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Review

Rationale for one stage exchange of infected hip replacement using uncemented implants and antibiotic impregnated bone graft

Heinz Winkler ✉

Osteitis Centre, Privatklinik Döbling, HeiligenstaedterStrasse 57-63, A-1190 Vienna, AUSTRIA

✉ Correspondence to: Heinz Winkler, Tel.: +43 136066 8000; Fax: +43 271920187; E-mail: h-winkler@aon.at. http://www.osteomyelitis.at

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Abstract

Infection of a total hip replacement (THR) is considered a devastating complication, necessitating its complete removal and thorough debridement of the site. It is undoubted that one stage exchange, if successful, would provide the best benefit both for the patient and the society. Still the fear of re-infection dominates the surgeons´ decisions and in the majority of cases directs them to multiple stage protocols. However, there is no scientifically based argument for that practice. Successful eradication of infection with two stage procedures is reported to average 80% to 98%. On the other hand a literature review of Jackson and Schmalzried (CORR 2000) summarizing the results of 1,299 infected hip replacements treated with direct exchange (almost exclusively using antibiotic loaded cement), reports of 1,077 (83%) having been successful. The comparable results suggest, that the major factor for a successful outcome with traditional approaches may be found in the quality of surgical debridement and dead space management. Failures in all protocols seem to be caused by small fragments of bacterial colonies remaining after debridement, whereas neither systemic antibiotics nor antibiotic loaded bone cement (PMMA) have been able to improve the situation significantly.

Reasons for failure may be found in the limited sensitivity of traditional bacterial culturing and reduced antibiotic susceptibility of involved pathogens, especially considering biofilm formation.

Whenever a new prosthesis is implanted into a previously infected site the surgeon must be aware of increased risk of failure, both in single or two stage revisions. Eventual removal therefore should be easy with low risk of additional damage to the bony substance. On the other hand it should also have potential of a good long term result in case of success. Cemented revisions generally show inferior long term results compared to uncemented techniques; the addition of antibiotics to cement reduces its biomechanical properties. Efficient cementing techniques will result in tight bonding with the underlying bone, making eventual removal time consuming and possibly associated with further damage to the osseous structures. All these issues are likely to make uncemented revisions more desirable.

Allograft bone may be impregnated with high loads of antibiotics using special incubation techniques. The storage capacities and pharmacological kinetics of the resulting antibiotic bone compound (ABC) are more advantageous than the ones of antibiotic loaded cement. ABC provides local concentrations exceeding those of cement by more than a 100fold and efficient release is prolonged for several weeks. The same time they are likely to restore bone stock, which usually is compromised after removal of an infected endoprosthesis. ABC may be combined with uncemented implants for improved long term results and easy removal in case of a failure. Specifications of appropriate designs are outlined.

Based on these considerations new protocols for one stage exchange of infected TJR have been established. Bone voids surrounding the implants may be filled with antibiotic impregnated bone graft; uncemented implants may be fixed in original bone. Recent studies indicate an overall success rate of more than 90% without any adverse side effects. Incorporation of allografts appears as after grafting with unimpregnated bone grafts.

Antibiotic loaded bone graft seems to provide sufficient local antibiosis for protection against colonisation of uncemented implants, the eluted amounts of antibiotics are likely to eliminate biofilm remnants, dead space management is more complete and defects may be reconstructed efficiently. Uncemented implants provide improved long term results in case of success and facilitated re-revision in case of failure. One stage revision using ABC together with uncemented implants such should be at least comparably save as multiple stage procedures, taking advantage of the obvious benefits for patients and economy.

Key words: Hip, Revision, Infection, Biofilm, Antibiotic, Uncemented implants, Allograft, Bone

