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Novel Approaches to the Diagnosis, Prevention and Treatment of Medical Device-Associated Infections

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Synopsis

The pathogenesis of device-associated infections is related to biofilm bacteria that exhibit distinct characteristics with respect to growth rate, structural features, and protection from host immune mechanisms when compared to planktonic counterparts. Biofilm-associated infections are prevented, diagnosed and treated differently than infections not associated with biofilms. This article reviews innovative concepts for the prevention of biofilm formation, such as use of antisense molecules, quorum-sensing inhibitors, and bacteriophages, and novel approaches for treatment, such as enhancement of antimicrobial activity against biofilm bacteria by use of electric current or ultrasound. Specific approaches for the diagnosis and prevention of catheter-associated urinary tract and bloodstream infections, infections associated with orthopedic implants, and cardiovascular implantable electronic devices, are also discussed.

Keywords

biofilm; medical device; catheter-associated urinary tract infection; catheter-associated bloodstream infection; orthopedic implant infection; cardiovascular implantable electronic device infection

Indwelling devices are increasingly used in many areas of medical practice. The pathogenesis of device-associated infections relates to bacteria that attach to and grow on surfaces in complex communities. Microbial biofilms develop when microorganisms adhere to a surface and produce extracellular polymers that facilitate adhesion and provide a structural matrix. In addition to structural features, such biofilm bacteria exhibit distinct characteristics with respect to growth rate and protection from host immune mechanisms.

Importantly, biofilm bacteria are up to 1000-fold more resistant to antimicrobial agents compared to planktonic bacteria, their free-living counterparts. An altered

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microenvironment, decreased growth rate with persister cells (a protected phenotypic state), antimicrobial destroying enzymes within the matrix, quorum-sensing signaling systems that coordinate biological activity, and up-regulation of stress-response genes are among the proposed mechanisms of reduced antimicrobial susceptibility.¹ Surgical implantation of a foreign body leads to tissue damage and consequently to an inflammatory response that enhances bacterial colonization. Chemical and physical properties of the foreign body also influence bacterial adherence. In addition to the innate antimicrobial resistance associated with the biofilm state, in the highly dense bacterial population within a biofilm, horizontal transfer of antimicrobial resistance genes can occur.

This article reviews innovative concepts for the prevention of biofilm formation, and biofilm-directed therapeutics. The authors also discuss novel approaches for the diagnosis and prevention of catheter-associated urinary tract and bloodstream infections, and infections associated with orthopedic implants and cardiovascular implantable electronic devices (CIEDs).

Prevention of biofilm formation

A novel potential approach to prevent biofilm formation (and consequently device-associated infection) is the use of antisense molecules that silence bacterial genes responsible for virulence.² Due to their chemical stability, peptide nucleic acids are potential therapeutic candidates. Genes encoding bacterial factors responsible for adhesion and biofilm formation are potential targets for an antisense strategy. These include a family of adhesins called Microbial Surface Components Recognizing Matrix Molecules (MSCRAMMs) that mediate bacterial adhesion to biomaterials,³ and the *ica* locus which harbors genes for production of polysaccharide intercellular adhesin, a component of the extracellular matrix of many staphylococcal biofilms.⁴ To date, attempts at silencing adhesin genes have not been successful.

Another prevention strategy is based on interference with bacterial cell-to-cell communication using quorum-sensing inhibitors. A quorum-sensing system in staphylococci consists of the ribonucleic-acid-III-activating peptide (RAP) and its target protein, target of RAP (TRAP).⁵ Staphylococcal virulence is inhibited by RNAIII-inhibiting peptide (RIP), a linear heptapeptide resembling the N-terminal sequence of RAP that acts as an antagonist to TRAP. RIP inhibits the phosphorylation of TRAP, leading to reduced cell adhesion and suppression of toxin synthesis. Evidence also suggests that TRAP is involved in bacterial DNA protection from oxidative stress.⁶ TRAP is conserved among staphylococcal species, hence RIP can theoretically suppress infections caused by any staphylococcal strain, including those resistant to methicillin or vancomycin. Synthetic RIP has been shown to be active in animal models of foreign body-associated infection,⁷⁻⁹ and may have future utility as an alternative or adjunct to antimicrobials.

