Review Article on Postoperative Spinal Implant Infection

Future directions of postoperative spinal implant infections

Max Jägersberg[1], Susanne Feihl[2], Florian Ringel[1]

[1]Department of Neurosurgery, University Medical Center Mainz, Mainz, Germany; [2]Department of Medical Microbiology, Immunology and Hygiene, Technische Universität München, Munich, Germany

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Correspondence to: Max Jägersberg, MD. Neurochirurgische Klinik und Poliklinik, Universitätsmedizin Mainz, Langenbeckstr. 1, 55131 Mainz, Germany. Email: max.jaegersberg@unimedizin-mainz.de.

Abstract: This article outlines some promising future concepts against postoperative spinal implant infections on the basis of today available literature. The ever-adapting bacteria causing this common complication compel a corresponding continuous research about best effective treatment. The aim is to give a perspective on several future attack-points: surgical infection prevention strategies such as technical optimization of implants and surgical technique; faster diagnostic tools to detect infection, especially in the context of late infections with low-virulent germs and with regard to decision-making in the course of the surgical workflow; and combined surgical and medical treatment options against implant infections. The surgical treatment section will also state open issues concerning implant removal, and the medical treatment section will give an outlook to promising medical alternatives in a post-antibiotic era. To keep up in this field will be important to retain spine surgery in the future as the state-of-the-art treatment option for mandatory spinal interventions in the presence of tumor or trauma and even more so as an attractive option for patients with degenerative spinal disorder for improvement of their life quality.

Keywords: Implant infections; prevention; implant processing; biofilm; coated; no-touch technique; bacteriophages; late infections; implant removal; alpha defensin test; post-antibiotic era

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Introduction

With the increasing use of instrumentation in degenerative, neoplastic, traumatic spinal disease and spinal deformities, we are facing an increasing number of surgical site infections associated with these instrumentations as a typical complication. These postoperative spinal implant infections (PSII) are usually classified as early (within 6 weeks after implantation) or late (more than 6 weeks after implantation). Late spinal infections can occur without the typical signs of infection but by spinal implant loosening and the associated symptoms, only. These low-grade infections are usually caused by low-virulent microorganisms growing in biofilms on implants. Pure swabs or tissue specimen cultivation often fail to detect the infection, hence diagnostic as well as treatment strategies need to be adapted for successful treatment.

To manage these early and late infections means (I) to implement infection prevention strategies, (II) to include all diagnostic measures necessary to detect any infection, and (III) to combine the necessary surgical and antimicrobial actions of infection eradication.

The present article aims to highlight some future aspects and open issues for prevention, diagnosis and treatment of implant-associated spinal infections.

Definition and diagnosis of peri-implant spine infections

Diagnosis of acute implant-associated surgical site

infections is mostly clear and typically associated with elevated C-reactive protein, an elevated leucocyte count, signs of wound infection, a purulent fluid within the surgical site around the implants and positive microbiological cultures from tissue samples or swabs (1,2). In contrast, the diagnosis of late infections including low-grade implant associated infections is challenging in spinal surgery. For periprosthetic joint infections several definitions have been published and the latest from 2018 includes a combination of major and minor criteria (3). However, this definition cannot be transferred to the spine as it includes analysis of synovial fluid not available around the spine, whereas late low-grade infections associated with implant loosening are not covered. Therefore, diagnostic criteria of late spinal infections need to be developed and largely accepted, including the recent aspect, that even implant loosening without any further signs of infection can be caused by an infection, not only by biomechanical failure. This development needs to include diagnostic criteria which include the necessity of implant sonication to identify low-grade implant associated infections. Especially in low-grade infections low microbial burden with microorganisms growing in biofilms leads to false negative conventional microbiological cultures. With sonication, biofilms can be dislodged from explanted implants and detection of causing pathogens can be improved. Several recent studies could elucidate that implant sonication can significantly increase the sensitivity and specificity to diagnose an infection in late implant-associated spinal infections. Here, low-virulent germs as *Cutibacterium acnes* and coagulase-negative staphylococci have been frequently identified (4,5).

Therefore, implant sonication and microbiological cultivation of sonication fluid should be a standard for all explanted loosened spinal instrumentation in order to select those cases of infected screws and to initiate the necessary antibiotic therapy.

