[99] demonstrated this using a rabbit model; gentamicin-impregnated microspheres were loaded into porous implants and completely prevented *S. aureus* infection without negatively influencing osseointegration.[99] This technique is efficacious and applicable to any implant material with pore diameters >20 μm. However, for implant components that are meant to be smooth (e.g., acetabular cup liners), microsphere delivery of antibiotics is not suitable. A possible alternative antibiotic strategy for smooth implants and other surfaces unfitting for localized delivery would be tethering them with antibiotics directly.

Antibiotic Tethering

Antibiotics can be immobilized and covalently tethered to an implant surface, thus remaining stable indefinitely at high concentrations.[103] Antoci et al.[100] examined the use of vancomycin tethered to Ti surfaces and revealed that exposed concentrations of *S. epidermidis* were much higher than would be encountered in situ, yet colonization was significantly reduced, even in the presence of serum proteins (e.g., fibronectin). Also promising was that after 8 weeks, antibiotic resistance was not detected. Although an exciting PJI-reduction strategy, this technique lacks effectiveness against *E. coli* (and likely other gram-negative bacteria),[100] and is limited to stable membrane-disrupting agents. But as a key component of temporal mitigation strategies that may specifically reduce the potential for long-term hematogenous PJIs, the tethering of antibiotics holds great potential, particularly in combination with broad-acting hydrogels adept at controlled release.

Hydrogels

As a way to broaden the activity range of antimicrobial treatments, hydrogels have the capability of delivering combinations of multiple antibiotics to the implant site. The basic principle is to coat the entire implant in a quickly resorbable hydrogel that administers a local antibiotic cocktail, eliminating early bacterial colonization. The advantages of the procedure are: customizable antibiotic selection, maintained dosages above minimum inhibitory concentration, application to implants that are already in use, and resorption of the hydrogel without impediment to osseointegration.[104] Although impregnation is effective, the overuse of antibiotics may further exacerbate antibiotic resistant PJIs (e.g., Enterobacteriaceae), as for the commonly used *Carbapenem*.[21,105,106] Furthermore, polymicrobial PJIs are more difficult to treat using hydrogels because drug-resistance is conferred in situ from one species to another via horizontal gene transfer.[105] A strategy that minimizes horizontal gene transfer would prevent the future generation of drug-resistance, while broad-spectrum antimicrobials will diminish the overall number of PJI occurrences.

Broad-Spectrum Antimicrobials

Considering the limitations of specific antibiotics, broad-spectrum antimicrobials such as N, N dodecyl, methyl-polyethylenimine (NNDMP), chitosan, and *Gendine* are becoming more relevant. Schaer et al.[107] used in vitro models to demonstrate the inhibition of biofilms, and treated sheep with NNDMP-coated fracture plates to validate bone healing and antimicrobial activity after inoculation with *S. aureus*.[107] Similarly, Chua et al.[108] combined chitosan with arginine-glycine-aspartic acid to increase antimicrobial activity, promote osteoblast proliferation, and minimize detrimental effects on host bone.[108] Coating implants with the aseptic dye *Gendine* also has broad range antimicrobial effects,[109] and inhibits *S. aureus* adherence in vivo.[110] Broad-spectrum antimicrobials are generally favorable because they are effective against both gram-positive and gram-negative bacteria, yet the mechanical delivery of superficial coating materials may require additional engineering to ensure adequate delivery to the implant-bone interface and localized retention within the site(s) of PJI establishment.

Mechanical Considerations

Beyond considerations for anti-microbial properties and/or strategies that promote osseointegration, it is important to note that implant coatings used to achieve this (whether biological or inorganic) may need to withstand significant mechanical forces during surgical insertion. Long-term or short-term losses of common coatings (e.g.,[111]) caused by shear forces and/or physical abrasion of the implant could compromise the desired delivery of antibiotics or cell-based enhancements. It is to be anticipated that infection-protective surface layers on implants will not entirely delaminate during surgery or that solutions could be engineered to minimize loss of such coatings.

CONCLUSION

PJIs are not only costly, but potentially devastating to a patients' joint function. The main challenges with treating PJIs are related to the taxonomic diversity of causative bacteria, and the increasing prevalence of polymicrobial and antibiotic-resistant bacteria. Suboptimal antibiotic delivery strategies can negatively affect patient host cells, reduce osseointegration, and compound the problem of diminished joint functionality. Nevertheless, some approaches have led to encouraging results, such as whole-implant coating with a generalized antibacterial. Antibiotic coating materials, which target a specific taxon of bacteria or implant component, will also continue to prove necessary. Ultimately, future strategies for preventing PJIs will require multifaceted and multidisciplinary approaches that leverage advanced physical and chemical techniques to both disrupt bacterial attachment, and kill bacteria by contact over short, intermediate and extended time scales (Fig. 1). Information obtained by ex vivo experimentation should be used to direct in vivo eradications of the most common and harmful bacteria species by exploiting their individual vulnerabilities. Customized, patient-based strategies that prevent PJIs will not only reduce the need for costly revision arthroplasty, but also will result in fewer patients that lose mobility.