Bacteriophages are viruses that infect bacteria; they may have a role in controlling biofilm.¹⁰ Bacteriophages may produce polysaccharide depolymerases that can hydrolyze polymeric substances in the biofilm matrix. The effect of bacteriophages on biofilms has been studied *in vitro*.^{11,12} A bacteriophage was engineered to express a biofilm-degrading enzyme and simultaneously attack bacterial cells in the biofilm and the biofilm matrix.¹³ The engineered enzymatic bacteriophage demonstrated greater *in vitro* efficacy than the nonenzymatic bacteriophage against biofilms. Use of bacteriophages to prevent colonization and subsequent infection may be applicable to urinary or intravascular catheters. In an *in vitro* model, pretreatment of hydrogel-coated silicone catheters with a single *Staphylococcus epidermidis* bacteriophage¹⁴ or a cocktail of five *Pseudomonas aeruginosa* bacteriophages¹⁵ reduced biofilm formation.

Enhancement of antimicrobial activity against biofilm bacteria

Electric current (EC) and ultrasound have been used adjunctively to antimicrobial agents to disrupt biofilms and treat infection. The “bioelectric effect” refers to the enhancement of antibacterial activity using EC. The proposed mechanisms include disruption of the biofilm matrix, membrane permeabilization and electrophoretic augmentation of the antimicrobial agent, generation of oxygen as a result of electrolysis, and generation of potentiating oxidants.¹⁶ The authors described an *in vitro* model using biofilm-coated polytetrafluoroethylene coupons exposed to a continuous flow of fresh medium with or without antimicrobial agents and/or EC. A significant effect was found when vancomycin was used against methicillin-resistant *Staphylococcus aureus* (MRSA) biofilms and when daptomycin or erythromycin was used against *S. epidermidis* biofilms.¹⁷ The bioelectric effect was not generalizable across microorganisms and antimicrobial agents. EC was also found to be active against bacterial biofilms when delivered without antimicrobials both *in vitro*¹⁸ and in a rat model of foreign body-associated osteomyelitis,¹⁹ an effect referred to as the “electricidal effect”.

The “bioacoustic effect” refers to the synergistic effect of ultrasound and antimicrobial agents in eradicating microbial biofilms. Simultaneous application of ultrasound and gentamicin to a polyethylene substrate reduced the viability of *P. aeruginosa* biofilms.²⁰ This was done using sufficiently low levels of ultrasonic power that ultrasound by itself did not kill the bacteria. Lower-frequency appears more effective than higher-frequency ultrasound in reducing bacterial viability within biofilms. The effect is also demonstrated in animal models of infection.²¹ Several mechanisms have been proposed to explain the effect. Sonication increases transport of gentamicin across biofilms that normally block or slow antimicrobial transport when not exposed to ultrasound.²² Low-frequency ultrasound increases outer membrane permeability of *P. aeruginosa*,²³ and high-intensity focused ultrasound mechanically disrupts *Escherichia coli* biofilms grown on microscope slides.²⁴

In clinical practice, ultrasound may be applied in combination with antimicrobial-impregnated cement. *E. coli*, *P. aeruginosa*, *S. aureus* and coagulase-negative staphylococci were tested *in vitro* using bone cements loaded with gentamicin or the combination of gentamicin and clindamycin. Application of pulsed ultrasound in combination with antibiotic release from bone cement yielded a reduction of both planktonic and biofilm bacterial viability compared to antibiotic release without application of ultrasound.²⁵ In a small animal study, bone cement discs loaded with gentamicin, on which *E. coli* biofilms were grown, were implanted in rabbits. Application of ultrasound from 24 h to 72 h after surgery resulted in a tendency towards improved efficacy of gentamicin.²⁶ The transducer was fixed to the rabbits using an acoustically conductive adhesive gel. Histopathological examination of skin showed no adverse effect associated with the applied pulsed ultrasound waves. Further data from *in vitro* and animal studies are necessary before applying these novel approaches to humans.