Introduction

Infection of a total hip replacement (THR) is considered a devastating complication. Due to the absence of well-designed prospective, randomised, controlled studies with a sufficient follow-up period, diagnosis and treatment of prosthetic joint infections is mainly based on tradition, personal experience and liability aspects. It is generally accepted, that implants and necrotic tissue are covered with bacterial colonies that show inherent resistance to both host defence mechanisms and antimicrobial chemotherapy making the treatment extremely difficult. Uncertainty on the most effective approach has lead to several suggestions for treatment. Surgical debridement with implant retention is limited to very selected cases; most authors consider thorough removal of all implants and necrotic tissue a prerequisite for cure. Most controversies arise about the timing of reinsertion of a new prosthesis. In recent years, two-stage exchange arthroplasty has been claimed being the gold standard for treating infection, mostly in combination with spacers in the form of antibiotic loaded polymethylmethacrylate (PMMA). But there are no evidence based publications, no randomized data and only few metaanalyses available on the topic. Many protocols base on assumptions making the treatment "more art than science". Several reasons for difficulties in orthopaedic device related infections (ODRI) have been elucidated in the last years but that knowledge still is not yet fully reflected in therapeutic consequences of general practice. Most suggestions still are based on the traditional conceptions of antimicrobial treatment dealing with freely floating bacteria. Planktonic bacteria may well be eliminated by conventional use of antibiotics, however, in ODRI we have to deal with phenotypically different forms of bacteria and our most obstinate opponents are not the familiar planktonic pathogens but their sessile forms embedded in biofilms [1,2] Addressing the issues related to the biofilm concept, a one stage approach seems to show results comparable with multiple stage revisions [3].

Bacterial cultures and antibiotic susceptibility

The gold standard for detection and classification of infection during the last 100 years has been bacterial culture. Most protocols for treating infected THR base on the microbiological results obtained perioperatively. However, it has turned out that the traditional and routinely used methods of culturing are likely to detect only a small detail of the whole spectrum of pathogens possibly involved in infection of a THR [4]. It is well known since decades that small colony variants (SCV) of staphylococci and other pathogens may survive[5] and even replicate[6] intracellularily, in osteoblasts, endothelial cells and even in polymorphonuclear leukocytes and macrophages. Such populations are often missed by conventional culture. The problem of diagnosis markedly increases taking into account the issue of bacterial phenotypes inside biofilms. Sonication of explanted devices may dislodge adherent biofilms, culturing the sonication fluid is likely to raise sensitivity of cultures significantly. Especially in patients having received antimicrobial therapy within 14 days before culture the sensitivities of periprosthetic tissue and sonicate-fluid culture rise from 45.0% to 75.0% [7]. Using immunofluorescence microscopy for visualizing dislodged pathogens after marking with specific antibodies reveals further 3 times more colonies than seen with light microscopy, amplification of bacterial genomes using PCR shows bacterial RNA in more than 70% of all THR revision cases, including the so called "aseptic" failures [8,9]. The more sophisticated tools also evidenced, that polymicrobial colonisation is rather the rule than the exception after prolonged persistence of infection[10]. All these findings indicate that the incidence and dimension of prosthetic joint infection is grossly underestimated by current culture detection methods[11,12].

Most of the bacteria cultured from orthopaedic implants show reduced susceptibility for antibiotics, even in their planktonic form [13], whereas there is a significant correlation with previous use of gentamicin loaded PMMA[14]. Most pathogens not identified with traditional cultures show elevated resistance

against antibiotics [15]. SCVs require up to 100 fold antibiotic concentrations for elimination, but usually are accessible by systemic antibiosis, as long as the chosen antibiotics show intracellular activity and application lasts long enough[16,17]. Biofilm embedded pathogens require up to 1000 fold concentrations for elimination[18] and such usually are inaccessible for systemic antibiotic therapy as well as for antibiotics released from PMMA [19,20].

Debridement

Radical debridement is prerequisite for cure in any orthopaedic infection but an infected operative site cannot be sterilized by debridement alone. Debridement shall remove the predominant amount of bioburden but even the most careful cleaning cannot prevent residual small bacterial colonies being displaced to new habitats in niches of the debrided site. Antibiotic concentrations reached by systemic antibiosis or local therapy with commercially available antibiotic carriers may provide eradication of planktonic residues but are not effective in eliminating micro-clusters disrupted from biofilms that may be the cause of recurrence after an indefinite period of time. Fragments of biofilms seem to be more vulnerable for antibiotics compared with intact biofilm systems [21,22] but their elimination still requires concentrations exceeding the ones provided by systemic or conventional local antibiotic therapy. For eliminating residual biofilm fragments a novel approach is necessary, providing sufficiently high local antibiotic concentrations for a prolonged period of time [23].

