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New Developments and Future Challenges in Prevention, Diagnosis, and Treatment of Prosthetic Joint Infection

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Abstract

Prosthetic joint infection (PJI) is a devastating complication that results in substantial costs to society and patient morbidity. Advancements in our knowledge of this condition have focused on prevention, diagnosis, and treatment, in order to reduce rates of PJI and improve patient outcomes. Preventive measures such as optimization of patient comorbidities, and perioperative antibiotic usage are intensive areas of current clinical research to reduce the rate of PJI. Improved diagnostic tests such as synovial fluid α-defensin ELISA, and nucleic acid-based tests for serum, synovial fluid, and tissue cultures, have improved diagnostic accuracy and organism identification. Increasing the diversity of available antibiotic therapy, immunotherapy, and alternative implant coatings remain promising treatments to improve infection eradication in the setting of PJI.

Keywords

Prosthetic joint infection; osteomyelitis; total joint replacement; revision total joint replacement

Introduction

Prosthetic joint infection (PJI) is a devastating complication that results in substantial costs to society and patient morbidity.[1] Despite being the focus of research efforts for many years, treatment failure of PJI remains high with failures rates up to 50%.[2-4] Current advancements in knowledge have focused on prevention, diagnosis, and treatment to reduce rates of PJI and improve patient outcomes. Preventive measures such as optimization of patient comorbidities, and perioperative antibiotic usage currently generate significant research interest and controversy[5-9]. Diagnosis of PJI remains challenging in certain cases due to false-negative cultures, non-diagnostic laboratory tests, and heterogeneous patient presentation[10-13]. Improved synovial fluid diagnostic tests such as α-defensins and nucleic

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acid-based tests for serum, synovial fluid, and tissue cultures attempt to improve diagnostic accuracy and organism identification in PJI[14-19]. Lastly, treatment outcomes remain poor in PJI. Increasing the diversity of available antibiotic therapy, immunotherapy, and alternative implant coatings remain promising treatments to improve infection eradication in the setting of PJI[19-23]. In this review, we will focus on recent advancements in the prevention, diagnosis, and treatment of PJI.

New Advancements in Prevention of PJI

Patient-specific risk optimization

In recent years, preoperative optimization of medical comorbidities has received substantial research attention. Several modifiable risk factors have been independently correlated with the development of PJI, and large database and registry data have attempted to define the risk correlated with each factor (Table 1).[5,6,24-43] The optimization of modifiable risk factors remains important in prevention efforts for PJI; however, significant controversies still exist regarding the best diagnosis and treatment strategies (Table 1).

The most important considerations for patient optimization are: 1) whether modification actually reduces perioperative risk, and 2) whether these risk factors can be successfully modified without reducing access to care. For example, morbid obesity, or a body mass index (BMI) greater than 40 (or 35 with obesity related health conditions), has been identified as an independent risk factor for PJI with a positive association with infection risk as BMI increases.[44] This has led to some hospitals rationing care by restricting candidacy for total joint arthroplasty (TJA) to patients with BMI less than 35-40. Unfortunately, many obese patients don't develop a PJI, and would otherwise benefit from surgery, making it difficult to identify the highest risk patients in this cohort. Other methods to define risk are needed; for example, anthropometric indices of adiposity, such as the thickness of subcutaneous fat, may be more reliable predictors of risk in obesity than BMI.[28] A similar rationing of care is taking place regarding risk factors such as perioperative glucose control and tobacco use (Table 1). Preoperatively predicting perioperative glucose control remains challenging, however, and the validity of using hemoglobin A1c, which measures a collective 90-days of serum glucose control, as a surrogate measure has recently been questioned.[29-31] Alternative tests such as perioperative serum glucose levels and fructosamine have been described as more sensitive measures of perioperative glucose control, and have demonstrated promise in preoperative screening for high risk patients.[32,33]. Multidisciplinary preoperative patient optimization strategies, such as the Perioperative Orthopedic Surgical Home model, as recently described by Kim et al., attempts to coordinate risk factor optimization amongst nutritional, medical and surgical specialists and may improve upon these optimization strategies.[45,46] Further studies are needed to define the best methods to balance risk factor modification with access to care.

