■ SPECIALTY UPDATE

The management of periprosthetic infections in the future

A REVIEW OF NEW FORMS OF TREATMENT

D. A. George,
V. Gant,
F. S. Haddad

From University College London Hospitals, London, United Kingdom

The number of arthroplasties being undertaken is expected to grow year on year, and periprosthetic joint infections will be an increasing socioeconomic burden. The challenge to prevent and eradicate these infections has resulted in the emergence of several new strategies, which are discussed in this review.

Cite this article: *Bone Joint J* 2015;97-B:1162–9.

Despite many initiatives to reduce it over the years, the rate of periprosthetic joint infection (PJI) remains at 1% to 2%.[1]

The most common pathogen is *Staphylococcus aureus* (*S. aureus*),[2-4] which adheres to the prosthesis, duplicates and colonises the surface and becomes resistant to antibiotics, resulting in persistent and recurrent infections (Fig. 1).[5,6] The key to this resilience is the formation of a protective membrane. The biofilm is composed of a matrix of polypeptides, polysaccharides and nucleic acids, forming a microenvironment enabling the bacteria to flourish and become inaccessible both to the patient's immune system and to systemic antibiotics.[7-9]

In this review of the literature, we discuss current and emerging treatment strategies in order to reduce further the incidence of PJI and report on novel and futuristic approaches to disrupt or inhibit biofilm formation.

Patients and Methods

We reviewed all papers with a full text or an abstract in English, published from 1970 to June 2014 using international databases such as PubMed/Medline, EMBASE and other non-indexed citations including Google Scholar. Keywords either alone or in various combinations were used to search for appropriate papers (Table I). Following the initial search, if a topic was identified that was deemed appropriate for inclusion, the review was expanded to include this.

Results

Theatre modifications. The internal environment of the operating room and its associated airborne bacterial count is extremely important. Surgical personnel are a major source of air contamination,[10,11] and the presence of five people increases the bacterial count by 34 times[12] due to their shedding pathogens from their skin, respiratory particles, hair and clothing.[13]

In the early 1980s, laminar airflow was introduced to reduce airborne contamination. This initially showed a significant reduction in PJI.[14,15] However, recent studies have revealed inconsistencies and that laminar flow has no clear benefit, and also there is a potential risk of increased PJI.[16-18]

An alternative approach is the use of ultraviolet light, which disrupts bacterial DNA, preventing replication and contamination.[19] During primary arthroplasty, one study demonstrated a rate of infection of 1.77% with laminar airflow, but only 0.57% with ultraviolet light ($p < 0.001$).[20] Ultraviolet light can also eliminate bacterial contamination on solid surfaces. However, its use is not currently recommended due to the potential harm it may cause theatre staff, who are at an increased risk of eye damage and skin cancer if exposed,[21-24] however, there may be other applications such as sterilising the operating room between patients or overnight,[25] as the handles, lights, keyboards, floors and walls are additional sources of pathogens.[26-29]

Operative modifications. Prophylactic systemic antibiotics and antibiotic-impregnated cement have been shown to reduce rates of infection.[30-32] The use of other adjuncts, such as pulsatile lavage[33-35] and antibiotic-impregnated plastic adhesive drapes[36-38] have had mixed reviews.

Modification of prostheses. The structure of the prosthesis varies between manufacturers, especially the composition of the surface, the texture and hydrophobicity.[39-41] It is necessary for osseointegration to occur at the same time as reducing foreign body reactions and bacterial adhesion.[42,43] Many novel strategies have

■ D. A. George, MBChB, BMedSc, MRCS (Eng), Specialist Registrar, Department of Trauma and Orthopaedic Surgery
■ V. Gant, PhD FRCP, MRCPath, Divisional Clinical Director for Infection
■ F. S. Haddad, BSc MD (Res), FRCS (Tr&Orth), Professor of Orthopaedic Surgery
University College London Hospitals, 235 Euston Road, London, NW1 2BU, UK.

Correspondence should be sent to Mr D. A. George; e-mail: davidgeorge@doctors.org.uk

doi: 10.1302/0301-620X.97B9.35295 $2.00

Bone Joint J 2015;97-B:1162–9.

Table I. Keywords used during the initial and expanded literature search

Keywords used during the initial search	Keywords used during the expanded search
Periprosthetic joint infections	Photodynamic therapy
Implant infections	Metal ions
Prosthesis infection	Nanoparticles
Hip infection	Magnetic fields
Knee infection	Electric fields
Shoulder infection	
Future	
Ideas	
Innovative	
Modifications	
Futuristic	
Theatre	
Patient	
Technique	
Revision procedure	
Antibiotic	

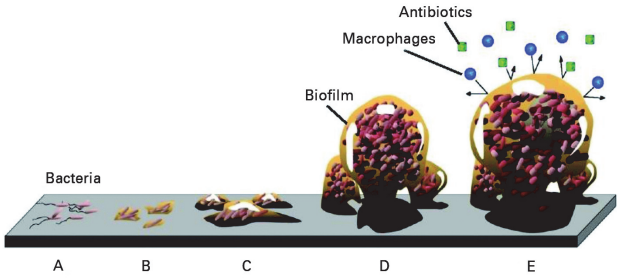

Fig 1

Diagram showing biofilm development; (a and b) initial attachment of bacteria to the surface of the prosthesis, (c) bacterial replication and formation of an immature biofilm, (d) maturation of the biofilm and expansion of the bacteria, (e) resistance of the biofilm to systemic antibiotics and the patient's immune system (reproduced from Monroe D. Looking for chinks in the armor of bacterial biofilms. PLoS Biol 2007;5:e307).[5]

focused upon modifying the composition of the prosthesis in particular the use of metal ions (or nanoparticles).

The broad-spectrum antibacterial properties of silver are effective against many organisms,[44] and are used in dressings and creams for chronic wounds and ulcers,[45,46]vascular and bladder catheters[47] and endotracheal tubes.[48]

Silver ions bind to bacterial DNA and to sulfhydryl groups in amino acids, resulting in the disruption of enzymes that control respiration and other critical cell functions.[42,49] Silver ions are rapidly bactericidal to *S. aureus* in susceptibility-testing media to levels equivalent to high doses of tetracycline and vancomycin, but they cannot eradicate the biofilm (Fig. 2).[50,51] Silver encourages the release of iron from iron-sulphur clusters and the formation of hydroxyl radicals, when tested against *Staphylococcus (S.) epidermidis*, which is lethal to this bacteria.[52]