Dead space management and reconstruction

After removal of infected endoprostheses and radical necrosectomy bony defects always will be present. Filling of dead space has been considered mandatory since the old days of septic surgery[24]. It may be presumed that whatever filler is used it needs some kind of protection against colonisation with remaining bacteria. Dead space management after infected THR may be performed with antibiotic loaded cement, spacers or bead chains. It should be kept in mind, that those devices beside their mechanical function cannot be considered as an antimicrobial tool; their antibiotic content provides short lived prophylactic aid against planktonic bacteria but is not capable of sterilizing sites contaminated with sessile bacteria and provide no protection against biofilm colonisation [25-28]. Reconstruction of defects seems to be favourable with regard to possible further revisions. Allograft bone is widely used for reconstruction of bony defects and performs favourably in two stage revisions of THR [29]. However, unvascularized bone grafts are at risk to become contaminated and need protection as well. When loading bone grafts with antibiotics it turned out, that their storage capability for antibiotics exceeds those of PMMA by far [30-32]. Especially when using highly purified cancellous bone as a carrier local concentrations of up to 20.000mg/l can be released with Vancomycin and up to 13.000mg/l with Tobramycin [33]. With this kind of impregnation the whole amount of loaded antibiotic is available for antimicrobial activity and the activity remains far beyond the susceptibility of relevant pathogens for several weeks. These capacities make them more attractive for local therapy and allow using uncemented implants. If cortical bone should become preferable out of whatever circumstances it can be loaded with antibiotics as well[34]. Using adequate impregnation technique antibiotics may elute similarly effective as is the case with cancellous bone [33]. Kinetics are different but still capable of eliminating surrounding pathogens.

Antibiotic delivery

Since concentrations provided by systemic antibiotic therapy and commonly available carrier systems are insufficient in eliminating biofilm bacteria new ways of antibiotic delivery are required. The criteria of antibiotics for efficacy against biofilms are different from those meant for action against planktonic bacteria. In any case the high concentrations needed are only feasible by local application. Failure of antibiotics to cure prosthesis-related infection is not only due to poor penetration of drugs into biofilm but likely due to delayed antimicrobial effect on stationary bacteria in the biofilm environment. In evaluating novel systems the used antibiotics must pass several tests qualifying them for that purpose. Few antibiotics have been identified to meet those criteria, among them Vancomycin seems to be the most widely evaluated one. Vancomycin is one of the antibiotics with intracellular bactericidal activity and therefore should cover SCVs of staphylococci [35]. It is likely to penetrate glycocalices very rapidly [36-38]. Once incorporated in biofilm Vancomycin shows a strain dependent bactericidal biofilm activity between 8 times [39] and 128 times [40] the MIC of planktonic bacteria. Vancomycin shows superior bactericidal activity against biofilm embedded staphylococci and especially MRSA [41] compared with most other antibiotics. Keeping local vamcomycin concentration at levels around 32x the MIC of planktonic forms the stationary phase pathogens are reduced by 2 logs within 24h [42]. Vancomycin shows the least cytotoxic effect of all commonly used antibiotics [43] and is not likely to cause systemic side effects after local application [44]. Van-

comycin shows very poor tissue penetration[45,46], which has been considered a disadvantage in intravenous application[47,48]; however the disadvantage turns into an advantage in local application since vice versa there is also reduced penetration from the implanted site into the vascular system, keeping local tissue levels high and systemic levels low . It therefore may be suggested that local application of antibiotics with similar properties as Vancomycin together with an appropriate carrier may be a valuable tool against ODRI. The carrier should provide for high initial levels to penetrate remaining glycocalices rapidly and consequently shall keep the concentrations above the critical level (which in the case of Vancomycin may be estimated to be between 200 and 500 mg/l) for a minimum of 72 hours.

To address the problem of potentially undetected polymicrobial colonisation it seems favourable to reserve monotherapy to cases with strong evidence of monomicrobial grampositive infection, i.e. acute onset of symptoms with typical clinical appearance (fever, pus) and unambiguous culture. Chronic infections the same as cases with prior infection related surgery or inexplicit cultures should be treated with a combination of two or more antibiotics, whereas combinations of vancomycin with tobramycin seem to be favourable, taking advantage of the synergistic activity of the two antibiotics [49,50]. This combined approach should be likely to cover most of the relevant pathogens since resistance to both antibiotics at the same time is found extremely rarely.