Perioperative Antibiotic Usage

Perioperative antibiotic usage is a proven strategy to reduce rates of PJI, and is routinely implemented as a part of existing national guidelines from the Center for Disease Control (CDC). Optimal antibiotic selection and dosages specifically for TJA, however, remain

controversial. For instance, a recent large database study noted a 32% higher risk of PJI when non-cephalosporin antibiotics such as vancomycin were used for preoperative prophylaxis.[7,47,48] This may be due to issues such as weight-based underdosage or improper administration protocols.[48] Another controversial topic regarding perioperative antibiotic prophylaxis in TJA is the use of single versus multiple perioperative doses. The revised CDC guidelines in 2017 recommended against 24 hours of perioperative antibiotics in favor of a single perioperative dose.[49] A recent meta-analysis and systematic review showed that single versus multiple doses of perioperative antibiotics does not seem to affect rates of PJI after TJA, however, the level of evidence supporting a single dose was low, and active randomized controlled trials will provide better guidance on these recommendations in the TJA population.[50]

Other prevention strategies have focused on the administration of local antibiotics during TJA. Unfortunately, this strategy has not proven effective in practice. The routine use of antibiotic loaded bone cement (ALBC) for cemented primary hip and knee arthroplasty is controversial, and it has not shown consistent efficacy or cost effectiveness in large scale studies to justify routine use in the United States.[8,9,51] Local administration of vancomycin powder may be effective in reducing PJI rates after complex spine surgery; however, low-quality data has demonstrated there may only be a slight decrease in PJI risk when used preventatively in TJA and may increase rates of wound seroma.[52-54] Intraoperative antiseptic prophylactic irrigation solutions have become more popular in the past decade. Recent large-scale studies have shown some benefit in the use of povidone-iodine solutions in infection prophylaxis prior to aseptic revision and primary TJA, however, it has not been consistent across all studies.[56-58] Other irrigants such as chlorhexidine-gluconate have not been shown to improve infection rates, when compared with current antisepsis protocols.[59]

Another alternative antibiotic administration strategy that has generated interest is post-operative extended antibiotic prophylaxis, particularly in high-risk patients. Inabathula et al. published a retrospective cohort study comparing an extended oral antibiotic protocol for 7 days to standard perioperative antibiotic administration following elective TJA in groups of patients with high risk comorbidities.[60] They found significantly reduced rates of PJI using this protocol with a 1% infection rate in the extended antibiotic group versus 2.2% in the perioperative administered group alone.[60] While this is promising data, others have been critical of the methodology, and the potential global health impact of widespread adoption of these protocols needs to be balanced with maintaining appropriate antibiotic stewardship.[61]

New Advancements in Diagnosis of PJI

Serum-based Markers for PJI Diagnosis

Reliable identification of PJI typically involves invasive procedures such as joint aspiration or intra-operative tissue sampling. The use of blood-based biomarkers for diagnosis is advantageous as it: 1) can provide an organism-specific diagnosis without the need for tissue culture, 2) minimally-invasive, 3) easy to administer, and 4) less time-consuming. Table 2 provides a summary of recent promising diagnostic markers for PJI. Currently, serum inflammatory cell counts and biomarkers such as erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) are measured routinely for diagnosis of PJI.[62] Previous studies

have shown that elevated white blood cell (WBC) is unreliable for identifying PJI with a pooled sensitivity of only 45% with specificity at 87%, and it is not currently recommended for PJI diagnosis.[10,63] Serum-based biomarkers such as CRP and ESR are currently the recommended first-line serum tests for identifying PJI with estimates of sensitivity and specificity at 86% and 72% for ESR and 87% sensitivity and 79% specificity for CRP.[11,64] As diagnostic tools, CRP, and ESR have limitations in monitoring response to treatment, diagnosis in the setting of low virulence organisms, and for those that have systemic inflammatory diseases. Given the limitations of current serum laboratory tests, recent studies have focused on the development of alternative serum biomarkers.

A few studies have explored proinflammatory cytokines produced in response to bacterial infections as potential serum biomarkers for identifying PJI.[63,65,66] Randau et al. observed that serum IL-6 levels were significantly elevated in patients presented with PJI compared to healthy controls and those with aseptic loosening of the implants.[67] A meta-analysis, based on 17 studies involving >700 patients, revealed that serum IL-6 could achieve diagnostic accuracies of 83%, with 72% sensitivity and 89% specificity.[68] Intriguingly, combining serum IL-6 with other serological tests such as CRP can markedly improve PJI diagnostic accuracy.[69,70] Non-cytokine biomarkers such as procalcitonin are also secreted during PJI-induced systemic inflammation, and therefore being explored as a potential biomarker. However, the lack of sensitivity may limit the usefulness of PCT for PJI diagnosis.[71-73] Other serum-based biomarkers such as D-Dimer, TNF-α, intracellular adhesion molecule-1, and lipopolysaccharide-binding protein have shown diagnostic promise[68-71]. Nonetheless, rigorous clinical studies are required to evaluate their clinical utility.