Silver has been applied to the prosthesis in a number of ways, including the incorporation of silver with ceramics,[53] silver coating,[52,54] or incorporating silver ions within the surface of the prosthesis (Fig. 2).[51] Gordon et al[52] developed a silver polymer as a coating for metallic prostheses and showed that *in vivo* that there was a slow release of silver ions with limited transient leucocyte cytotoxicity. *In vitro*, the coating demonstrated strong biofilm sugar-independent bactericidal activity on biofilms and prevented *S. epidermidis* periprosthetic infection.[52] A custom-made implant with silver augmentation has been developed by Stanmore Implants Worldwide Limited (Elstree, United Kingdom).[55] Mid-term results of 85 oncology patients with these implants showed lower rates of early PJI following a two-stage exchange arthroplasty using the silver implant ($p = 0.03$), but not following a single-stage or primary arthroplasty.[56]

Patients exposed to higher levels of silver may develop local skin pigmentation due to exposure to silver (argyria), which may occur after two years.[57] However, patients with local argyria did not develop neurological symptoms, renal or hepatic failure and had similar levels of silver in the blood and aspiration fluids to patients that did not develop argyria.[57] In addition, resistance has been shown to develop *in vitro* following repeated exposure by *Escherichia (E.) coli*.[58]

Other ions such as iron, zinc, titanium, and carbon can reduce microbial adhesion, proliferation and biofilm growth. They can also enhance the function of keratinocytes and osteoblasts.[59-61]

Antibiotic prosthetic coatings. Hickok[39] hypothesised that the role of antibiotic-bonded prostheses was in preventing bacterial adhesion to the prosthesis, thus reducing the biofilm formation and preventing its ability to harbour bacteria.

Vancomycin has been used due to its action against gram-positive bacteria,[62-65] inhibiting the synthesis of structural proteins of the bacteria cell wall. Other antibiotics have been studied, such as gentamicin, ceftriaxone, kanamycin, tetracycline, doxycycline, levofloxacin and novel porphyrin antibacterial drugs, XF-70 and XF-73.[39,66-69]

One method of emitting the antibiotics is through a 'controlled-release system' that enables it to be released over a period of several days to weeks.[39] These systems are based upon biodegradable or non-biodegradable polymers as a prosthetic coating or a sleeve.[70-72] Biodegradable polymers have a short period of release and may be beneficial at the time of surgery and in the early post-operative period.[73] Non-biodegradable polymers, such as spacers used in two-stage revision procedures, release antibiotics for up to six weeks.[73]

An alternative to the controlled-release system is the use of antibiotics which are covalently tethered to the prosthesis enabling longer-term action.[39] Using animal models, vancomycin which was covalently tethered to a modified surface on a titanium plate showed no evidence of biofilm formation compared to controls when inoculated with *S. aureus*.[72]

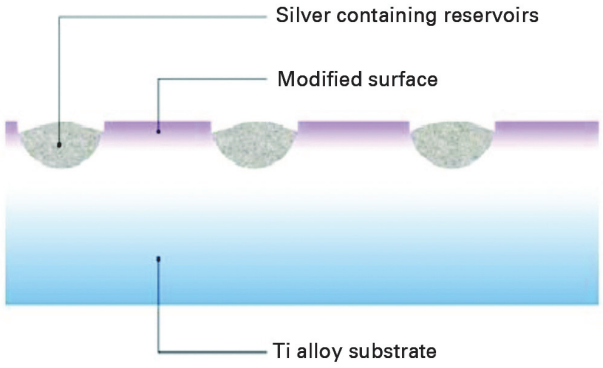

Fig. 2a

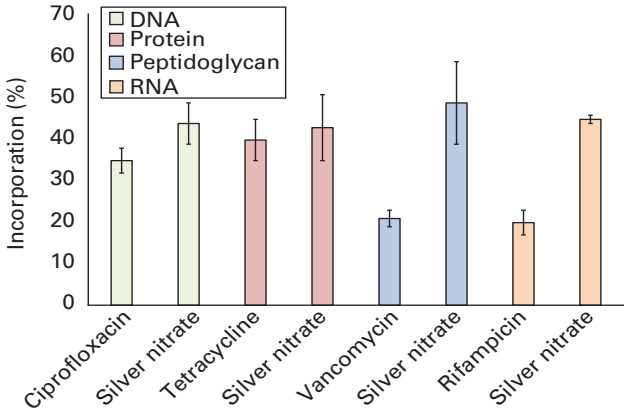

Fig. 2b

Alloy surface of the prosthesis (reproduced with permission from Accentus Medical Limited, Oxfordshire, United Kingdom[51] and b) graph showing the ability of silver ions in the form of silver nitrate to cause substantial inhibition of four biosynthetic pathways (DNA, RNA, protein and peptidoglycan) compared with antibacterial agents (ciprofloxacin, rifampicin, tetracycline and vancomycin, respectively) (reproduced with permission from Oxford University Press).[50]

Furthermore, the investigators were able to demonstrate through immunofluorescence staining, that after three months of implantation, vancomycin homogenously covered the surface of the prosthesis, was stable and still active, and produced minimal disturbance of the titanium surface.[72]

Phage therapy may also have a role in PJIs. This involves the use of bacteriophages to target specific pathogens and kill them.[74] In doing so, the phages multiply, increasing the number of cells present to target specific bacteria, which is unlike other antibiotic based delivery systems where the antimicrobial action soon reduces to a subtherapeutic level.[74] A biodegradable polymer has been developed to incorporate linezolid, and a broad spectrum lytic bacteriophage that targets MRSA, in animal models.[75] Applied to stainless steel Kirschner-wires, a significant reduction in bacterial adhesion was achieved compared with non-coated wires, without the development of resistant mutants.[75] Phage therapy appears free of local tissue toxicity or adverse effects.[76] The polymer presents a high concentration of bacteriophage and antibiotic around the prosthesis and such a combination can avert bacterial adherence, colonisation, biofilm formation and the entire infection process.[75-78]

Antibiofilm prosthetic coatings. Once adhered to the prosthesis, the bacteria become resistant to antibiotics and inaccessible to the immune system as a result of biofilm formation. This can delay bone healing and osteointegration, with subsequent loosening of the prosthesis.[79]

Within the matrix of the biofilm, antibiotic-specific enzymes may be present which limit the diffusion of agents into the biofilm.[80,81] Within the biofilm, bacterial growth and division slows, if not stops altogether.[82-84]

Targeted therapy has been developed to interrupt the physical integrity of the matrix, such as deoxyribonuclease (DNase) I and Dispersin B.[85] DNase I degrades extracellular DNA, known to cause firmness and stability of the biofilm and inhibit biofilm formation *in vitro*, making it more susceptible to various antibiotics.[42,85]

