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

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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 safe 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. Addressing the issues related to the biofilm concept, a one stage approach seems to show results comparable with multiple stage revisions.

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. It is well known since decades that small colony variants (SCV) of staphylococci and other pathogens may survive and even replicate intracellularly, 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%. 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. The more sophisticated tools also evidenced, that polymicrobial colonisation is rather the rule than the exception after prolonged persistence of infection. All these findings indicate that the incidence and dimension of prosthetic joint infection is grossly underestimated by current culture detection methods.

Most of the bacteria cultured from orthopaedic implants show reduced susceptibility for antibiotics, even in their planktonic form, whereas there is a significant correlation with previous use of gentamicin loaded PMMA. 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 enough16,17. Biofilm embedded pathogens require up to 1000 fold concentrations for elimination18 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 surgery24. 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 well34. 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 vancomycin 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\textsuperscript{45,46}, which has been considered a disadvantage in intravenous application\textsuperscript{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\textsuperscript{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\textsuperscript{51}. Cemented revisions generally show inferior long term results compared to uncemented techniques\textsuperscript{52,53}; the addition of antibiotics further reduces the biomechanical properties of cement\textsuperscript{54,56}. Bone cement (PMMA) has been shown to be the ideal substrate for bacterial attachment and replication of sessile bacterial phenotypes\textsuperscript{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\textsuperscript{57}, prevent biofilm formation on its surface\textsuperscript{20,58} or even eliminate established biofilms\textsuperscript{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\textsuperscript{60-62} and meanwhile proven to be superior compared with cemented systems\textsuperscript{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\textsuperscript{3}. The most common defects up to Paprosky type 3 such can be supplied favourably\textsuperscript{63,64}. Other uncemented designs may provide comparable results as long as a safe distal fixation can be obtained\textsuperscript{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\%\textsuperscript{68,69} whereas there are no significant differences between revisions with\textasciitilde or without\textasciitilde 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\textsuperscript{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. 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.

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