Catheter-associated urinary tract infection

A catheterized patient with symptoms or signs referable to the urinary tract and significant bacteriuria is diagnosed as having a catheter-associated urinary tract infection (UTI). The exact relationship between asymptomatic bacteriuria and UTI remains unclear. Even though treatment of asymptomatic bacteriuria is generally not recommended (except in certain clinical conditions), it is plausible that preventing asymptomatic bacteriuria will decrease the incidence of symptomatic infection in catheterized patients.

Silver has broad-spectrum antimicrobial activity. *In vitro* studies show that coating urinary catheters with silver prevents adherence and growth of bacteria and inhibits biofilm

formation.²⁷ A silver coating may be applied to the external and/or internal surface of a urinary catheter. The addition of hydrogel protects the mucosa and facilitates release of silver ions.²⁸ Hydrogel/silver-alloy catheters are latex- or silicone-based. Silver oxide-coated catheters have been withdrawn from the market. Nitrofurazone-coated urinary catheters are silicone-based. Nitrofurazone is chemically related to nitrofurantoin. A disadvantage of this type of urinary catheter is that nitrofurazone is inactive against some uropathogens (e.g., *P. aeruginosa*). Minocyclin/rifampin-impregnated urinary catheters are not available in the US.

Table 1 summarizes the evidence from randomized and quasi-randomized trials on the efficacy of antimicrobial-coated catheters in preventing asymptomatic bacteriuria during short-term use.^{29,30} The effect size varies among studies and the quality of evidence is considered fair. Data are conflicting with some studies showing efficacy and others showing that silver coating is not effective. No published trial has directly compared different antimicrobial-coated catheters; hence it is unclear which type of catheter is most active. Development of symptomatic UTI, a clinically relevant endpoint, rather than development of bacteriuria, needs to be studied in well-designed, adequately powered, randomized clinical trials. The efficacy of antimicrobial-coated catheters also needs further study in chronically catheterized patients.

Another potential approach to prevent UTI is based on bacterial interference, the antagonism between bacteria during the process of surface colonization. Based on this concept, non-pathogenic organisms are used to compete with virulent bacteria.³¹ In a pilot trial, patients with spinal cord injury and neurogenic bladder requiring indwelling (transurethral or suprapubic) or intermittent catheter drainage were randomized to this experimental treatment *versus* placebo. In 21 patients, the bladder was inoculated with a non-pathogenic strain of *E. coli*. In 7 patients the bladder was inoculated with normal saline. Patients colonized with the non-pathogenic *E. coli* were significantly less likely than noncolonized patients to develop at least one episode of UTI during the year follow-up period.³²

Catheter-associated bloodstream infection

Central venous catheters are the most frequent source of nosocomial bloodstream infection. Accurate diagnosis is essential in the management of these infections. Intravascular catheter colonization is usually detected using the semi-quantitative or roll-plate method, wherein a 5-cm catheter segment is rolled back and forth across the surface of a blood agar plate at least four times. The presence of 15 or more colony-forming units (CFU) after overnight incubation reflects catheter colonization. The roll-plate method samples the external catheter surface and may miss organisms colonizing the internal surface. This limitation may be overcome by quantitative culture methods, in which the catheter segment is flushed or immersed in a liquid and subsequently vortexed or sonicated.

A correlation between the frequency of concordant positive blood cultures and the number of organisms recovered from the vascular catheters after sonication has been reported.³³ Growth of more than 10² CFU from a catheter by quantitative (sonication) broth culture reflects catheter colonization. In a prospective, randomized, comparative study, the quantitative techniques of sonication or vortexing were not, however, superior to the semi-quantitative technique for detecting catheter colonization.³⁴ Furthermore among hematological patients with long-term tunneled catheters, sonication was not superior to the roll-plate method to diagnose catheter colonization.³⁵ Given its simplicity and performance, the semi-quantitative technique remains the most widely applied method in clinical laboratories.