One limitation of the previously described serum biomarkers is that they are not pathogen-specific, which often forces clinicians to prescribe broad empiric antimicrobial agents until tissue samples are surgically obtained and cultured. There has been a recent push to utilize pathogen-specific B cell responses and antibodies as diagnostic and prognostic markers of PJI, particularly *S. aureus* PJI. This pathogen has evolved many strategies to efficiently evade host immune responses to cause chronic PJI.[74,75] Nonetheless, anti-*S. aureus* antibody responses during an infection can be utilized to diagnose *S. aureus* infections. The authors of this review have developed a serum-based multiplex immunoassay for reliably diagnosing *S. aureus* PJI.[76] Utilizing this immunoassay, it was shown that antibody responses against certain *S. aureus* antigens dominate during PJI. Employing *S. Aureus* specific antigens either singly or in combination, this assay was able to achieve a diagnostic accuracy of 89%.[76] Additionally, assessing anti-*S. aureus* antibody titers expressed by a subset of pathogen-specific B cells called “circulating plasmablasts” or antibody secreting cells (ASCs) achieved a greater than 85% diagnostic and prognostic accuracy to follow treatment response in patients with *S. aureus* diabetic foot infections.[77] A recent study by Wood et al. demonstrated the utility of serologic anti-cytotoxin LukAB antibodies for diagnosing orthpaedic *S. aureus* infections in children. Interestingly, the authors observed that serum anti-LukAB antibody titers reliably discriminated children with *S. aureus* infections from uninfected controls with greater than 80% accuracy.[78] Nonetheless, antibody-based diagnostic studies such as ours and others, are still at the proof-of-concept stage.[76-78]

Synovial-fluid Based Markers for PJI Diagnosis

The synovial spaces in joints are the sites where most infections actually occur, and they are consequently particularly apt places for tissue sampling of suspected infections. During an ongoing infection, synovial fluid experiences a drop in viscosity and a massive increase in innate and adaptive immune cells, predominantly polymorphonuclear cells (PMNs). These changes are reflected by other features including: 1) transformation from the normally clear, pale-yellow fluid to one that is dark yellow, and cloudy or opaque; 2) increase in volume; and 3) the presence of inflammatory mediators and anti-inflammatory products secreted by the resident synovial cells and by the infiltrating immune cells. Furthermore, these synovial products are retained in the joint and not diluted by rapid mixing with the plasma because they are constrained by the synovial capsule. Given these dramatic changes in the synovial fluid, many investigators have sought distinctive synovial markers to indicate the presence of an ongoing infection.[12]

Recent studies have attempted to identify unique biomarkers independent of traditional synovial fluid culture or cell count for the diagnosis and prognosis of infection. CRP and D-dimer have been examined for their increase in synovial fluid during ongoing PJI. [13,79] Their performance has generally been good-to-excellent with sensitivities as high as 99%, however, many wonder if they provide the sensitivity needed for identifying low-virulence pathogens such as *S. epidermidis*. In fact, a recent critical examination of the clinical utility of the serum-borne analytes, even in combination with WBC in the synovial fluid, revealed that while the analytic power is quite good, its accuracy remains only about 85% with substantial opportunity for improvement.[12] Other promising synovial fluid biomarkers include PMN derived products such as neutrophil gelatinase-associated lipocalin and α-defensins.

Because the joint becomes heavily populated by PMN during infection, high abundance secretory proteins produced by those cells accumulate in the small volumes of the synovial capsule. One family of polypeptides that have demonstrated diagnostic promise in recent years are α-defensins. Produced primarily by PMN, α-defensins are a set of related low molecular weight polypeptides (called antimicrobial peptides) that have anti-bacterial activity.[14] When used for the diagnosis of PJI in synovial fluid, it achieved sensitivity and specificity of over 90% in the hands of multiple investigators.[14,80-85] In addition, a recently introduced lateral flow immunoassay kit, Synovasure™, is now recommended for rapid analysis (~20 minutes) in the surgical suite, though it was found to be slightly less sensitive. [15,16,85] Leukocyte esterase (LE) is a 168-kDa enzyme also secreted primarily by PMN. Recent reports are very encouraging about the diagnostic power of LE in a conventional immunoassay format that is both sensitive and specific, and in an immunoassay strip format, like Synovasure™, that can be used in the surgical suite and can yield results in 20 minutes, albeit with slightly reduced sensitivity. Another promising synovial fluid biomarker produced by neutrophils is lipocalin-2.[86] A recent study by Vergara et al. showed an 86% sensitivity and 77% specificity to discriminate PJI versus aseptic revision failures.[86] Recently, a third neutrophil-expressed marker protein that has been examined: Calprotectin is a 24-kDa heterodimer that can be as much as 60% of the soluble protein in the cytoplasm of PMN. In one report, calprotectin had greater than 95% specificity and sensitivity in

distinguishing infected from aseptic patients.[87] All three of these biomarkers reflect the high abundance of PMN that enter the synovial space and there is promise for each to be a useful tool alone or in combination with other markers. With this impressive success in the recent past, one cautionary note in regards to low virulence pathogens like *S. epidermidis* or *C. acnes*. There is at least one report which claims that low virulence organisms elicit modest and not readily measurable changes in these assays potentially yielding false negatives.[88] A second concern regards the impact of metallosis from certain implants that can cause false positives in the α-defensin assay. This can be corrected by a complementary marker like synovial CRP, which is typically not elevated in the setting of metallosis even with a positive α-defensin assay.[17]