Dispersin B, a soluble beta-N-acetylglucosaminidase, targets intercellular adhesin produced by the biofilm.[85] *In vivo* studies have found Dispersin B to have antibiofilm and antibacterial activity against *S. aureus, S. epidermidis*, and *E. coli* when combined with antiseptics, such as triclosan or chlorhexidine.[86,87] Compounds secreted or extracted from selected marine microorganisms have natural compounds with antibiofilm and bacteriostatic activity[88,89] and have the potential to be adapted as biological coatings (Table II).[90-98]

Intra-operative applied therapies. The most basic and commonly used method is cancellous allograft bone impregnated with antibiotics,[99] however, more novel approaches have been used to administer antibiotics locally, such as a gentamicin-impregnated bovine collagen sponge.[100] This sponge (or fleece) continuously releases gentamicin until fully resorbed within eight to 14 days, with a concentration peak within the first 48 hours.[101,102] However, its role has declined due to a marked cytokine and cellular inflammatory response following insertion,[103,104] with some studies identifying an increase in rates of infection.[105] An alternative approach has recently been developed and is used at the bone–prosthetic interface. DAC (disposable antibacterial coating) enables a high concentration of antibiotics to be released over a short period of time demonstrating both antibiofilm and antibacterial properties. Composed of a biodegradable hydrogel, DAC is a combination of hyaluronic acid and polylactic acid, to which the microbe-specific antibiotic of choice is added.[106] Spread on the uncemented prosthesis prior to insertion, it releases antibiotics at the prosthetic surface for up to 96 hours (Fig. 3).[107]Initial *in vitro* tests confirmed its physical and chemical stability, safety and modes of action,[108] whilst clinical studies are emerging showing its benefits.[108]

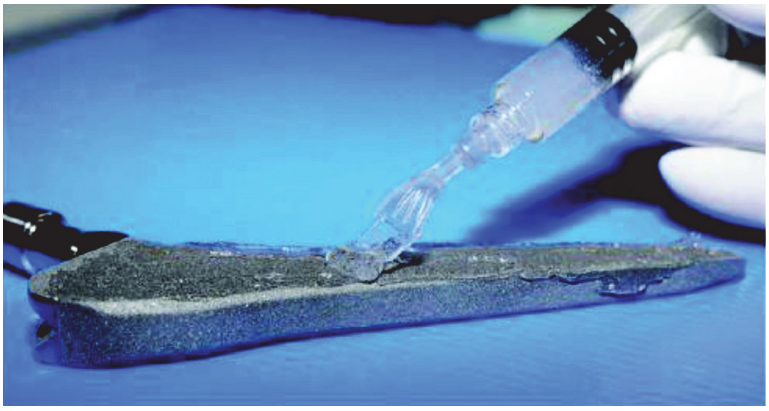

Fig. 3a

Fig. 3b

Photographs showing a disposable antibacterial coating (DAC) hydrogel; (a) hydrogel spread on a titanium prosthesis using a syringe, (b) layers of the hydrogel on the prosthesis (reproduced from Drago L, Boot W, Dimas K, et al. Does implant coating with antibacterial-loaded hydrogel reduce bacterial colonization and biofilm formation in vitro? Clin Orthop Relat Res 2014;472:3311-3323)[107]

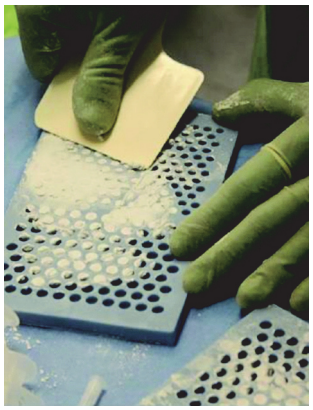

Fig. 4a

Fig. 4b

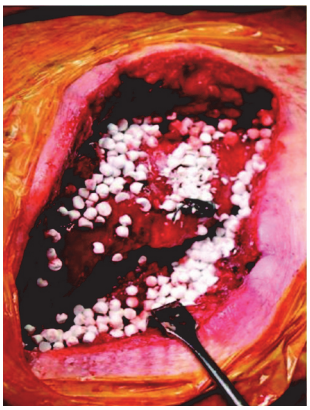

Fig. 4c

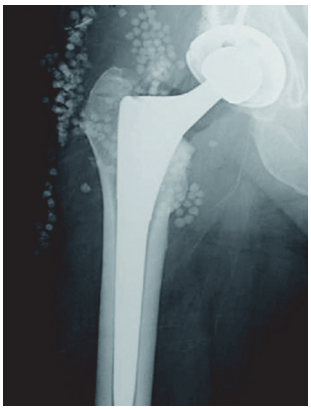

Fig. 4d

Photographs showing absorbable antibiotic pellets; (a) the intra-operative mixture of synthetic calcium sulphate with antibiotics, placed in moulds, (b) pellets, (c) placement in the wound prior to closure, (d) pellets visible on a post-operative radiograph.

Within the wound, bone–prosthetic interface, or within bone dead space, a combination of pharmaceutical-grade calcium sulphate mixed with antibiotics enables a prolonged release of antibiotics (vancomycin). In either a fully absorbable pellet or paste form (Fig. 4), concentrations of vancomycin of > 1000 ug/ml last for over 30 days.[109] This is comparable with previous attempts to add antibiotics to the soft tissue by irrigation[110] or as a powder,[111] which proved relatively unreliable in controlling local concentrations and distribution. The calcium sulphate beads are absorbed within three months.[112]

During wound closure, sutures must maintain their tensile strength long enough to enable the wounds to heal, but dissolve at such a time that prevents microbial colonisation of the suture material.[113,114] In order to prevent colonisation, antibiotic-coated sutures have been developed. Vicryl Plus (polyglactin 910) sutures may be coated with triclosan, a broad-spectrum antiseptic effective against *S. aureus* and *S. epidermidis* including methicillin-resistant strains.[115-117]

External antimicrobial therapy

Photodynamic therapy (PDT). PDT is currently used in the treatment of cancer[118] and age-related macular degeneration.[119] A photosensitive molecule, or non-toxic dye, is administered topically or systemically and subsequently activated by low-intensity visible light.[120,121] Antibacterial PDT has already proved successful in treating periodontal infections,[122] and may be a new approach in treating PJIs.[123]

The efficiency of PDT is secondary to the endocellular concentration of the photosensitiser within the biofilm matrix[124] and in the upregulation of neutrophil function.[125] Experimental studies treating the non-infected joint with

PDT demonstrated significant protection once the joint was inoculated with infection.[125]

Several barriers need to be overcome, however, to enable PDT to be used in clinical practice for the treatment of PJI. These include the accessibility and depth of the prosthesis for the appropriate penetration of light at the correct wavelength, the pharmacokinetics of the photosensitiser, its ability to accumulate at the site of infection, and also in the timing of irradiation.[126]

Magnetic and electric fields. Iron oxide demonstrates activity against PJIs by causing disruption of the bacterial cell wall via direct mechanisms and the production of free radicals,[127] enhanced by its magnetic properties.[128] In animal models it was shown that a magnetic field directed iron oxide ions to a specific area, increasing both the local concentration[129] and the penetration of paramagnetic ions into bacterial biofilms.[59] Clinically, if the prosthesis was magnetically charged prior to insertion, or was accessible to externally placed magnetic fields, metal ions could be focused on areas demonstrating signs of infection, disrupting the biofilm, which could enable systemic antibiotics to penetrate the vulnerable biofilm layer and eradicate the infection.