Choice of Implants

Whenever a new prosthesis is implanted into a recently infected site the surgeon must be aware of increased risk of failure, both in single or two stage revisions. Eventual removal therefore should be easy with low risk of additional damage to the bony substance in such a case. On the other hand it should also have potential of a good long term result in case of success. This limits the choice of advisable implants. Cemented systems seem to be less likely for that purpose since efficient cementing techniques will result in strong bonding with the underlying bone. Eventual removal such will be time consuming and possibly associated with further damage to the osseous structures[51]. Cemented revisions generally show inferior long term results compared to uncemented techniques [52,53]; the addition of antibiotics further reduces the biomechanical properties of cement [54-56]. Bone cement (PMMA) has been shown to be the ideal substrate for bacterial attachment and replication of sessile bacterial phenotypes[40]. Addition of antibiotics may be likely to act as a prophylactic aid against low bacterial numbers during the first days after implantation but cannot avoid colonization with high inocula[57], prevent biofilm formation on its surface [20,58] or even eliminate established biofilms[59]. On the acetabular side uncemented hemispherical cups are well suited since stability mainly can be supplied by good contact at the rim or additional screw fixation, while the bottom may be filled with cancellous bone graft. The mode of fixation makes it also easy to remove it again without compromising the natural bone. The use of uncemented hemispherical cups with or without screws in supplying acetabular defects is well established [60-62] and meanwhile proven to be superior compared with cemented systems [52,62]. On the femoral side a stem with rectangular diameter may offer several advantages: fixation relies mainly on contact of its medial and lateral edges with original bone while the anterior and posterior aspect may be covered with antibiotic impregnated bone graft. Stability of that design has been shown to be reliable as long as its distal third is safely anchored in healthy own bone while eventual removal usually is achievable without major difficulties [3]. The most common defects up to Paprosky type 3 such can be supplied favourably [63,64]. Other uncemented designs may provide comparable results as long as a safe distal fixation can be obtained [65-67]. In the case of a large type 4 defect longer sized types may become necessary, whereas modular systems seem to be favourable.

One stage –two stage

It is undoubted that one stage protocols, if successful, provide the best benefit both for the patient and the society. Still the fear of reinfection dominates the surgeons' decisions and directs them to multiple stage protocols. However, there is no scientifically based argument for that practice. Successful eradication of infection with two stage procedures is reported to average 80% to 98%,[68,69] whereas there are no significant differences between revisions with [70]or without[71] antibiotic loaded cement, with short or long term antibiotic therapy, with or without the use of spacers and other differences. On the other hand a literature review of Jackson and Schmalzried[72] summarizing the results of 1,299 infected hip replacements treated with direct exchange (almost exclusively using antibiotic loaded cement), reports of 1,077 (83%) having been successful. It may be calculated, that adding a second one stage procedure for treating the failed cases the overall result with two operations may improve to >95%, an outcome which is at least as good as the best results after two stage revisions, while requiring two surgical interventions for only a minority in the direct exchange group. Spacers have

been proven to be useful for improving final functional results; however, concerning infection control no benefit could be shown. These results suggest, that the major factor for a successful outcome with traditional approaches may be found in the quality of the surgical debridement and dead space management [71]. Dead space management is performed by a new prosthesis the same as with a spacer with the additional advantage of a definitive prosthesis providing stability, which a spacer does not. As long as protection against colonization is granted by high local antibiotic concentrations a well fixed prostheses is likely to provide better results than a spacer. Failures in all protocols seem to be caused by small fragments of bacterial micro-colonies remaining after debridement, whereas neither systemic antibiotics nor antibiotic loaded PMMA seem to be able to eliminate them. Antibiotic loaded bone graft seems to provide efficient antibiosis with respect to ODRI. Implants may sufficiently be protected against colonisation, the eluted amounts of antibiotics are likely to eliminate biofilm remnants, dead space management is more complete and as a positive side effect defects may be reconstructed efficiently. One stage revision using uncemented implants and antibiotic impregnated bone graft such should be comparably save as multiple stage procedures, taking advantage of the obvious benefits for patients and economy.

Conflict of Interest

The authors have declared that no conflict of interest exists.