An alternative approach that demonstrates promise includes nucleic acid-based techniques. Nucleic acid-based approaches such as polymerase chain reaction (PCR) or more recently next generation sequencing (NGS) have offered great hope for rapid and accurate identification of infecting pathogens. At the same time, they raised substantial concerns about the creation of confounding, potentially incorrect diagnostic information.[89] As with culture, pathogens collected from the skin can be problematic contaminants. Possibly more confusing is the potential for residual nucleic acids from dead cells to be collected in the synovial samples taken for analysis[90] Another concern in these nuclei acid-based methods is their potential vulnerability to recent antibiotic use.[18,91] NGS approaches can readily distinguish multiple species but may also be vulnerable to similar contamination issues and further studies are warranted.[19]

Aware of these concerns, several investigators have begun to explore the utility of the following potentially powerful, and reasonably rapid, approaches. One alternative method to DNA-based methods of PCR, which may be complicated by false positive results, is the use of reverse transcriptase PCR (RT-PCR) of bacterial ribosomal RNA[18]. In contrast to DNA, rRNA degrades at the time of cell death, theoretically reducing the rates of false positive results. In support of this theory, a recent examination of SF samples from culture-positive PJI patients showed thatRT-PCR of 16S/28S rRNA genes yielded higher specificity and sensitivity than conventional markers like serum CRP and PMN.[18] Additionally, Two recent papers have reported significant correlation with culture methods in culture positive samples. In addition, these groups have identified potential pathogens in culture negative synovial fluid raising the prospect that nucleic acid testing may be a significant advance in treatment of these culture negative cases in particular. [19,92]

Implant-based Markers for PJI Diagnosis

Microbiological culture from periprosthetic tissue is a necessary step for correct identification of an infecting organism in PJIs. Despite modern diagnostic methods, isolation of the infecting organism in the setting of PJI can be challenging, and approximately 15% are reported as culture negative.[75,93-96] One method to improve upon our current culture techniques includes implant sonication.

Implant sonication describes the process of subjecting an implant material to ultrasonic waves through a buffer fluid to mechanically disrupt intercellular connections. This disruption releases bacterial cells from the implant surface into the fluid medium, while

dissociating large cell aggregates.[97] Following sonication, the fluid can be cultured to diagnose the infecting organism. Since the introduction of implant sonication there have been mixed opinions on the ability for sonicate fluid culture to diagnose infection with more accuracy than periprosthetic tissue culture. Several studies have concluded that sonication alone is superior to periprosthetic tissue culture and especially when culturing in optimal conditions such as blood culture.[98-100] Other studies have shown that tissue culture may be more sensitive than sonicate culture for the diagnosis of PJI.[97,101-103] Ultimately, studies agree that the addition of sonicate culture to classic tissue culture methods may improve the likelihood of identifying the causative organism.[101] Recently, Erivan et al. demonstrated that sonicate fluid recovered the causative organism in 10 patients with PJI, where periprosthetic tissue culture was negative.[97] From these results, the authors suggested that if implant sonication is feasible in a particular clinic, it should be included in the diagnosis workflow as it has superior ability to recover the infecting organism. Alternatively, sonicate fluid can be analyzed using multiplex PCR methods in order to determine the infecting organisms without the need for culture.[104] The addition of molecular diagnosis by PCR may improve the accuracy of sonicate fluid because it has the ability to identify viable and non-viable bacteria as well as decreasing the overall time to diagnose from days to hours.[105] Ultimately, future studies are warranted to achieve consensus on the use of sonication in the clinic.

New Advancements in the Treatment of Musculoskeletal Infection

The failure rate of PJI treatment remains high despite surgical debridement, prosthetic exchange, and targeted systemic antimicrobial agents. Emerging antibiotic resistance, formation of biofilm, and migration of bacteria to immune privileged locations such as the osteocyte lacuna-canalicular network all contribute to the challenge of treating these infections.[106-108] A summary of promising treatment strategies in PJI are shown in Table 3.