Within orthopaedics, an approach has been used to anodise and charge nanotubular titanium using a voltage of 15 to 30 volts. *S. aureus* biofilm formation significantly decreased secondary to the formation of fluorine on the surfaces of the anodised titanium.[130] Similarly bioceramic hydroxyapatite has been electrically polarised with marked deceleration of the growth of *S. aureus* and *E. coli* on a positively charged surface.[131] Accordingly, the use of nanoparticles to create a charged surface following insertion may be a possibility following activation by a systemic or local agent.

Shockwave treatment. Unlike the manipulation of magnetic forces to prevent bacterial adherence and biofilm formation, ultrasonic and laser-generated shockwaves can transmit mechanical energy, disrupt bacterial adhesion and dislodge biofilm.[132] The disrupted biofilm enables greater exposure of the pathogen to systemic or local antibiotics. *In vivo* studies using 24 hours of ultrasonic treatment combined with gentamicin acting on established E. coli biofilms have demonstrated a reduction of viable bacteria.[133] However, practical applications of shockwave may be limited. Shockwave lithotripsy is currently used in the treatment of renal calculi and its success is dependent on targeting a specific small area[134] If used in PJI, the whole prosthesis will need to be included in the field of treatment, and it may not be tolerated, especially if the therapy lasted for 24 hours.

Discussion

Novel strategies have shown promising results in the treatment of PJI, however, most of these therapies are still in preclinical development. The tests demonstrate that bacteria can adhere to the surface of the prosthesis, but this is not sufficient to cause infection, which requires persistent adhesion, colonisation and a lack of host clearance.[135] In addition, *in vitro* bacterial adhesion assays have many translational issues as non-physiological media are used and the observed decreases in bacterial load, however significant in the laboratory, may be clinically irrelevant. Furthermore, *in vivo* infection models tend to use healthy young animals and the strains selected for these experiments may bear little resemblance to those implicated in human infection.[136]

Infection exists as an epidemiological triangle, between the pathogen, the wound and the host. We found no papers that presented novel experimental findings relating to enhancing the host's interaction with the pathogen, particularly investigating or modulating aspects of the patients immunity.

S. aureus is a human commensal, adding the risk of infection to every incision, despite skin antisepsis. Bacteria cannot be fully eradicated from the skin without formal sterilisation. Greater understanding is required of the patient's predisposition to developing a PJI in order to explain why some patients develop infection whilst others do not, despite identical peri-operative precautions and comorbidities.

The evolving field of human genomics may have a role in our understanding of a patient's susceptibility, and in improving host resistance. Several mechanisms have been identified which limit the responses of the host's T-cells to proteins expressed by bacteria. These may be modulated by drugs to amplify[137] or suppress the host's responses,[138] as used in the treatment of cancer.[137,138] If applied to bacterial infection, those who use such attempts at modulation need to bear in mind that tissue destruction may, equally if not more, be driven by excessive inflammatory responses as much as by the organisms themselves.[139] Other gene products and intracellular pathways may emerge and may be found to be useful in the control of PJI.

Infection is variable, unpredictable and its causes are multifactorial, resulting from interactions between the surface of the prosthesis and the bacteria, the acute foreign body response of the host to colonisation and soft-tissue pathogen reservoirs around the implant.[135]

These novel therapies, if transferrable to clinical practice, hold the key to reducing further or eliminating the currently low, but certainly not negligible, rates of PJI.

Author contributions:
D. A. George: Researched and analysed the data, Wrote the manuscript.
V. Gant: Edited and approved the manuscript.
F. S. Haddad: Edited and approved the manuscript.

No benefits in any form have been received or will be received from party related directly or indirectly to the subject of this article.

This article was primary edited by S. P. F. Hughes and first proof edited by J. Scott.

References

1. **Blom AW, Brown J, Taylor AH, et al.** Infection after total knee arthroplasty. *J Bone Joint Surg [Br]* 2004;86-B:688–691.
2. **Tsukayama DT, Estrada R, Gustilo RB.** Infection after total hip arthroplasty. A study of the treatment of one hundred and six infections. *J Bone Joint Surg [Am]* 1996;78-A:512–523.