References

1. Gristina AG, Costerton JW. Bacterial adherence to biomaterials and tissue. The significance of its role in clinical sepsis. J Bone Joint Surg Am 1985;67(2):264-73.
2. Costerton JW. Biofilm theory can guide the treatment of device-related orthopaedic infections. Clin Orthop Relat Res 2005;437:7-11.
3. 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;90:1580-4.
4. Fux CA, Stoodley P, Hall-Stoodley L, Costerton JW. Bacterial biofilms: a diagnostic and therapeutic challenge. Expert Rev Anti Infect Ther 2003;1(4):667-83.
5. Easmon CS. The effect of antibiotics on the intracellular survival of Staphylococcus aureus in vitro. Br J Exp Pathol 1979;60(1):24-8.
6. Qazi SN, Harrison SE, Self T, Williams P, Hill PJ. Real-time monitoring of intracellular Staphylococcus aureus replication. J Bacteriol 2004;186(4):1065-77.
7. Trampuz A, Piper KE, Jacobson MJ, Hanssen AD, Unni KK, Osmon DR, Mandrekar JN, Cockerill FR, Steckelberg JM, Greenleaf JF, Patel R. Sonication of removed hip and knee prostheses for diagnosis of infection. N Engl J Med 2007;357(7):654-63.
8. Tunney MM, Patrick S, Curran MD, Ramage G, Hanna D, Nixon JR, Gorman SP, Davis RI, Anderson N. Detection of prosthetic hip infection at revision arthroplasty by immunofluorescence microscopy and PCR amplification of the bacterial 16S rRNA gene. J Clin Microbiol 1999;37(10):3281-90.
9. Nelson CL, McLaren AC, McLaren SG, Johnson JW, Smeltzer MS. Is aseptic loosening truly aseptic? Clin Orthop Relat Res 2005;437:25-30.
10. Marrie TJ, Costerton JW. Mode of growth of bacterial pathogens in chronic polymicrobial human osteomyelitis. J Clin Microbiol 1985;22(6):924-33.
11. Dempsey KE, Riggio MP, Lennon A, Hannah VE, Ramage G, Allan D, Bagg J. Identification of bacteria on the surface of clinically infected and non-infected prosthetic hip joints removed during revision arthroplasties by 16S rRNA gene sequencing and by microbiological culture. Arthritis Res Ther 2007;9(3):R46.
12. Tunney MM, Patrick S, Curran MD, Ramage G, Hanna D, Nixon JR, Gorman SP, Davis RI, Anderson N. Detection of prosthetic hip infection at revision arthroplasty by immunofluorescence microscopy and PCR amplification of the bacterial 16S rRNA gene. J Clin Microbiol 1999;37(10):3281-90.
13. Tunney MM, Ramage G, Patrick S, Nixon JR, Murphy PG, Gorman SP. Antimicrobial susceptibility of bacteria isolated from orthopedic implants following revision hip surgery. Antimicrob Agents Chemother 1998;42(11):3002-5.
14. Chang CC, Merritt K. Microbial adherence on poly(methyl methacrylate) (PMMA) surfaces. J Biomed Mater Res 1992;26(2):197-207.
15. Zimmerli W, Trampuz A, Ochsner PE. Prosthetic-joint infections. N Engl J Med 2004;351(16):1645-54.
16. von Eiff C, Peters G, Becker K. The small colony variant (SCV) concept -- the role of staphylococcal SCVs in persistent infections. Injury 2006;37 (Suppl 2):S26-33.