Novel Antibiotic Strategies

Systemic antibiotic therapy is a critical aspect to treating PJI, however, increasing bacterial resistance to conventional antimicrobial agents creates significant treatment challenges.[109,110] Over the past decade, novel antibiotics with broad spectrum activity against gram-positive organisms such as daptomycin, which is a cyclic lipopeptide, and linezolid, an oxazolidinone, have been developed to expand treatment options for resistant infections.[111-113] For instance, daptomycin had greater than an 80% treatment success rate for a mix of chronic and acute PJIs in the setting of resistant *Staphylococcal* infection when alternative antibiotics such as vancomycin could not be used due to resistance or patient intolerance.[111] Next generation oxadolidinones or semisynthetic glycopeptides have shown excellent *in vitro* activity against resistant gram-positive infections, while improving upon the oral bioavailability (tedizolid) or half-life (oritavancin, dalbavancin) relative to previous agents, allowing for less frequent dosing periods or use of oral regimens.[20]

The addition of biofilm active agents and antibiotics that target metabolically quiescent bacterial colonies, termed small colony variants are also an important component of treating PJI. The minimum inhibitory concentrations (MIC) that are used as susceptibility tests for cultured bacteria do not reflect the susceptibility of the bacteria within a biofilm, which can

require many fold higher concentrations to achieve the minimum biofilm eradication concentration (MBEC). *In vitro* studies from clinical isolates of *S. aureus* isolated from PJI suggest that rifampin and doxycycline, are among the few common antibiotics with measurable biofilm bactericidal concentrations (90% of *S. aureus* biofilms tested could be killed by rifampin and 50% by doxycycline).[114] These findings are supported by clinical studies that show rifamycin-based antibiotics such as rifampin improve treatment of PJI, however, as a monotherapy, rapid resistance develops, emphasizing the importance of combination antimicrobial therapy in *S. aureus* PJI.[21,115]

The development of novel antibiotic or small molecule delivery systems may be a successful strategy to target biofilm formation and improve infection eradication. Both resorbable and non-resorbable antibiotic carriers such as polymethylmethacrylate (PMMA) or calcium sulfate respectively have been shown to increase local antibiotic concentrations well above MIC values for many different antibiotic combinations in vitro. [116,117] These local delivery systems are frequently used in the setting of PJI; however, there is no strong evidence to support their ability to improve eradication of clinical infection. For example, the use of gentamicin impregnated beads and/or sponges resulted in increased failure after debridement and implant retention for acute PJI with failure rates 40% in the local gentamicin group versus 26% in the control group after propensity matching.[118] Additionally, antibiotic-impregnated calcium sulfate beads did not improve outcomes after debridement and implant retention in acute PJI.[119] Another method of local antibiotic delivery by an intra-articular catheter showed some success in a limited number of patients.[120] Well-controlled studies are still needed to justify the added cost, risk of resistant organisms, and morbidity of additional local antibiotic therapy to treat PJI.

Immunotherapy

Immunotherapy is another major area of interest to improve both the prevention and treatment of PJI. Both active and passive immunization strategies have been attempted in the past to target common PJI associated bacteria. Unfortunately, active immunization strategies focusing on prevention strategies utilizing vaccines to common sources of PJI such as *S. aureus* have not been successful beyond Phase I clinical trials.[121-123] Vaccine strategies targeting components of the cell wall not universally expressed across strains such as poly-N-acetyl glucosamine, LTA acid and capsular polysaccharides have failed to reduce infection in the clinical setting.[121,124] Another vaccine targeting iron-regulated surface determinant system (Isd) B, which is a cell wall-anchored protein that allows iron scavenging from hemoglobin in *S. aureus*, from Merck (V710) showed preclinical promise. However, it failed to reduce infection rates or mortality in a phase 2b/3 trial focused on prevention of *S. aureus* infection after cardiothoracic surgery.[122] Additionally, increased rates of mortality due to sepsis was found in patients who did get infected, suggesting that this vaccine may have been detrimental to host immunity to *S. aureus*.[122] Given these previous failures, newer strategies are utilizing a multi-agent vaccine with three or four *S. aureus* surface/capsular antigens, and these vaccines have shown improved immunogenicity in preclinical and early stage clinical trials in healthy volunteers.[125] Further clinical trials in the setting of infection are needed to assess the efficacy of these approaches. Other approaches for active immunization against *S. aureus* have included targeting other virulence

factors such as alpha-toxin, Panton-Valentine Leukocidin, surface protein A (SpA), and secretory proteins, however, these have not progressed beyond preclinical or early stage healthy human trials.[126,128]