3. **Sanderson PJ.** Infection in orthopaedic implants. *J Hosp Infect* 1991;18(SupplA):367–375.
4. **Harris LG, Richards RG.** Staphylococci and implant surfaces: a review. *Injury* 2006;37(Suppl2):S3–14.
5. **Monroe D.** Looking for chinks in the armor of bacterial biofilms. *PLoS Biol* 2007;5:307.
6. **Gristina AG, Costerton JW.** Bacterial Adherence in biomaterial and tissue: The significance of its role in clinical sepsis. *J Bone Joint Surg [Am]* 1985;67-A:264–273.
7. **Prosser BL, Taylor D, Dix BA, Cleeland R.** Method of evaluating effects of antibiotics on bacterial biofilm. *Antimicrob Agents Chemother* 1987;31:1502–1506.
8. **Nickel JC, Ruseska I, Wright JB, Costerton JW.** Tobramycin resistance of Pseudomonas aeruginosa cells growing as a biofilm on urinary catheter material. *Antimicrob Agents Chemother* 1985;27:619–624.
9. **Evans RC, Holmes CJ.** Effect of vancomycin hydrochloride on Staphylococcus epidermidis biofilm associated with silicone elastomer. *Antimicrob Agents Chemother* 1987;31:889–894.
10. **Quraishi ZA, Blais FX, Sottile WS, Adler LM.** Movement of personnel and wound contamination. *AORN J* 1983;38:146-147, 150-156.:.
11. **Hughes SPF, Anderson FM.** Infection in the Operating Room. *J Bone Joint Surg [Br]* 1999;81B:754–755.
12. **Ritter MA, Eitzen H, French ML, Hart JB.** The operating room environment as affected by people and the surgical face mask. *Clin Orthop Relat Res* 1975;111:147–150.
13. **Trampuz A, Widmer AF.** Hand hygiene: a frequently missed lifesaving opportunity during patient care. *Mayo Clin Proc* 2004;79:109–116.
14. **Charnley J.** Postoperative infection after total hip replacement with special reference to air contamination in the operating room. *Clin Orthop Relat Res* 1972;87:167–187.
15. **Lidwell OM, Lowbury EJ, Whyte W, et al.** Effect of ultraclean air in operating rooms on deep sepsis in the joint after total hip or knee replacement: a randomised study. *Br Med J (Clin Res Ed)* 1982;285:10–14.
16. **Miner AL, Losina E, Katz JN, Fossel AH, Platt R.** Deep infection after total knee replacement: impact of laminar airflow systems and body exhaust suits in the modern operating room. *Infect Control Hosp Epidemiol* 2007;28:222–226.
17. **Hooper GJ, Rothwell AG, Frampton C, Wyatt MC.** Does the use of laminar flow and space suits reduce early deep infection after total hip and knee replacement?: the ten-year results of the New Zealand Joint Registry. *J Bone Joint Surg [Br]* 2011;93-B:85–90.
18. **Breier AC, Brandt C, Sohr D, Geffers C, Gastmeier P.** Laminar airflow ceiling size: no impact on infection rates following hip and knee prosthesis. *Infect Control Hosp Epidemiol* 2011;32:1097–1102.
19. **Thai TP, Keast DH, Campbell KE, Woodbury MG, Houghton PE.** Effect of ultraviolet light C on bacterial colonization in chronic wounds. *Ostomy Wound Manage* 2005;51:32–45.
20. **Ritter MA, Olberding EM, Malinzak RA.** Ultraviolet lighting during orthopaedic surgery and the rate of infection. *J Bone Joint Surg [Am]* 2007;89-A:1935–1940.
21. **Mangram AJ, Horan TC, Pearson ML, Silver LC, Jarvis WR.** Guideline for Prevention of Surgical Site Infection, 1999. Centers for Disease Control and Prevention (CDC) Hospital Infection Control Practices Advisory Committee. *Am J Infect Control* 1999;27:97-132;quiz 133-134;discussion 96.:.
22. **Lowell JD, Kundsin RB, Schwartz CM, Pozin D.** Ultraviolet radiation and reduction of deep wound infection following hip and knee arthroplasty. *Ann N Y Acad Sci* 1980;353:285–293.
23. **Moggio M, Goldner JL, McCollum DE, Beissinger SF.** Wound infections in patients undergoing total hip arthroplasty. Ultraviolet light for the control of airborne bacteria. *Arch Surg* 1979;114:815–823.
24. **Berg M, Bergman BR, Hoborn J.** Ultraviolet radiation compared to an ultra-clean air enclosure. Comparison of air bacteria counts in operating rooms. *J Bone Joint Surg [Br]* 1991;73-B:811–815.
25. **Parvizi J, Gehrke T, Chen AF.** Proceedings of the international consensus on periprosthetic joint infection. *Bone Joint J* 2013;95-B:1450–1452.
26. **Pittet D, Simon A, Hugonnet S, et al.** Hand hygiene among physicians: performance, beliefs, and perceptions. *Ann Intern Med* 2004;141:1–8.
27. **Stone PW, Larson E, Kawar LN.** A systematic audit of economic evidence linking nosocomial infections and infection control interventions: 1990-2000. *Am J Infect Control* 2002;30:145–152.
28. **Allo MD, Tedesco M.** Operating room management: operative suite considerations, infection control. *Surg Clin North Am* 2005;85:1291–1297.
29. **Howard JL, Hanssen AD.** Principles of a clean operating room environment. *J Arthroplasty* 2007;22(7Suppl3):6–11.
30. **Hill C, Flamant R, Mazas F, Evrard J.** Prophylactic cefazolin versus placebo in total hip replacement. Report of a multicentre double-blind randomised trial. *Lancet* 1981;1:795–796.
31. **Mauerhan DR, Nelson CL, Smith DL, et al.** Prophylaxis against infection in total joint arthroplasty. One day of cefuroxime compared with three days of cefazolin. *J Bone Joint Surg [Am]* 1994;76-A:39–45.
32. **Enzler MJ, Berbari E, Osmon DR.** Antimicrobial prophylaxis in adults. *Mayo Clin Proc* 2011;86:686–701.
33. **Maistrelli GL, Antonelli L, Fornasier V, Mahomed N.** Cement penetration with pulsed lavage versus syringe irrigation in total knee arthroplasty. *Clin Orthop Relat Res* 1995;312:261–265.
34. **Kalteis T, Pförringer D, Herold T, et al.** An experimental comparison of different devices for pulsatile high-pressure lavage and their relevance to cement intrusion into cancellous bone. *Arch Orthop Trauma Surg* 2007;127:873–877.
35. **Hargrove R, Ridgeway S, Russell R, et al.** Does pulse lavage reduce hip hemiarthroplasty infection rates? *J Hosp Infect* 2006;62:446–449.
36. **Lewis DA, Leaper DJ, Speller DC.** Prevention of bacterial colonization of wounds at operation: comparison of iodine-impregnated ('loban') drapes with conventional methods. *J Hosp Infect* 1984;5:431–437.
37. **Webster J, Alghamdi A.** Use of plastic adhesive drapes during surgery for preventing surgical site infection. *Cochrane Database Syst Rev* 2013;1:CD006353.
38. **Bady S, Wongworawat MD.** Effectiveness of antimicrobial incise drapes versus cyanoacrylate barrier preparations for surgical sites. *Clin Orthop Relat Res* 2009;467:1674–1677.
39. **Hickok NJ, Shapiro IM.** Immobilized antibiotics to prevent orthopaedic implant infections. *Adv Drug Deliv Rev* 2012;64:1165–1176.
40. **Duarte PM, Reis AF, de Freitas PM, Ota-Tsuzuki C.** Bacterial adhesion on smooth and rough titanium surfaces after treatment with different instruments. *J Periodontol* 2009;80:1824–1832.
41. **Kouidhi B, Zmantar T, Hentati H, Bakhrouf A.** Cell surface hydrophobicity, biofilm formation, adhesives properties and molecular detection of adhesins genes in Staphylococcus aureus associated to dental caries. *Microb Pathog* 2010;49:14–22.
42. **Arciola CR, Montanaro L, Costerton JW.** New trends in diagnosis and control strategies for implant infections. *Int J Artif Organs* 2011;34:727–736.
43. **Goodman SB, Yao Z, Keeney M, Yang F.** The future of biologic coatings for orthopaedic implants. *Biomaterials* 2013;34:3174–3183.
44. **Ellis JR.** The many roles of silver in infection prevention. *Am J Infect Control* 2007;35:E26.
45. **Atiyeh BS, Costagliola M, Hayek SN, Dibo SA.** Effect of silver on burn wound infection control and healing: review of the literature. *Burns* 2007;33:139–148.
46. **Dunn K, Edwards-Jones V.** The role of Acticoat with nanocrystalline silver in the management of burns. *Burns* 2004;30(suppl1):S1–S9.
47. **Francolini I, Donelli G.** Prevention and control of biofilm-based medical-device-related infections. FEMS Immunology & Medical Microbiology. *Special Issue: Biofilms* 2010;59:227–238.
48. **Li X, Yuan Q, Wang L, Du L, Deng L.** Silver-coated endotracheal tube versus non-coated endotracheal tube for preventing ventilator-associated pneumonia among adults: a systematic review of randomized controlled trials. *J Evid Based Med* 2012;5:25–30.
49. **Petering HG.** Pharmacology and toxicology of heavy metals: silver. *Pharmacol Ther* 1976;1:127–130.
50. **Randall CP, Oyama LB, Bostock JM, Chopra I, O'Neill AJ.** The silver cation (Ag+): antistaphylococcal activity, mode of action and resistance studies. *J Antimicrob Chemother* 2013;68:131–138.
51. **No authors listed.** Accentus Medical Limited, 2015. www.accentus-medical.com (date last accessed 04 June 2015).
52. **Gordon O, Vig Slenters T, Brunetto PS, et al.** Silver coordination polymers for prevention of implant infection: thiol interaction, impact on respiratory chain enzymes, and hydroxyl radical induction. *Antimicrob Agents Chemother* 2010;54:4208–4218.
53. **Kose N, Otuzbir A, Pekşen C, Kiremitçi A, Doğan A.** A silver ion-doped calcium phosphate-based ceramic nanopowder-coated prosthesis increased infection resistance. *Clin Orthop Relat Res* 2013;471:2532–2539.
54. **Tobin EJ, Karimy H, Barry JE, et al.** Infection-resistant external fixation pins. *Trans Soc Biomater* 1997;20:390.
55. **Unwin P, Pickford M, Shawcross J, et al.** Surface Treating of Endoprosthesis by Stitching-in Silver. *Orthopaedic Proceedings* 2012;94-B(SupXX):251.
56. **Wafa H, Grimer F, Carter S, et al.** Retrospective evaluation of the incidence of early periprosthetic infection with silver-treated custom endoprostheses in high risk patients: case control study [abstract]. Presented at the ISOLS conference, Bologna, 2013.