17. Neut D, van der Mei HC, Bulstra SK, Busscher HJ. The role of small-colony variants in failure to diagnose and treat biofilm infections in orthopedics. Acta Orthop 2007;78(3):299-308.
18. Saginur R, Stdenis M, Ferris W, Aaron SD, Chan F, Lee C, Ramotar K. Multiple combination bactericidal testing of staphylococcal biofilms from implant-associated infections. Antimicrob Agents Chemother 2006;50(1):55-61.
19. van de Belt H, Neut D, Schenk W, van Horn JR, van der Mei HC, Busscher HJ. Infection of orthopedic implants and the use of antibiotic-loaded bone cements. A review. Acta Orthop Scand 2001;72(6):557-71.
20. Dunne N, Hill J, McAfee P, Todd K, Kirkpatrick R, Tunney M, Patrick S. In vitro study of the efficacy of acrylic bone cement loaded with supplementary amounts of gentamicin: effect on mechanical properties, antibiotic release, and biofilm formation. Acta Orthop 2007;78(6):774-85.
21. El-Azizi M, Rao S, Kanchanapoom T, Khardori N. In vitro activity of vancomycin, quinupristin/dalfopristin, and linezolid against intact and disrupted biofilms of staphylococci. Ann Clin Microbiol Antimicrob 2005;4:2.
22. Fux CA, Wilson S, Stoodley P. Detachment characteristics and oxacillin resistance of Staphyloccocus aureus biofilm emboli in an in vitro catheter infection model. J Bacteriol 2004;186(14):4486-91.
23. Smith AW. Biofilms and antibiotic therapy: is there a role for combating bacterial resistance by the use of novel drug delivery systems? Adv Drug Deliv Rev 2005;57(10):1539-50.
24. Prigge EK. THE TREATMENT OF CHRONIC OSTEOMYELITIS BY THE USE OF MUSCLE TRANSPLANT OR ILIAC GRAFT. J. Bone Joint Surg. Am. 1946;28(3):576-93.
25. Greene N, Holtom PD, Warren CA, Ressler RL, Shepherd L, McPherson EJ, Patzakis MJ. In vitro elution of tobramycin and vancomycin polymethylmethacrylate beads and spacers from Simplex and Palacos. Am J Orthop 1998;27(3):201-5.
26. Masri B, Duncan C, Beauchamp C. Long-term elution of antibiotics from bone-cement: an in vivo study using the prosthesis of antibiotic-loaded acrylic cement (PROSTALAC) system. J Arthroplasty 1998;13(3):331-8.
27. Bertazzoni Minelli E, Benini A, Magnan B, Bartolozzi P. Release of gentamicin and vancomycin from temporary human hip spacers in two-stage revision of infected arthroplasty. J Antimicrob Chemother 2004;53(2):329-34.
28. Walenkamp GH. Gentamicin PMMA beads and other local antibiotic carriers in two-stage revision of total knee infection: a review. J Chemother 2001;13:66-72.
29. Ammon P, Stockley I. Allograft bone in two-stage revision of the hip for infection. Is it safe? J Bone Joint Surg Br 2004;86(7):962-5.
30. Witso E, Persen L, Loseth K, Benum P, Bergh K. Cancellous bone as an antibiotic carrier. Acta Orthop Scand 2000;71(1):80-4.
31. Witso E, Persen L, Loseth K, Bergh K. Adsorption and release of antibiotics from morselized cancellous bone. In vitro studies of 8 antibiotics. Acta Orthop Scand 1999;70(3):298-304.