Passive immunization strategies may show more promise than vaccine-based approaches as a complement to systemic antimicrobial therapy in both the treatment and prevention setting, however, these are mostly in preclinical stages of development. For example, monoclonal antibodies (mAb) of the IgG3 class against SpA derived from human hosts are able to bind with high affinity to wild type *S. aureus* SpA even in the presence of other host antibodies, promote opsonization and associated phagocytic clearance, and reduced the rate of septic death in a mouse model of (methicillin resistant *S. aureus*) MRSA bacteremia in combination with vancomycin.[129] Passive immunization can also be used to target components of biofilm, and a mAb against DNA binding proteins from the DNABII family, which have conserved homologs across many bacterial species, reduced both planktonic and adherent biofilm bacteria in a murine implant-associated infection model relative to daptomycin monotherapy alone.[130] A combination of mAb to multiple *S. aureus* antigens has also shown promise in targeting biofilm formation, and mAb to α-toxin and clumping factor A (ClfA) resulted in decreased bacterial load in the periprosthetic tissue, reduced propensity for infection, and less biofilm aggregates in a murine model of hematogenous MRSA infection.[22] Other novel strategies include targeting intracellular reservoirs of *S. aureus*. For example, an antibody-antibiotic conjugate (AAC) that consists of a monoclonal antibody recognizing specific sugars on wall teichoic acids (WTAs) bound to rifamycin class derivative antibiotic has been shown to bind to the surface of *S. aureus*, and then upon opsonization, the proteolytic environment of the phagolysosome of the host cell causes release of the active antibiotic form (Figure 1).[23] This approach was effective in a wide range of host cells including murine and human macrophages, osteoblasts, endothelial and epithelial lining cells.[23] In a murine model of hematogenous MRSA infection, use of the AAC reduced *S. aureus* bacteremia relative to systemic vancomycin alone in both wild type and severe combined immune deficiency spontaneous mutation (SCID) mice.[23] A similar approach showed no toxicity in human phase I clinical trials.[131]

Bacteriophages

Bacteriophages (phage) are naturally occurring viruses that target bacterial cells with high specificity while causing minimal damage to host cells making them promising preclinical agents for treatment of PJI.[132] Phages are able to adhere to the bacterial cell surface, insert its genomic material into the bacterial cell, replicate within the host cell, and lyse the bacterial cell wall resulting in cell death.[132] Importantly, decreased cellular metabolic activity such as seen in small colony variants and biofilm can effectively be targeted and killed by phages in contrast to systemic antimicrobial agents.[133] *In vivo* studies have shown synergism between the use of systemic antimicrobial agents and phage to treat biofilm associated infection in a rat model.[134] Limited early clinical studies have shown that topically applied phages are safe in the setting otitis media and venous leg ulcers, however, no clinical data exists on its use in PJI.[135,136]

Local Implant Treatments

Improving the biofilm resistance of existing implant materials would serve both as primary prevention of PJI and reduce rates of treatment failure. One promising strategy that is used clinically for infection prevention in limited cases are silver-based implant coatings. Silver is one of the oldest antimicrobial agents known, exhibiting anti-bacterial effects to multiple intracellular and cell wall targets resulting in cell death, however, historical concerns about toxicity have limited its clinical use.[137] Recently, silver coated implants have shown promising results in preclinical and limited clinical studies in orthopedic trauma and limb reconstruction.[138-140] A silver coated megaprosthesis reduced rates of postoperative infection (11.8% versus 22.4%), and had improved success after debridement and implant retention relative to titanium implants in a small study.[139] Alternative approaches involving the use of nanoparticle-based delivery systems have attempted to reduce off target effects to surrounding tissues while retaining the antimicrobial activity of the silver ions, and this may be a promising strategy in the future.[141] Chemotherapeutic agents such as cisplatin have shown antibiofilm activity, however, research is limited to the preclinical setting.[142]

Other modifications to the implant surface have not progressed beyond preclinical studies, however, there are some promising strategies. Covalent bonding of an antibiotic to titanium may allow local antibiotic delivery without impairing host cell function or prosthetic osseointegration for both prevention and treatment strategies.[143] Surface modifications that enhance osseointegration of titanium in combination with antibiotic coatings may be another strategy to increase biofilm resistance of existing implants while promoting host cell adhesion in favor of bacterial cell adhesion.[144] Use of antibiotic carriers such as hydrogels or phosphatidylcholine-based materials may allow point of care application of antibiotic eluting implant coatings from the implant surface for both PJI prevention and treatment.[145-147]

Dispersal Agents

Another strategy that targets biofilm directly is the use of dispersal agents. Converting biofilm bacteria to their planktonic form may increase bacterial cell susceptibility to commonly used systemic antibiotics. Some examples that target the matrix components of biofilm include enzymatic treatments such as trypsin, Dispersin B, Lysostaphin, and DNases.[148-150] Additionally, fibrinolytics like streptokinase or nattokinase break down the fibrin matrix within biofilm and decrease the MBEC of available systemic antibiotics.[149,150] Another strategy for triggering biofilm dispersal includes targeting the quorum sensing system.For example, treatment *in vitro* with autoinducing peptide type I (AIP-1), a critical component of the quorum sensing system, was able to trigger dispersal of MRSA on titanium discs.[150] RNAIII-Inhibiting peptide (RIP) is another peptide that targets the quorum sensing system in *S. aureus* by competing with RNAIII-activating peptide (RAP) which results in decreased cell adhesion and *agr* activation and has been investigated to reduce *S. aureus* adhesion to foreign materials.[152] This also remains in the preclinical stages. Other possible local treatments to improve biofilm dispersal include the use of pulsed laser therapy and gold nanoparticles.[153] One major concern about dispersal agents is that planktonic bacteria cells disassembled from their biofilms may be capable of exacerbating systemic infection. Therefore, dispersal agents must be used in combination with systemic therapies

such as antibiotics.[149-151] These treatments remain in the preclinical stages in the treatment of musculoskeletal infection.