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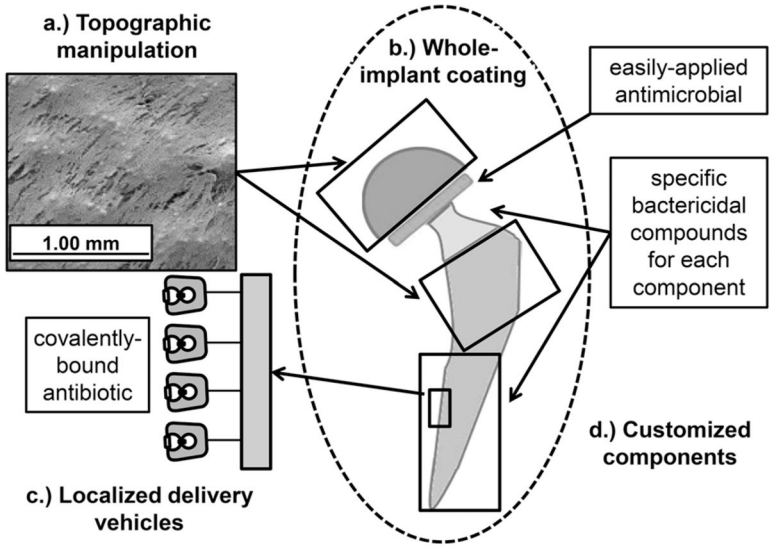

Figure 1.

Conceptual schematic of a hip implant depicting multiple strategies that could be used in combination for the prevention of prosthetic joint infections. The strategies illustrated are: (a) topographic manipulations to improve osseointegration and minimize bacterial adhesion (e.g., scanning electron microscopy shows a porous implant surface covered by osteoblast-like mesenchymal cells), (b) whole implant coating with a generalized antibiotic (e.g., N,N-dodecyl methyl polyethylenimine), (c) localized antibiotic delivery vehicles (e.g., tethering implant surface with covalently bound antibacterial agents), and (d) customized components (e.g., specific antibiotic method designed for each implant component) to reduce susceptibility to PJIs.

Table 1

Examples of Organisms Commonly Detected in Prosthetic Joint Infections of the Hip and Knee (by Percentage of Isolated Samples Within Each Study)

Reference	66	112	113	114	15	22
Cohort timeframe	2000–03	1999–06	2001–06	10 studies	2004–10	2013–14
Number of patients	699	147	63	—	109	—
Staphylococcus sp.	76%	53%	65%	50%	60%	66%
Pseudomonas sp.	7%	5%	2%	—	11%	2%
Enterococcus sp.	5%	6%	5%	3%	11%	6%
Streptococcus sp.	2%	7%	11%	8%	—	4%
Enterobacteriaceae	8%	18%	11% gram (−)	10% gram (−)	36% gram (−)	17%
Polymicrobial	—	—	7%	16%	17%	—

Table 2

Strategies to Prevent Prosthetic Joint Infections by Improving the Antimicrobial Surface Properties of Titanium-Based Orthopaedic Implant Materials

Method	Organism(s)	Antibacterial	System	Observation(s)	Ref
Oxidative nanopatterning of Ti	MRSA, *Candida albicans*	Surface topography	in vitro	*S. aureus* adhesion reduced; *C. albicans* aggregations reduced	90
Antibiotic impregnated microspheres	*S. aureus*	Tobramycin	in vivo	Total absence of infection; no effect on bone ingrowth	99
Covalently tethered vancomycin	*S. epidermidis*	Vancomycin	in vitro	Prevention of colonization and biofilm formation	100
Antiseptic dye coating	*S. aureus*	Gendine (chlorhexidine)	in vitro	Total prevention of bacterial adherence	110
Galvanic Cu deposition	*S. aureus*	Inactivate catabolic pathways	in vitro	Total clearing of adherent bacteria	95
HA-chitosan polyelectrolyte with RGD	*S. aureus*	Chitosan	in vitro	Adhesion reduced by 80% for 21 days	108
Antibiotic loaded hydrogel coating	*S. aureus, S. epidermidis*	Various antibiotics	in vitro	Inhibition of biofilm and planktonic growth	104
UV irradiation	*S. aureus, S. epidermidis*	Spontaneous wettability	in vitro	Bacteria adhere, not firmly attached	85
UV C irradiation	*S. aureus, S. epidermidis*	Increased ROS	in vitro	Bacteria killed for 60 min after UV treatment	86
Zn TiO_2	*E. coli, S. aureus*	ZnO mediated ROS	in vitro	Inhibition attachment	115
Zn-implanted Ti	*E. coli, S. aureus*	Zn ions	in vitro	Partial antibacterial effect; *E. coli* more inhibited than *S. aureus*	116
Alkali treatment	*S. aureus, E. coli*	Nanoroughness, increase local pH	in vitro	Bacteriostatic effect, reduced proliferation	117
Ag coating	*Staphylococcus sp., Bacillus sp., Enterococcus sp., Corneybacterium*	Ag ions	in vivo	Reduced infection rate	97
Material painting of N,N-dodecyl, methyl-PEI coating	*S. aureus*	Immobilized hydrophobic polycationic chains	both	Total absence of infection	107
Superhydrophobic TiO_2 nanotube	*S. aureus*	Superhydrophobic surface	in vitro	Reduced adhesion	118
Mesoporous TiO_2 coating	*E. coli*	Cephalothin controlled release	in vitro	All bacteria killed on contact	119
Photocatalytic TiO_2 layer	*S. aureus, S. epidermidis, P. aeruginosa*	Increased ROS	in vitro	Antibacterial effect after 60 min UV treatment	120
Silk Sericin surface	*S. aureus, S. epidermidis*	Silk sericin	in vitro	Reduced adhesion	121
Ag-doped TiO_2 nanotube	*S. aureus*	Ag ions	in vitro	Planktonic clearing, reduced adhesion	91