57. Glehr M, Leithner A, Friesenbichler J, et al. Argyria following the use of silver-coated megaprostheses: no association between the development of local argyria and elevated silver levels. *Bone Joint J* 2013;95-B:988–992.

58. Li XZ, Nikaido H, Williams KE. Silver-resistant mutants of Escherichia coli display active efflux of Ag+ and are deficient in porins. *J Bacteriol* 1997;179:6127–6132.

59. Taylor E, Webster TJ. Reducing infections through nanotechnology and nanoparticles. *Int J Nanomedicine* 2011;6:1463–1473.

60. Colon G, Ward BC, Webster TJ. Increased osteoblast and decreased Staphylococcus epidermidis functions on nanophase ZnO and TiO2. *J Biomed Mater Res A* 2006;78:595–604.

61. Puckett SD, Taylor E, Raimondo T, Webster TJ. The relationship between the nanostructure of titanium surfaces and bacterial attachment. *Biomaterials* 2010;31:706–713.

62. Lawson MC, Bowman CN, Anseth KS. Vancomycin derivative photopolymerized to titanium kills S. epidermidis. *Clin Orthop Relat Res* 2007;461:96–105.

63. Edin ML, Miclau T, Lester GE, Lindsey RW, Dahners LE. Effect of cefazolin and vancomycin on osteoblasts in vitro. *Clin Orthop Relat Res* 1996;333:245–251.

64. Parvizi J, Wickstrom E, Zeiger AR, et al. Frank Stinchfield Award. Titanium surface with biologic activity against infection. *Clin Orthop Relat Res* 2004;429:33–38.

65. Lawson MC, Hoth KC, Deforest CA, Bowman CN, Anseth KS. Inhibition of Staphylococcus epidermidis biofilms using polymerizable vancomycin derivatives. *Clin Orthop Relat Res* 2010;468:2081–2091.

66. Hart E, Azzopardi K, Taing H, et al. Efficacy of antimicrobial polymer coatings in an animal model of bacterial infection associated with foreign body implants. *J Antimicrob Chemother* 2010;65:974–980.

67. Moskowitz JS, Blaisse MR, Samuel RE, et al. The effectiveness of the controlled release of gentamicin from polyelectrolyte multilayers in the treatment of Staphylococcus aureus infection in a rabbit bone model. *Biomaterials* 2010;31:6019–6030.

68. Ooi N, Miller K, Randall C, et al. XF-70 and XF-73, novel antibacterial agents active against slow-growing and non-dividing cultures of Staphylococcus aureus including biofilms. *J Antimicrob Chemother* 2010;65:72–78.

69. Ooi N, Miller K, Hobbs J, et al. XF-73, a novel antistaphylococcal membrane-active agent with rapid bactericidal activity. *J Antimicrob Chemother* 2009;64:735–740.

70. Sinclair KD, Pham TX, Farnsworth RW, et al. Development of a broad spectrum polymer-released antimicrobial coating for the prevention of resistant strain bacterial infections. *J Biomed Mater Res A* 2012;100:2732–2738.

71. Lee CT, Lee CW, Hu CW, Lai KA, Yeh ML. PLGA encapsulating antibiotic loaded titanium prosthesis in osteomyelitis prevention in rats [abstract]. Presented at the 2012 Annual Meeting of the Orthopaedic Research Society, San Francisco, California, February, 2012.

72. Stewart S, Barr S, Engiles J, et al. Vancomycin-modified implant surface inhibits biofilm formation and supports bone-healing in an infected osteotomy model in sheep: a proof-of-concept study. *J Bone Joint Surg [Am]* 2012;94-A:1406–1415.

73. Panyam J, Labhasetwar V. Biodegradable nanoparticles for drug and gene delivery to cells and tissue. *Adv Drug Deliv Rev* 2012;64:61–71.

74. 74 **Abedon ST, Kuhl SJ, Blasdel BG, Kutter EM.** Phage treatment of human infections. *Bacteriophage* 2011;1:66–85.

75. Kaur S, Harjai K, Chhibber S. Bacteriophage mediated killing of Staphylococcus aureus in vitro on orthopaedic K wires in presence of linezolid prevents implant colonization. *PLoS One* 2014;9:90411.