Quantitative cultures drawn through the catheter and concomitantly by venipuncture from a peripheral vein or another catheter can be used for diagnostic purposes if the device is not removed. Quantitative cultures are obtained with the pour-plate technique or using the lysis-centrifugation system. In the case of catheter infection, blood drawn through it typically shows a greater than 5-fold increased concentration of organisms compared to blood drawn from a peripheral vein or another catheter. In a meta-analysis, the paired quantitative blood culture technique was found to be the most accurate among diagnostic methods not necessitating catheter removal.³⁶ However, quantitative blood cultures are labor intensive and expensive.

An alternative technique is based on the differential time to positivity of blood cultures. Positivity in a blood culture drawn from the catheter more than 2 hours before positivity of a culture drawn from a peripheral vein is highly predictive of catheter-associated bloodstream infection (CABSI). In a prospective study, the sensitivity and specificity of the method in patients with short-term catheters (<30 days) were 81 and 92%, respectively; for those with long-term catheters (≥30 days), differential time to positivity had a sensitivity of 93% and a specificity of 75%.³⁷ In patients with multi-lumen catheters, when blood cultures are drawn to diagnose CABSI, they should be collected through all catheter lumens.³⁸

In terms of CABSI prevention, use of antiseptic/antimicrobial-impregnated catheters is recommended if infection rates are elevated despite use of maximal sterile barrier precautions, and skin antisepsis with chlorhexidine during insertion.³⁹ Evidence from a meta-analysis is summarized in Table 2.⁴⁰ Antiseptic catheters are coated with chlorhexidine and sulfadiazine silver. First-generation catheters are coated only on the external surface, whereas second-generation catheters are coated on both the external and internal surfaces. First-generation catheters reduced the risk for CABSI compared with standard non-coated catheters. Second-generation catheters demonstrate a reduction in catheter colonization, but the studies were underpowered to show a difference in CABSI.^{41–43} The silver iontophoretic catheter is impregnated with silver, platinum, and carbon, and releases silver ions topically. One study showed a reduction in the incidence of catheter colonization and CABSI,⁴⁴ but others found no difference.^{45,46}

The antimicrobial-coated catheter approved by the FDA is impregnated with minocycline and rifampin on both internal and external surfaces. In a prospective, randomized clinical trial use of minocycline/rifampin-impregnated catheters was associated with a lower rate of CABSI than first generation chlorhexidine/silver-impregnated catheters (0.3 versus 3.4%, $p<0.002$).⁴⁷ A comparison with second-generation chlorhexidine/silver-impregnated catheters has not been conducted. In a study among cancer patients, long-term nontunneled silicone catheters impregnated with minocycline/rifampin were also efficacious in reducing CABSI.⁴⁸ No emergence of antimicrobial resistance was detected in these studies.

Use of catheter lock solutions is another strategy to prevent biofilm formation and/or eradicate established biofilm. Using this technique, parenteral antimicrobials or antiseptics are infused into the catheter hub and allowed to dwell at supratherapeutic concentrations. The antimicrobial or antiseptic (e.g., alcohol, taurolidine, trisodium citrate) is usually combined with an anticoagulant, such as heparin or EDTA. Most studies focus on patients at high risk for CABSI. Antimicrobial lock solutions reduce the risk of CABSI in patients undergoing hemodialysis,⁴⁹ and immunocompromised pediatric patients.⁵⁰ Similarly, alcohol lock solution decreases the risk of infection among immunosuppressed hematology patients.⁵¹ In general, prophylactic administration of lock solution is recommended for patients with long-term catheters who have a history of multiple infections despite maximal adherence to aseptic techniques.³⁹ Antibiotic lock therapy in conjunction with systemic

antimicrobial therapy is used in patients with CABSIs involving long-term catheters with no signs of exit site or tunnel infection for whom catheter salvage is the goal.⁵²