Conclusion

In summary, promising prevention strategies include identifying high-risk patients for PJI and the use of the perioperative surgical home to optimize these risks before surgery. Alternative antibiotic strategies such as dual antibiotic therapy for preoperative administration, single versus multiple doses of preoperative antibiotics, the use of local antibiotic treatment such as vancomycin powder are promising, but need to be investigated further especially in high risk patient populations. Diagnostic strategies should focus on increasing the accuracy of synovial fluid- and serum-based tests and providing accurate, organism-specific diagnoses. Promising strategies include α-defensin and nucleic acid-based tests such as rRNA PCR or NGS. Further expansion of existing antibiotic classes such as the next generation oxadolidinones and improving the development of biofilm active agents such as rifampin to target biofilm more effectively is necessary for systemic antibiotic therapy improvements. Novel treatment strategies including immunotherapy, implant-based coatings, and dispersal agents may all improve biofilm treatment and eradication in PJI.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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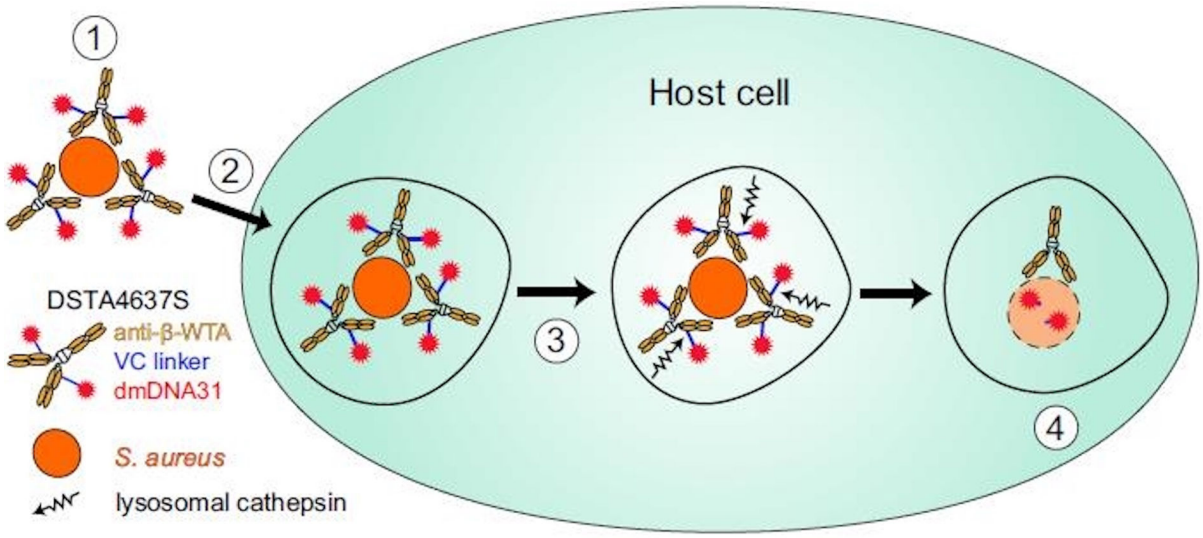

Figure 1. DSTA4637S mechanism for killing intracellular *S. aureus.*

Step 1, DSTA4637S binds *S. aureus.* Step 2, host cells internalize DSTA4637S-bound *S. aureus.* Step 3, fusion occurs with the phagolysosome where lysosomal cathepsins cleave the VC linker, releasing dmDNA31. Step 4, unconjugated dmDNA31 kills the intracellular bacteria. Reproduced with permission from: Peck M, Rothenberg ME, Deng R et al. A Phase 1, Randomized, Single-Ascending-Dose Study To Investigate the Safety, Tolerability, and Pharmacokinetics of DSTA4637S, an Anti-Staphylococcusaureus Thiomab Antibody-Antibiotic Conjugate, in Healthy Volunteers. Antimicrob Agents Chemother. 2019; 63(6). pii: e02588-18.

Table 1.

Summary of recent modifiable risk factors independently correlated with PJI development.