76. Sulakvelidze A, Alavidze Z, Morris JG. Bacteriophage therapy. *Antimicrob Agents Chemother* 2001;45:649–659.

77. Chhibber S, Kaur T, Sandeep Kaur. Co-therapy using lytic bacteriophage and linezolid: effective treatment in eliminating methicillin resistant Staphylococcus aureus (MRSA) from diabetic foot infections. *PLoS One* 2013;8:56022.

78. Yilmaz C, Colak M, Yilmaz BC, et al. Bacteriophage therapy in implant-related infections: an experimental study. *J Bone Joint Surg [Am]* 2013;95-A:117–125.

79. Costerton JW. Biofilm theory can guide the treatment of device-related orthopaedic infections. *Clin Orthop Relat Res* 2005;437:7–11.

80. Suci PA, Mittelman MW, Yu FP, Geesey GG. Investigation of ciprofloxacin penetration into Pseudomonas aeruginosa biofilms. *Antimicrob Agents Chemother* 1994;38:2125–2133.

81. Anderl JN, Franklin MJ, Stewart PS. Role of antibiotic penetration limitation in Klebsiella pneumoniae biofilm resistance to ampicillin and ciprofloxacin. *Antimicrob Agents Chemother* 2000;44:1818–1824.

82. Brown MR, Allison DG, Gilbert P. Resistance of bacterial biofilms to antibiotics: a growth-rate related effect? *J Antimicrob Chemother* 1988;22:777–780.

83. Tuomanen E, Durack DT, Tomasz A. Antibiotic tolerance among clinical isolates of bacteria. *Antimicrob Agents Chemother* 1986;30:521–527.

84. Fukagawa S, Matsuda S, Miura H, et al. High-dose antibiotic infusion for infected knee prosthesis without implant removal. *J Orthop Sci* 2010;15:470–476.

85. Kaplan JB. Therapeutic potential of biofilm-dispersing enzymes. *Int J Artif Organs* 2009;32:545–554.

86. Darouiche RO, Mansouri MD, Gawande PV, Madhyastha S. Efficacy of combination of chlorhexidine and protamine sulphate against device-associated pathogens. *J Antimicrob Chemother* 2008;61:651–657.

87. Darouiche RO, Mansouri MD, Gawande PV, Madhyastha S. Antimicrobial and antibiofilm efficacy of triclosan and DispersinB combination. *J Antimicrob Chemother* 2009;64:88–93.

88. Selvin J, Ninawe AS, Kiran GS, Lipton AP. Sponge-microbial interactions: ecological implications and bioprospecting avenues. *Crit Rev Microbiol* 2010;36:82–90.

89. Sayem SM, Manzo E, Ciavatta L, et al. Anti-biofilm activity of an exopolysaccharide from a sponge-associated strain of Bacillus licheniformis. *Microb Cell Fact* 2011;10:74.

90. Shakir A, Elbadawey MR, Shields RC, Jakubovics NS, Burgess JG. Removal of biofilms from tracheoesophageal speech valves using a novel marine microbial deoxyribonuclease. *Otolaryngol Head Neck Surg* 2012;147:509–514.

91. Reed M. Marine nuclease and biofilm: a new approach to periprosthetic infection? [abstract] Presented at the London Knee Meeting, London, United Kingdom, October 2013.

92. Ren D, Bedzyk LA, Ye RW, Thomas SM, Wood TK. Stationary-phase quorum-sensing signals affect autoinducer-2 and gene expression in Escherichia coli. *Appl Environ Microbiol* 2004;70:2038–2043.

93. You J, Xue X, Cao L, et al. Inhibition of Vibrio biofilm formation by a marine actinomycete strain A66. *Appl Microbiol Biotechnol* 2007;76:1137–1144.

94. Thenmozhi R, Nithyanand P, Rathna J, Pandian SK. Antibiofilm activity of coral-associated bacteria against different clinical M serotypes of Streptococcus pyogenes. *FEMS Immunol Med Microbiol* 2009;57:284–294.

95. Pandian SK. Inhibition of biofilm formation in Streptococcus pyogenes by coral associated Actinomycetes. *Curr Microbiol* 2010;60:454–460.

96. Dheilly A, Soum-Soutéra E, Klein GL, et al. Antibiofilm activity of the marine bacterium Pseudoalteromonas sp. strain 3J6. *Appl Environ Microbiol* 2010;76:3452–3461.

97. Papa R, Parrilli E, Sannino F, et al. Anti-biofilm activity of the Antarctic marine bacterium Pseudoalteromonas haloplanktis TAC125. *Res Microbiol* 2013;164:450–456.

98. Klein GL, Soum-Soutéra E, Guede Z, et al. The anti-biofilm activity secreted by a marine Pseudoalteromonas strain. *Biofouling* 2011;27:931–940.

99. Winkler H, Stoiber A, Kaudela K, Winter F, Menschik F. One stage uncemented revision of infected total hip replacement using cancellous allograft bone impregnated with antibiotics. *J Bone Joint Surg [Br]* 2008;90-B:1580–1584.

100. El-Husseiny M, Patel S, MacFarlane RJ, Haddad FS. Biodegradable antibiotic delivery systems. *J Bone Joint Surg [Br]* 2011;93-B:151–157.

101. von Hasselbach C. Clinical aspects and pharmacokinetics of collagen-gentamicin as adjuvant local therapy of osseous infections. *Unfallchirurg* 1989;92:459-470. (in German):.

102. Swieringa AJ, Goosen JH, Jansman FG, Tulp NJ. In vivo pharmacokinetics of a gentamicin-loaded collagen sponge in acute periprosthetic infection: serum values in 19 patients. *Acta Orthop* 2008;79:637–642.

103. Mehta S, Humphrey JS, Schenkman DI, Seaber AV, Vail TP. Gentamicin distribution from a collagen carrier. *J Orthop Res* 1996;14:749–754.

104. Kilian O, Hossain H, Flesch I, et al. Elution kinetics, antimicrobial efficacy, and degradation and microvasculature of a new gentamicin-loaded collagen fleece. *J Biomed Mater Res B Appl Biomater* 2009;90:210–222.

105. Hayes G, Gibson T, Moens N. Safety assessment of a gentamicin impregnated collagen sponge (GICS) placed in the canine stifle joint: effect on joint in- flammation and renal function. *Vet Comp Orthop Traumatol* 2013;26:251–259.

106. No authors listed. Information IDAC Project. http://www.i-dac.eu/news/4 (date last accessed 04 June 2015).

107. Drago L, Boot W, Dimas K, et al. Does implant coating with antibacterial-loaded hydrogel reduce bacterial colonization and biofilm formation in vitro? *Clin Orthop Relat Res* 2014;472:3311–3323.

108. Romano C. Resorbable hydrogel provides effective antibacterial coating of implants in vitro and in vivo [abstract]. Presented at the Musculoskeletal Infection Society Annual Meeting, Philadelphia, United States, August 2013.