Infection associated with orthopedic implants

Orthopedic implants include prosthetic joints, spine implants, fracture-fixation devices, pins, screws, plates as well as intramedullary nails. The microbiologic diagnosis of orthopedic implant-associated infection is traditionally based on culture of synovial fluid and surgically obtained peri-implant tissue. For hip and knee prosthetic joint infection (PJI), the collection of five or six tissue specimens has been recommended.⁵³ An alternate diagnostic approach is directed towards detecting biofilm bacteria that attach to the surface of the implant. Using this method, the implant is placed in a container with sterile saline, vortexed and sonicated in an ultrasonic bath. This causes biofilm bacteria to dislodge and disaggregate. Aliquots of the sonicate fluid are then cultured on sheep blood agar plates; growth in significant quantity correlates with implant infection.

Culture of samples obtained by sonication is more sensitive than conventional periprosthetic tissue culture for the diagnosis of infection associated with hip or knee,⁵⁴ shoulder,⁵⁵ and spine implants⁵⁶ (Table 3). For prosthetic elbow infection, culture of the implant using sonication is at least as sensitive as periprosthetic tissue culture.⁵⁷ Notably for hip or knee infection, the sensitivity of sonicate culture was similar to tissue culture if five or more tissue specimens were cultured. An added benefit is that sonicate cultures have a shorter time to positivity than tissue cultures.⁵⁸

Molecular techniques are attractive tools for the diagnosis of PJI. Broad-range polymerase chain reaction (PCR) may be applied (e.g., amplifying the 16S ribosomal RNA gene). For organism identification, amplified product analysis (e.g., by sequencing) is needed. Multiplex PCR may be used to amplify genomic DNA using multiple primers allowing direct species identification. PCR has been evaluated in synovial fluid, periprosthetic tissue, and most recently sonicate fluid. In the authors' experience, *Propionibacterium acnes* and *Staphylococcus* spp. account for most positive sonicate fluid cultures among subjects with prosthetic shoulder infection; these cases can be detected by PCR of sonicate fluid.⁵⁵

In a study of 69 orthopedic implants, the sensitivity of PCR of sonicate fluid was similar to that of the combined cultures of periprosthetic tissue and sonicate fluid (92.3 versus 92.9%).⁵⁹ In another study of 37 cases of PJI, the causative organisms were identified in periprosthetic tissue culture in 65% of cases, in sonication fluid culture in 62%, and by multiplex PCR in 78%.⁶⁰ The approach is particularly useful in those receiving pre-operative antibiotics. In addition, molecular approaches may be more rapid than culture-based diagnostics. Molecular techniques may, however, yield false-positive results. In a prospective study of patients undergoing revision total hip or knee arthroplasty due to prosthesis failure, synovial fluid was collected intraoperatively. Twelve joints (13%) were found to be infected, but PCR was positive in 32 cases.⁶¹ The positive predictive value was only 34%. The clinical significance of detection of microbial nucleic acid in not obviously infected implants and/or representing organisms not traditionally associated with PJI need further study.

Inflammatory serum markers used to identify PJI preoperatively include white blood cell (WBC) count, erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP). Novel diagnostic markers include interleukin-6 (IL-6), procalcitonin and tumor necrosis factor- α . In a meta-analysis of 30 studies including 3,909 revision total hip or knee arthroplasties, IL-6 and CRP level had a higher diagnostic odds ratio than ESR and WBC count in discriminating infectious from noninfectious causes of prosthesis failure.⁶² Only three studies of IL-6 were included and the authors concluded that further investigation is

warranted. High serum IgM antibody levels to staphylococcal slime polysaccharide antigens may aid in the detection of the immune response elicited by biofilm colonization. An enzyme-linked immunosorbent assay has been developed and tested in a single study of 90 patients. The assay demonstrated a sensitivity of 89.7% and a specificity of 95.1% in detecting PJI caused by *S. aureus* and/or coagulase-negative staphylococci.⁶³ For patients with abnormal ESR and/or CRP, joint aspiration should be performed. Aspirated fluid should be sent for WBC count with differential and culture. The diagnostic utility of novel synovial fluid biomarkers (e.g., IL-1 β , granulocyte colony stimulating factor, IL-6) is being evaluated.⁶⁴