Risk Factor	Risk of Infection (Odds Ratio)[5,6,25-27]	Proposed Interventions	Controversies
Obesity	1.7 – 6.4	BMI cutoffs (>35-40)[5,6,25-27,43] Weight loss/nutrition counseling[39] Bariatric surgery[37,38] Anthropometric indices of adiposity at site of surgery[28]	Weight loss counseling has not been reliably shown to lead to appropriate weight reduction in most patients. Outcomes of bariatric surgery to reduce post-operative complications remains controversial and has not consistently shown decreased perioperative risk. Thickness of subcutaneous fat at surgical site as opposed to body mass index may be more indicative of complication risk. May increase health disparities in TJA. Obesity alone may not be as strong a risk factor as other issues and patients benefit significantly from surgery.
Diabetes Mellitus	1.6 – 6.1	Hemoglobin A1C cutoffs (7.0, 7.5, 8.0) [29-31] Serum fructosamine cut offs (> 292μmol/L)[32] Perioperative serum glucose measurement (> 150-200mg/dl)[33]	Improved perioperative glucose control does seem to improve postoperative outcomes. Low cutoffs < 7.0 may be difficult for patients to achieve. Hemoglobin A1C may not correlate as strongly as other markers of glycemic control.
Active Smoking	1.4 – 3.7	Smoking cessation counseling[34-36] Nicotine replacement products[34-36] Serum cotinine testing[34]	Smoking cessation does improve outcomes after TJA. Hard to monitor compliance. Serum cotinine testing may be useful to improve compliance with smoking cessation recommendations.
Malnutrition	5.0 – 7.0	Laboratory cut off values (albumin cutoffs <3.5 g/dL; total lymphocyte count <1,500 cells/mm^3 ; transferrin level <200 mg/dL)[40-42] Nutritional modification	Need more data on whether this is modifiable or indicative of underlying poor host.

Table 2.

Summary of New Developments in Diagnostic Strategies in PJI.

Tissue Source	Proposed Diagnostic Markers	Limitations
Serum	Interleukin 6[69,70,73] Procalcitonin[71-73] D-dimer[12,13] Tumor necrosis factor – α[69] Intracellular adhesion molecule-1 [70] Lipopolysaccharide-binding protein[70] Blood Antibodies[76-78]	May not improve diagnostic accuracy of existing combination of ESR/CRP and clinical criteria and adds expense. Markers except organism-specific antibody production are not pathogen specific so need further tissue sampling for microbial culture. Serum antibodies may be confounded by pre-exposure to previous infection.
Synovial Fluid	α-defensins[14-16,80-85] Synovial CRP[12,13,81,82] Synovial D-dimer[12,13,82] Leukocyte esterase[12,81] Lipocalin[86] Calprotectin[87]	High sensitivity and specificity as single agents or in combination ranging from 75% - 100% depending on the marker and study. Some available as point-of-care test (Synovasure lateral flow immunoassay kit for α-defensins) False positives can occur such as in the setting of metallosis, and a combination of markers may be better than any single agent alone. False negatives may occur in the setting of low virulence organisms. Not as useful to diagnose persistent infection in the setting of reimplantation surgery.
Periprosthetic Tissue and Implant	RT-PCR of RNA[18,91] NGS[19,92,93] Implant sonication[97-100]	May improve upon tissue or synovial fluid culture in identification of organisms especially in culture-negative settings. May be confounded by contamination from skin or non-infecting microorganisms.

Table 3.

Summary of New Developments in Treatment Strategies.

Treatment Category	Promising Strategies	Examples
Antibiotics	Novel agents with activity against resistant bacteria. Biofilm active agents. Local antibiotic delivery systems	New cyclic lipopeptides (daptomycin), oxazolidinones (tedizolid), or synthetic glycopeptides (oritavancin)[20,111-113]. Rifampin, doxycycline[21,114,115]. Calcium sulfate beads[119], intra-articular catheter[120], PMMA[116,117]
Immunotherapy	Active Immunization (prevention) Passive Immunization (prevention and treatment)	Vaccines targeting cell wall components of *S. aureus* (LTA acid, capsular polysaccharides), cell wall anchored proteins (IsdB), toxins (α-toxin, Panton-Valentine Leukicidin, SpA).[121-128] Monoclonal antibodies to SpA, DNA binding proteins, α-toxin, ClfA.[22,129,130] Antibody-antibiotic conjugates[23,131]
Bacteriophages	Phages targeting biofilm.	Synergism between systemic antibiotics and phages, use against low metabolic persister cells[132-135]
Local Implant Treatments	Silver Antibiotic coatings Chemotherapeutic Agents	Silver coating, nanoparticle-based delivery systems[138-141] Covalent bonding of antibiotic to titanium, antibiotic carriers such as hydrogels or phosphatidylcholine [143-147] Cisplatin, mitomycin C have anti-biofilm activity even in low metabolic cell states[142]
Dispersal	Enzymatic Treatments Fibrinolytics Targeting quorum sensing	Dispersin B, lysostaphin, DNases[148,149] Streptokinase[149,150] Autoinducing peptide type I, RNAIII-inhibiting peptide[149,150,152]