109. McPherson EJ, Dipane MV, Sherif SM. *Dissolvable antibiotic beads in treatment of periprosthetic joint infection - the use of synthetic pure calcium sulfate (STIMULAN) impregnated with vancomycin and tobramycin.* Reconstructive Review, Joint Implant Surgery & Research Foundation;2013:32–43.

110. Sørensen TS, Andersen MR, Glenthøj J, Petersen O. Pharmacokinetics of topical gentamicin in total hip arthroplasty. *Acta Orthop Scand* 1984;55:156–159.

111. Sweet FA, Roh M, Sliva C. Intrawound application of vancomycin for prophylaxis in instrumented thoracolumbar fusions: efficacy, drug levels, and patient outcomes. *Spine (Phila Pa 1976)* 2011;36:2084–2088.

112. McPherson EJ, Dipane MV, Sherif SM. Dissolvable antibiotic beads in treatment of periprosthetic joint infection and revision arthroplasty. the use of synthetic pure calium sulphate (stimulin) impregnated with vancomycin and tobramycin. *Joint Implant Surgery and Research Foundation* 2013:32–43.

113. Uff CR, Scott AD, Pockley AG, Phillips RK. Influence of soluble suture factors on in vitro macrophage function. *Biomaterials* 1995;16:355–360.

114. Rodeheaver GT, Kurtz LD, Bellamy WT, et al. Biocidal braided sutures. *Arch Surg* 1983;118:322–327.

115. Barbolt TA. Chemistry and safety of triclosan, and its use as an antimicrobial coating on Coated VICRYL* Plus Antibacterial Suture (coated polyglactin 910 suture with triclosan). *Surg Infect (Larchmt)* 2002;3(Suppl1):S45–S53.

116. Edmiston CE, Seabrook GR, Goheen MP, et al. Bacterial adherence to surgical sutures: can antibacterial-coated sutures reduce the risk of microbial contamination? *J Am Coll Surg* 2006;203:481–489.

117. Rothenburger S, Spangler D, Bhende S, Burkley D. In vitro antimicrobial evaluation of Coated VICRYL* Plus Antibacterial Suture using zone of inhibition assays. *Surg Infect (Larchmt)* 2002;3(Suppl1):S79–S87.

118. Bressler NM; Treatment of Age-Related Macular Degeneration with Photodynamic Therapy (TAP) Study Group. Photodynamic therapy of subfoveal choroidal neovascularization in age-related macular degeneration with verteporfin: two-year results of 2 randomized clinical trials-tap report 2. *Arch Ophthalmol* 2001;119:198–207.

119. Dai T, Huang YY, Hamblin MR. Photodynamic therapy for localized infections-state of the art. *Photodiagnosis Photodyn Ther* 2009;6:170–188.

120. Jori G. Photodynamic therapy of microbial infections: state of the art and perspectives. *J Environ Pathol Toxicol Oncol* 2006;25:505–519.

121. Ochsner M. Photophysical and photobiological processes in the photodynamic therapy of tumours. *J Photochem Photobiol B* 1997;39:1–18.

122. Usacheva MN, Teichert MC, Biel MA. Comparison of the methylene blue and toluidine blue photobactericidal efficacy against gram-positive and gram-negative microorganisms. *Lasers Surg Med* 2001;29:165–173.

123. Soukos NS, Wilson M, Burns T, Speight PM. Photodynamic effects of toluidine blue on human oral keratinocytes and fibroblasts and evaluated. *Lasers Surg Med* 1996;18:253–259.

124. Hamblin MR, Hasan T. Photodynamic therapy: a new antimicrobial approach to infectious disease? *Photochem Photobiol Sci* 2004;3:436–450.

125. Saino E, Sbarra MS, Arciola CR, et al. Photodynamic action of Tri-meso (N-methyl-pyridyl), meso (N-tetradecyl-pyridyl) porphine on Staphylococcus epidermidis biofilms grown on Ti6Al4V alloy. *Int J Artif Organs* 2010;33:636–645.

126. Tanaka M, Mroz P, Dai T, et al. Photodynamic therapy can induce a protective innate immune response against murine bacterial arthritis *via* neutrophil accumulation. *PLoS ONE* 2012;7:39823.

127. Zhang L, Jiang Y, Ding Y, Povey M, York D. Investigation into the antibacterial behaviour of suspensions of ZnO nanoparticles (ZnO nanofluids). *J Nanopart Res* 2007;9:479–489.

128. Trana N, Webster TJ. Magnetic nanoparticles: biomedical applications and challenges. *J Mater Chem* 2010;20:8760–8767.

129. Chertok B, Moffat BA, David AE, et al. Iron oxide nanoparticles as a drug delivery vehicle for MRI monitored magnetic targeting of brain tumors. *Biomaterials* 2008;29:487–496.

130. Ercan B, Kummer KM, Tarquinio KM, Webster TJ. Decreased Staphylococcus aureus biofilm growth on anodized nanotubular titanium and the effect of electrical stimulation. *Acta Biomater* 2011;7:3003–3012.

131. Ueshima M, Tanaka S, Nakamura S, Yamashita K. Manipulation of bacterial adhesion and proliferation by surface charges of electrically polarized hydroxyapatite. *J Biomed Mater Res* 2002;60:578–584.

132. Hansen EN, Zmistowski B, Parvizi J. Periprosthetic joint infection: what is on the horizon? *Int J Artif Organs* 2012;35:935–950.

133. Rediske AM, Roeder BL, Brown MK, et al. Ultrasonic enhancement of antibiotic action on Escherichia coli biofilms: an in vivo model. *Antimicrob Agents Chemother* 1999;43:1211–1214.

134. Charig CR, Webb DR, Payne SR, Wickham JE. Comparison of treatment of renal calculi by open surgery, percutaneous nephrolithotomy, and extracorporeal shockwave lithotripsy. *Br Med J (Clin Res Ed)* 1986;292:879–882.

135. Grainger D. Issues in translational infection research [abstract]. Presented at the 33rd annual meeting of the European Bone & Joint Infection Society, Utrecht, The Netherlands, September 2014.

136. Prestwich GD, Bhatia S, Breuer CK, et al. What is the greatest regulatory challenge in the translation of biomaterials to the clinic? *Sci Transl Med* 2012;4:160–114.

137. Pardoll DM. The blockade of immune checkpoints in cancer immunotherapy. *Nat Rev Cancer* 2012;12:252–264.

138. Cheever MA. Twelve immunotherapy drugs that could cure cancers. *Immunol Rev* 2008;222:357–368.

139. Hotchkiss RS, Moldawer LL. Parallels between cancer and infectious disease. *N Engl J Med* 2014;371:380–383.