However, a certain disadvantage of sonication fluid microbiological analysis for loosened spinal implants is the time interval between surgery and the availability of microbiological cultivation results. An earlier diagnosis of low-grade infections prior to or during surgery would have an impact on the decision of a potential preservation of not loosened implants, or the removal or change of all implants and the initiation of antibiotic therapy after surgery.

Therefore, a preoperative or at least intraoperative diagnosis of an implant associated infection would be desirable for cases of suspected low-grade infections. Techniques under assessment are preoperative positron emission tomography (PET) imaging and intraoperative fast tests of biomarkers of an infection (6,7).

So far, few studies with small numbers of heterogenous patients assessed the value of ^{18}F-fluorodeoxyglucose PET to detect spinal implant-related infections. A recent study could report a sensitivity of 80% and a specificity of 100%, however, in a very small cohort of 9 patients (6). Therefore, the technique seems promising but future studies including large numbers of patients especially with late low-grade infections needs to be awaited to clarify the potential of PET imaging in this indication.

To diagnose periprosthetic infections after hip and knee replacement the pre- or intraoperative analysis of alpha-defensin, a biomarker that is emitted by neutrophilic granulocytes upon contact with bacteria, can be analyzed from synovial fluid. A qualitative alpha-defensin test with instant response is under evaluation and has so far shown sensitivity and specificity rates that are not optimal and remain inferior to cultivation, but present a promising base (8). Depending on the assay, test results are available within 10 min and could guide the further surgical strategy. However, from the procedural point of view, the importance of fast intraoperative diagnostic tools remains somewhat questionable: in acute PSII, the clinical diagnosis will be straight forward in most cases. It is hence the delayed PSII that comes into account for such intraoperative diagnostic tools. If in these cases PSII is accompanied or suspected by implant loosening, then explantation (in case of achieved bony fusion) or one or two staged implant replacement is mandatory anyway. If infection is suspected in the absence of implant loosening, then the negative result of a single part of the implant, even with excellent sensitivity and specificity, will not be able to rule out bacteria or biofilm presence at other (covered) parts of the implant. An advantage of an instant diagnosis of infection would be present in those cases where a screw loosening requires an implant change. Upon instant infection diagnosis an antimicrobial therapy would be initiated, but not if test results were negative. Without an immediate test result, an antimicrobial therapy needs to be initiated in all cases of suspected low-grade infection to avoid potential new implant colonization until final approval or exclusion of infection by tissue or sonication fluid cultivation is available. So far, no instant test with convincing data is available for PSII. Such a diagnostic tool, comparable to the alpha-defensin test for synovial fluid, would be a valuable addition.

PSII prevention

Several infection prevention bundles reduce the incidence of infections. These contain basic measures as perioperative body temperature and blood sugar control, patient decontamination as well as specific measures around the implants. The works of Agarwal *et al.* show a potential contamination risk from reprocessed implants that become prone to corrosion, fat or soap (9). This observation is being addressed by the industry in form of single packed implants, leaving their special packaging only at the moment of implantation. A rigorous "no touch" technique, possibly with capping devices, thereby avoiding any other implant contact than bone, is equally emphasized (10,11). Implant coating with antibiotics, antiseptics, and nano-silver has long been evaluated on an experimental basis, but has failed to become available as clinical routine implants due to different drawbacks (12). Antibiotic coating of spinal implants includes the use of predetermined antibiotics, a limited duration of drug elution and the risk of inducing microbial resistance. Antiseptic agents as chlorhexidine and chloroxylenol have a general low-grade germ toxicity and therefore seem not ideal for implant coating. Nano-silver coating does show good antimicrobial effectiveness but there are hints towards a mild toxicity of nano-silver upon long-term exposure (13). So far, no antimicrobial coating technique for spinal implants is clinically available to prevent implant colonization.

Treatment of PSII

Surgical strategy

In acute PSII we expect at the worst the presence of an immature biofilm, and implant preservation is preferable as long as correct early surgical debridement together with biofilm active antibiotic therapy are applied (14). In late infections with potential mature biofilm presence, the likelihood of successful implant preservation is low. Therefore, in delayed PSII, explantation of all possibly explantable implants and new implantation within the same procedure or a secondary staged reimplantation after microbiological recovery are discussed (15). It remains unclear whether a strategy of implant removal or change upon late infections needs to include interbody cages or whether the removal of posterior instrumentation alone is sufficient.