32. Buttaro MA, Pusso R, Piccaluga F. Vancomycin-supplemented impacted bone allografts in infected hip arthroplasty. Two-stage revision results. J Bone Joint Surg Br 2005;87(3):314-9.
33. Winkler H, Janata O, Berger C, Wein W, Georgopoulos A. In vitro release of vancomycin and tobramycin from impregnated human and bovine bone grafts. J Antimicrob Chemother 2000;46(3):423-8.
34. Khoo PPC, Michalak KA, Yates PJ, Megson SM, Day RE, Wood DJ. Iontophoresis of antibiotics into segmental allografts. J Bone Joint Surg Br 2006;88:1149-57.
35. Barcia-Macay M, Lemaire S, Mingeot-Leclercq MP, Tulkens PM, Van Bambeke F. Evaluation of the extracellular and intracellular activities (human THP-1 macrophages) of telavancin versus vancomycin against methicillin-susceptible, methicillin-resistant, vancomycin-intermediate and vancomycin-resistant Staphylococcus aureus. J Antimicrob Chemother 2006;58(6):1177-84.
36. Dunne WMJr., Mason EOJr., Kaplan SL. Diffusion of rifampin and vancomycin through a Staphylococcus epidermidis biofilm. Antimicrob Agents Chemother 1993;37(12):2522-6.
37. Jefferson KK, Goldmann DA, Pier GB. Use of confocal microscopy to analyze the rate of vancomycin penetration through Staphylococcus aureus biofilms. Antimicrob Agents Chemother 2005;49(6):2467-73.
38. Darouiche RO, Dhir A, Miller AJ, Landon GC, Raad II, Musher DM. Vancomycin penetration into biofilm covering infected prostheses and effect on bacteria. J Infect Dis 1994;170(3):720-3.
39. Rose WE, Poppens PT. Impact of biofilm on the in vitro activity of vancomycin alone and in combination with tigecycline and rifampicin against Staphylococcus aureus. J Antimicrob Chemother 2009;63(3):485-8.
40. Gristina AG, Jennings RA, Naylor PT, Myrvik QN, Webb LX. Comparative in vitro antibiotic resistance of surface-colonizing coagulase-negative staphylococci. Antimicrob Agents Chemother 1989;33(6):813-6.
41. Smith K, Perez A, Ramage G, Gemmell CG, Lang S. Comparison of biofilm-associated cell survival following in vitro exposure of meticillin-resistant Staphylococcus aureus biofilms to the antibiotics clindamycin, daptomycin, linezolid, tigecycline and vancomycin. Int J Antimicrob Agents 2009;33(4):374-8.
42. Murillo O, Domenech A, Garcia A, Tubau F, Cabellos C, Gudiol F, Ariza J. Efficacy of high doses of levofloxacin in experimental foreign-body infection by methicillin-susceptible Staphylococcus aureus. Antimicrob Agents Chemother 2006;50(12):4011-7.
43. Edin ML, Miclau T, Lester GE, Lindsey RW, Dahners LE. Effect of cefazolin and vancomycin on osteoblasts in vitro. Clin Orthop Relat Res 1996;333:245-51.
44. Buttaro MA, Gimenez MI, Greco G, Barcan L, Piccaluga F. High active local levels of vancomycin without nephrotoxicity released from impacted bone allografts in 20 revision hip arthroplasties. Acta Orthop 2005;76(3):336-40.
45. Matzke GR, Zhanel GG, Guay DR. Clinical pharmacokinetics of vancomycin. Clin Pharmacokinet 1986;11(4):257-82.
46. Garazzino S, Aprato A, Baietto L, D'Avolio A, Maiello A, De Rosa FG, Aloj D, Siccardi M, Biasibetti A, Masse A, Di Perri G. Glycopeptide bone penetration in patients with septic pseudoarthrosis of the tibia. Clin Pharmacokinet 2008;47(12):793-805.
47. Skhirtladze K, Hutschala D, Fleck T, Thalhammer F, Ehrlich M, Vukovich T, Muller M, Tschernko EM. Impaired target site penetration of vancomycin in diabetic patients following cardiac surgery. Antimicrob Agents Chemother 2006;50(4):1372-5.
48. Deresinski S. Counterpoint: Vancomycin and Staphylococcus aureus--an antibiotic enters obsolescence. Clin Infect Dis 2007;44(12):1543-8.
49. Watanakunakorn C, Tisone JC. Synergism between vancomycin and gentamicin or tobramycin for methicillin-susceptible and methicillin-resistant Staphylococcus aureus strains. Antimicrob Agents Chemother 1982;22(5):903-5.
50. Gonzalez Della Valle A, Bostrom M, Brause B, Harney C, Salvati EA. Effective bactericidal activity of tobramycin and vancomycin eluted from acrylic bone cement. Acta Orthop Scand 2001;72(3):237-40.
51. Paprosky WG, Weeden SH, Bowling JWJr. Component removal in revision total hip arthroplasty. Clin Orthop Relat Res 2001;393:181-93.
