ECRONICON OPEN ACCESS

ORTHOPAEDICS
Research Article

Radiostereometric Analysis as a Need for Early Detection of Septic Loosening

Stefan Sesselmann[1]*, Tino Hausotte[2], Martin Timmermann[2], Gregor Liebsch[3], Raimund Forst[1], AndrejTrampuz[4], Anne Jacobsen[1]

[1]Department of Orthopaedic Surgery, Friedrich-Alexander-University of Erlangen-Nuremberg (FAU), Germany

[2]Institute of Manufacturing Metrology, Friedrich-Alexander-University of Erlangen-Nuremberg (FAU), Germany

[3]PreSens Precision Sensing GmbH, Regensburg, Germany

[4]Center for Musculoskeletal Surgery, Charité, University Medicine, Berlin, Germany

***Corresponding Author:** Stefan Sesselmann, Department of Orthopaedic Surgery, Friedrich-Alexander-University of Erlangen-Nuremberg (FAU), Germany.

Received: September 19, 2015; **Published:** October 03, 2015

Abstract

The previous increase of joint replacement surgery will continue to rise in the next decades. Although joint replacements belong to the most successful surgeries, particularly those of the hip and knee joints, complications may occur. One of the most difficultto treat complications is the periprosthetic joint infection specially if it is caused by microorganisms embedded in biofilms. The fact that biofilms are involved in implants makes diagnosis and treatment of periprosthetic joint infection demanding. Furthermore, scientific evidence for many diagnostic and therapeutic approachesis still missing. Diagnosis of infection involves clinical symptoms, laboratory parameters, histopathology, microbiology and imaging. Therapy, consisting of surgical treatment (prosthesis retention or exchange) and antimicrobial treatment, is complex and not always successful. A new approach for successful treatment of periprosthetic infection is being developed and investigated using radiostereometric analysis and new sensor techniques to detect biofilms on prosthesis surface earlier and in vivo, so that optimized antimicrobial therapy may be started before clinical symptoms appear.

Keywords: *Arthroplasty; Radiostereometric analysis; Implant loosening, periprosthetic joint infection, optical biofilm characteristics; Oxygen consumption of biofilms*

Abbreviations: CRP: C-reactive protein:; ESR: Erythrocyte sedimentation rate:; PJI: Periprosthetic joint infection;: RSA: Radiostereometric analysis

Introduction

In the past few years the number of primary and revision hip and knee arthroplasties increased in the western societies, and a further enormous increase is estimated in the next decades [1,2]. Hip and knee replacements belong to the most successful surgical procedures and implant-related problemsoccur in less than 10% of the patients [3]. One dreaded complication is implant loosening necessitating revision surgery, which has not only serious consequences for the patient and demands special treatment, but has also an enormous economic impact [4]. The Hip Society proposes implant loosening as one of 19 complications of total hip arthroplasty,and it is one of 22 complications of total knee arthroplasty according to the Knee Society [5,6]. According to the Swedish Hip Arthroplasty Register the most common reason for implant loosening after hip replacement is aseptic loosening (55,9%) followed by periprosthetic joint infection (12,3%) [7]. Although aseptic loosening is more common, periprosthetic joint infection (PJI) is the most devastating complication of arthroplasty, often followed by revision surgery [3]. As the treatment of aseptic and septic implant failure differs completely, precise determination of the reason for loosening is crucial for the clinical outcome. Especially PJI has to be detected to avoid an early relapse of infection after revision surgery and the consequences involved [8,9]. But diagnosis and therapy of PJI, particularly of late chronic infections, are still challenging, not least because of biofilms that make both difficult [10].

In this paper, we review the diagnostic procedures for PJI and the role of biofilms for diagnosis and treatment of PJI. Furthermore it should be argued, how radiostereometric analysis (RSA) as a screening method could assist with the diagnosis of not only aseptic but also septic implant loosening. Finally, we discuss the use of RSA in combination with modern techniques for in-vivo detection of biofilms, being under development, and how it may influence and improve the treatment algorithm of implant loosening.

Methodology

The literature research for the review about PJI includes the following search items: "periprosthetic joint infection", "joint infection", "prosthetic joint infection", "infection", "loosening of joint implant", "implant loosening", "biofilm", "joint implant", "micromotion", "radiostereometric analysis", "radiostereometry". Different combinations of these items were used and filtered with Boolean operators.

Discussion

The development of PJI after primary arthroplasty is related to bacteria existing in biofilms [11]. There are three ways how bacteria can contaminate prosthesis: perioperative inoculation, haematogenous spread from a remote infectious focus or contiguous spread from an adjoining focus (e.g. tissue lesion). Perioperative infection usually results in early (< 3 months after primary surgery) or delayed (3-24 months) infection onset depending on whether it is caused by highly or less virulent organisms. Late infection (> 24 months) is rather a consequence of haematogenous spread [3]. Early infections and acute haematogenous infections, often caused by high virulent organisms, are usually easy to diagnose.The more common late chronic infections aredifficult to detect and rathercaused by less virulent microorganisms [10].