Arguably, orthopedic implant infections are best prevented. Preoperative intravenous antimicrobial prophylaxis is recommended for patients undergoing primary arthroplasty. Use of antibiotic-impregnated bone cement is another strategy but is not universally applied in primary arthroplasty. In a study using the Norwegian Arthroplasty Register, the risk of subsequent revision hip arthroplasty (due to aseptic failure or infection) was lowest when antibiotic prophylaxis was given both systemically and in the cement.⁶⁵ Concerns regarding the prophylactic use of antibiotic-impregnated cement include selection of antimicrobial resistance, allergic reactions, compromise of cement mechanical properties, and cost.

Post-operatively, bacteremia from any source may lead to hematogenous seeding and infection of the prosthetic implant. The American Academy of Orthopaedic Surgeons has issued an information statement favoring antimicrobial prophylaxis in all patients with prosthetic joints undergoing dental, gastrointestinal, genitourinary or other invasive procedures. Nonetheless, the available evidence does not support this recommendation. In a prospective case-control study, dental procedures were not associated with an increased risk of prosthetic knee or hip infection.⁶⁶ Furthermore, prophylactic antimicrobials prior to dental procedures were not associated with a decreased risk of infection.

Based on the concept of quorum-sensing signaling systems that coordinate biological activity, development of a microelectromechanical systems-type biosensing device has been proposed.⁶⁷ This would function as an “intelligent implant” detecting bacterial communication systems associated with quorum sensing. Upon intercepting bacterial signals, the biosensor would send a signal to gated reservoirs that would release compounds inhibitory to biofilm formation, and local antibiotics that would eradicate planktonic bacteria in proximity to the implant before establishment of biofilm.

Infection of cardiovascular implantable electronic devices

CIEDs include pacemakers, implantable cardioverter-defibrillators, and cardiac resynchronization therapy devices. Microbiologic diagnosis of CIED infections is based on organism isolation from the pocket site, the infected generator, the lead, or the bloodstream. The sensitivity of tissue culture of the fibrous capsule is higher compared to swab culture from the deep pocket site.⁶⁸ The explanted generator and lead tips can also be cultured. Sonication of the explanted device may aid in the diagnosis of CIED infection. However, it remains unclear whether this approach provides value beyond conventional strategies. A study of generators infected *in vitro* with a biofilm-producing strain of MRSA demonstrated that the use of vortexing, sonication, and incubation of the device in trypticase soy broth yielded similar results to broth incubation alone.⁶⁹ The sonication technique has been evaluated in a small clinical study.⁷⁰ Sonicate fluid cultures demonstrated a diagnostic yield that was comparable to that of tissue cultures. Both were superior to swab cultures. The combined use of sonication, tissue, blood, and lead-tip cultures resulted in detection of bacteria in all patients with pocket infections.

The significance of bacteria colonizing CIEDs is not entirely clear. Such bacteria may represent asymptomatic colonization or subclinical infection. In a study of patients with explanted cardiac devices without clinical signs of infection, bacteria were detected in 38% of sonicate fluid and 27% of conventional generator pocket swab cultures.⁷¹ *P. acnes* and coagulase-negative staphylococci, both common skin commensals, were the most frequently isolated bacteria. In a similar study of 108 asymptomatic patients, 47% demonstrated bacterial DNA on devices replaced for battery depletion.⁷²

Early CIED infections generally result from wound contamination at the time of placement and preventive strategies have been developed to reduce this risk. Perioperative antibiotic prophylaxis can reduce the incidence of CIED infection, as was shown in a randomized, double-blind, controlled trial of single dose cefazolin.⁷³ Despite prophylactic measures, the number of infections continues to rise out of proportion to implantation rates,⁷⁴ probably due to the increasing complexity of cases. Novel preventive approaches, such as local antimicrobial delivery methods, are needed. In a multi-center study of 624 consecutive procedures, use of a polypropylene mesh envelope releasing minocycline and rifampin in the generator pocket was associated with a low infection rate at a mean follow-up of 1.9 months.⁷⁵ This novel technique needs additional study in a prospective randomized fashion.