52. Lie SA, Havelin LI, Furnes ON, Engesaeter LB, Vollset SE. Failure rates for 4762 revision total hip arthroplasties in the Norwegian Arthroplasty Register. J Bone Joint Surg Br 2004;86(4):504-9.
53. Rothman RH, Cohn JC. Cemented versus cementless total hip arthroplasty. A critical review. Clin Orthop 1990;254:153-69.
54. Baleani M, Persson C, Zolezzi C, Andollina A, Borrelli AM, Tigani D. Biological and biomechanical effects of vancomycin and meropenem in acrylic bone cement. J Arthroplasty 2008;23(8):1232-8.
55. Klekamp J, Dawson JM, Haas DW, DeBoer D, Christie M. The use of vancomycin and tobramycin in acrylic bone cement: biomechanical effects and elution kinetics for use in joint arthroplasty. J Arthroplasty 1999;14(3):339-46.
56. Dunne NJ, Hill J, McAfee P, Kirkpatrick R, Patrick S, Tunney M. Incorporation of large amounts of gentamicin sulphate into acrylic bone cement: effect on handling and mechanical properties, antibiotic release, and biofilm formation. Proc Inst Mech Eng [H] 2008;222(3):355-65.
57. Neut D, van De Belt H, Stokroos I, van Horn JR, van Der Mei HC, Busscher HJ. Biomaterial-associated infection of gentamicin-loaded PMMA beads in orthopaedic revision surgery. J Antimicrob Chemother 2001;47(6):885-91.
58. van de Belt H, Neut D, Schenk W, van Horn JR, van der Mei HC, Busscher HJ. Gentamicin release from polymethylmethacrylate bone cements and Staphylococcus aureus biofilm formation. Acta Orthop Scand 2000;71(6):625-9.
59. Tunney MM, Dunne N, Einarsson G, McDowell A, Kerr A, Patrick S. Biofilm formation by bacteria isolated from retrieved failed prosthetic hip implants in an in vitro model of hip arthroplasty antibiotic prophylaxis. J Orthop Res 2007;25(1):2-10.
60. Jasty M. Jumbo cups and morsalized graft. Orthop Clin North Am 1998;29(2):249-54.
61. Obenaus C, Winkler H, Girtler R, Huber M, Schwagerl W. Extra-large press-fit cups without screws for acetabular revision. J Arthroplasty 2003;18(3):271-7.
62. Park DK, Della Valle CJ, Quigley L, Moric M, Rosenberg AG, Galante JO. Revision of the Acetabular Component without Cement. A Concise Follow-up, at Twenty to Twenty-four Years, of a Previous Report. J Bone Joint Surg Am 2009;91(2):350-5.
63. Zweymuller KA, Steindl M, Melmer T. Anterior windowing of the femur diaphysis for cement removal in revision surgery. Clin Orthop Relat Res 2005;441:227-36.
64. Stedry V, Dungl P, Hajny P, Biegel M, Podskubka A. [The Zweymuller endoprosthesis in hip joint revision surgery]. Acta Chir Orthop Traumatol Cech 2001;68(4):230-8.
65. Schuh A, Werber S, Holzwarth U, Zeiler G. Cementless modular hip revision arthroplasty using the MRP Titan Revision Stem: outcome of 79 hips after an average of 4 years' follow-up. Arch Orthop Trauma Surg 2004;124(5):306-9.
66. Bohm P, Bischel O. [Cement-free diaphyseal fixation principle for hip shaft exchange in large bone defects--analysis of 12 years experience with the Wagner revision shaft]. Z Orthop Ihre Grenzgeb 2001;139(3):229-39.
67. Grunig R, Morscher E, Ochsner PE. Three-to 7-year results with the uncemented SL femoral revision prosthesis. Arch Orthop Trauma Surg 1997;116(4):187-97.
68. Lai KA, Shen WJ, Yang CY, Lin RM, Lin CJ, Jou IM. Two-stage cementless revision THR after infection. 5 recurrences in 40 cases followed 2.5-7 years. Acta Orthop Scand 1996;67(4):325-8.
69. Younger A, Duncan C, Masri B. Treatment of infection associated with segmental bone loss in the proximal part of the femur in two stages with use of an antibiotic-loaded interval prosthesis. J Bone Joint Surg Am 1998;80(1):60-9.
70. Stockley I, Mockford BJ, Hoad-Reddick A, Norman P. The use of two-stage exchange arthroplasty with depot antibiotics in the absence of long-term antibiotic therapy in infected total hip replacement. J Bone Joint Surg Br 2008;90(2):145-8.
71. Disch AC, Matziolis G, Perka C. Two-stage operative strategy without local antibiotic treatment for infected hip arthroplasty: clinical and radiological outcome. Arch Orthop Trauma Surg 2007;127(8):691-7.
72. Jackson WO, Schmalzried TP. Limited role of direct exchange arthroplasty in the treatment of infected total hip replacements. Clin Orthop Relat Res 2000;381:101-5.