However, well-designed studies assessing the treatment of late and especially late low-grade infections are required with special focus on implant change *vs.* removal.

The general possibility to explant must be appreciated as a striking advantage of PSII over the analogous infection after arthroplasty: while the loss of movement of infected prosthetic implants (e.g., knee) is a catastrophic surgical outcome, spinal intervertebral fusion presents the desired result for spondylodesis procedures. This means that treatment strategies in PSII must include analysis of achieved bony fusion, since the proof of fusion (occurred PSII after achieved fusion) offers the option to remove implants (16).

Occurred PSII prior to achieved fusion leads to the decision-making process of the surgical revision strategy for new implantation, i.e., one or two or more-staged revision surgeries. Two special conditions must be mentioned in this context: First, certain surgical techniques [pedicle subtraction osteotomy (PSO), Smith-Petersen osteotomy (SPO)] cause spinal instability in the absence of the implant before fusion will be achieved. Two-staged strategies can hence lead to prolongated immobilization periods with known negative effects. Second, certain implants in PSII are considered un-explantable under acceptable risks and effort by many surgeons. This accounts for most anterior interbody fusion devices as ALIF, XLIX, TLIF, OLIF and vertebral cages. The dilemma might harbor a positive information: the today rates of successful cure of PSII (17) are obviously observed in spite of the named anterior column implants often left *in situ* and do not generally render microbial eradication impossible.

New antibiotic and non-antibiotic molecules with biofilm penetrance

So far, only few antibiotics have demonstrated activity on adherent and biofilm-producing microorganisms. This property has been shown for rifampin in staphylococcal implant-associated infections in *in vitro*, animal and clinical studies (18-21). Combination of rifampin with another drug is essential to prevent development of antimicrobial resistance. Therefore, antibiotics with good bioavailability should be used for oral combination with rifampin (22). As data for biofilm activity of antimicrobial agents are limited and emergence of resistance is increasing, antibiotics have to be kept in the future armamentarium by responsible usage. Furthermore, new approaches for eradication of adherent microorganisms are desirable (21,23). Antibiotic agent efficacy to penetrate biofilms can be increased by linking them to nanoparticles for antibiotic delivery. These

nanoparticles of 10 to 100 nm diameter can be of organic or inorganic material and mediate biofilm penetrance of the linked antibiotic agent (24,25). Similar effects have been shown for antibiotic conjugation with liposomes or antibacterial antibodies. The conjugated molecules allow for intracellular uptake of the antibiotic agent in host cells, where intracellular bacteria remain otherwise protected from antibiotics (26,27). New antibiotic molecules can at least temporarily overcome resistance. Oritavancin (28,29) and dalbavancin (30,31) are mentioned as two new molecules that show bactericidal effects in *S. aureus*. For oritavancin, *in-vitro* activity against *S. aureus* in stationary phase and biofilm has been shown (32). At day, they are not approved for PSII.

Finally, several alternative treatments to antibiotics are under development: some reports about antimicrobial peptides, small molecules of 5–100 amino acids, attest efficacy against bacteria and biofilm eradication power. The resistance of bacteria to antibiotic agents does not apply to these peptides, making them an interesting modality in the context of rising resistance and a potentially upcoming post-antibiotic era (16,33-35). The same accounts for bacteriophages, viruses of ubiquitary presence attacking and killing bacteria. Their specific direction of action towards bacteria including biofilm penetrance without harm for human cells, make bacteriophages a highly specific and promising means against PSII. The adapting resistance of bacteria to bacteriophages is counterstriked by the viral DNA adaption (36-40). In addition, monoclonal antibodies that bind to bacterial surface proteins have been reported. The immunotherapy works by the human clearance of opsonized bacteria by immune cells (41,42). Pilot studies about electrical stimulation of implants have been published. The concept is to break the biofilm pattern and kill bacteria within the film as well as in the surrounding tissue and liquid. Single studies of cathodic voltage-controlled stimulation of titanium document no adverse observations of the implant surrounding area (43,44).

Conclusions

Several promising attack-points have been identified and are emerging in the prevention, diagnosis and treatment of PSII. To keep up in this field will be important to retain spine surgery in the future as the state-of-the-art treatment option for mandatory spinal interventions in the presence of tumor or trauma and even more so as an attractive option for patients with degenerative spinal disorder for improvement of their life quality.

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