Summary

The pathogenesis of device-associated infections relates to bacteria that attach to and grow on surfaces in complex communities. Biofilm bacteria are several-fold more resistant to antimicrobial agents compared to planktonic counterparts. Novel diagnostic approaches directed towards detecting biofilm bacteria have been developed. Innovative approaches to prevention and treatment being evaluated include the use of antisense molecules, quorum-sensing inhibitors, bacteriophages that hydrolyze biofilm matrix, and bacterial interference. EC and ultrasound may be used in the future adjunctively to antimicrobials to disrupt biofilms and treat infection, and EC alone may be useful to prevent and/or treat biofilm-associated infections.

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Table 1

Evidence from randomized and quasi-randomized clinical trials on the efficacy of antimicrobial-coated urinary catheters in reducing the risk of asymptomatic bacteriuria during short-term (less than 30 days) use.

	Silver-alloy-impregnated catheter	Nitrofurazone-impregnated catheter	Minocycline/rifampin-impregnated catheter
Schumm et al, ²⁹	<1 week catheter use: RR 0.54 (95%CI 0.43–0.67) >1 week use: RR 0.64 (95%CI 0.51–0.80)	<1 week use: RR 0.52 (95%CI 0.34–0.78) >1 week use: RR 0.31 (95%CI 0.06–1.66)	<1 week use: RR 0.36 (95%CI 0.18–0.73) >1 week use: RR 0.94 (95%CI 0.86–1.03)
Drekonja et al, ³⁰	4 pre-1995 trials [*] : RRs 0.24–0.44 (median, 0.32) Absolute risk reduction 13%–32% (median, 28%) 5 post-1995 trials [*] : RRs 0.53–0.94 (median, 0.84) Absolute risk reduction 0.5%–5% (median, 2%)	4 trials [*] : RRs 0.08–0.68 (median, 0.45) Absolute risk reduction 3%–16% (median, 9.5%)	Not included

* Quantitative pooling of data not performed.

RR, risk ratios. 95% CI, 95% confidence interval. Risk ratio <1.0 favors antimicrobial-coated catheter use.

Table 2

Evidence from randomized controlled trials on the efficacy of antimicrobial-coated central venous catheters in reducing the risk of catheter colonization and catheter-associated bloodstream infection.

Catheter type	Central venous catheter colonization	Catheter-associated bloodstream infection
First-generation chlorhexidine/silver sulfadiazine	0.51 (0.42–0.61)	0.68 (0.47–0.98)
Second-generation chlorhexidine/silver sulfadiazine	0.39 (0.25–0.60)	0.47 (0.20–1.10)
Silver iontophoretic	0.84 (0.60–1.16)	1.98 (0.40–9.95)
Minocycline/rifampin	0.39 (0.27–0.55)	0.29 (0.16–0.52)

Values represent pooled odds ratios (95% confidence interval). Odds ratio <1.0 favors antimicrobial-coated catheter use. *Data from* Casey AL, Mermel LA, Nightingale P, et al. Antimicrobial central venous catheters in adults: A systematic review and meta-analysis. *Lancet Infect Dis.* 2008;8(12):763–776.

Table 3

Comparison of sonicate fluid and periprosthetic tissue culture for the diagnosis of infection associated with orthopedic implants

Implant type	Sonicate fluid	Periprosthetic tissue	p-value	Reference
Prosthetic hip/knee joint	Sensitivity	78.5%	<0.001	Trampuz et al, ⁵⁴
	Specificity	98.8%		
Prosthetic shoulder joint	Sensitivity	66.7%	0.046	Piper et al, ⁵⁵
	Specificity	98.0%		
Prosthetic elbow joint	Sensitivity	89%	0.18	Vergidis et al, ⁵⁷
	Specificity	100%		
Spine implant	Sensitivity	91%	0.046	Sampedro et al, ⁵⁶
	Specificity	97%		