Biofilms

When bacteria attach to the prosthesis surface which offers an avascular area protecting from body's defences, they form microcolonies and synthesize an extracellular matrix [11]. This is the beginning of the formation of a biofilm. Biofilms are complex three-dimensional structures which consist of microcolonies embedded in an intensely hydrated polymeric matrix. Bacteria at the surface are metabolically active whereas bacteria in the depth are inactive and grow slowly. Via interstitial voids (water channels resembling a simple circulatory system) the bacteria transpose nutrient and information in the form of signaling molecules. So they are able to react in a way called "quorum sensing": all bacteria of a population activate the same pattern of gene expression as a collective reaction. For example, these signals can induce differentiation of the biofilm by activating the relevant genes. Besides, there are excellent conditions in biofilms for the exchange of extrachromosomal DNA, so-called plasmids, which probably allows exchange of resistance factors, too. Another important ability of bacteria in biofilms is probably the programmed cell death when cells are injured [12,13]. There are some reasons which could explain the increased resistance of bacteria in biofilms against antimicrobials:

a. The extracellular matrix of the biofilm decelerates the saturation of antimicrobials through the biofilms.
b. The slow growth or stationary (non-growing) state of microorganisms in biofilms reduces the uptake of antimicrobial agents.
c. free floating subpopulations, actually susceptible to antibiotics, can develop phenotypical resistance [13].

Diagnosis

The diagnosis of PJI is difficult not only due to presence of biofilms. Constant joint pain, erythema, oedema, warmth and fever are not specific signs for PJI [11]. Furthermore aseptic and septic loosening of a joint implant sometimes can barely be differed, particularly in case of a low-grade infection when only continuous pain and early loosening occur or when clinical signs are completely missing [3]. Today PJI is typically diagnosed, if one of the following criteria is existent:

a. A sinus tract communicating with the prosthesis.
b. Purulence in the synovial fluid or around the prosthesis observed during surgery.
c. Acute inflammation in histopathologic examination of periprosthetic tissue specimens.
d. Inflammation in joint aspirates before surgery (knee prosthesis: leukocyte count > 1.7g/L or > 65% neutrophils, hip prosthesis: leukocyte count > 4.2g/L or > 80% neutrophils.
e. Positive microbiology of joint aspirates, periprosthetic tissue specimens or sonication fluid culture [8,14,15].

The risk of infection after primary hip or shoulder arthroplasty is < 1%, for knee replacement < 2% and for elbow prosthesis it is < 9%, but it rises substantially up to 40% after revision arthroplasty. However, it is assumed that PJI is underdiagnosed because of undetected infections which are misdiagnosed as aseptic failures [3]. Probably the rates of septic loosening are higher because of low-grade infections which couldn't be identified by common methods. Newer in vitro methods as e.g. sonication or molecular diagnostics facilitate the detection of infection because they are more sensitive [7,14,16].

Laboratory parameters

Blood leukocyte count and differential are not specific enough to differ between septic and aseptic prosthesis failure.C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) superiorly provide detection of PJI after hip and knee replacement. But as they are non-specific parameters of inflammation and cannot indicate the reason of an inflammation, postoperative increase can also result from other inflammatory illness [17]. In combination with clinical evaluation they show good sensitivity [18]. There is evidence that leukocyte count and differential of synovial fluid were able to detect a PJI in knee prosthesis of patients without inflammatory joint disease as they have a sensitivity of 94% and 97%, and specificity of 88% and 98%, respectively, for the cut-off values mentioned above [19].

Histopathology

In case of PJI the so-called periprosthetic membrane, a tissue layer between bone and prosthesis, shows a typical histological picture, especially distinguished by neutrophilic granulocytes [20]. Thus, histopathological analysis of periprosthetic tissue can detect inflammation which is defined as 1 to 10 or greater neutrophils per high-power field (sensitivity > 80%, specificity > 90%) [21]. It also allows differing between high-grade and low-grade infections which both show typical histological patterns [22].

Imaging

Imaging in general can support the diagnosis of PJI but cannotsufficiently differ between infection and aseptic loosening. Plain radiographs may give notice to infection showing radiolucent lines (> 2 mm) or severe osteolysis in the first year after arthroplasty. But prosthesis migration and osteolysis also occur with aseptic implant loosening. Contrast arthrography can indicate implant loosening and abscesses. Nuclear medicine imaging techniques seem to be sensitive but not specific in detecting PJI. Whereas computed tomography (CT), compared to plain radiography, is superior in the delineation of joint space, magnetic resonance imaging (MRI) shows soft tissue lesions in a higher resolution, but both are only conditionally applicable due to artefacts caused by interferences of metal implants [3,23].

Microbiology

Microbiological examinations can use three different specimens: Pre- or intraoperative specimens and removed implants. Preoperative specimens of wounds or sinus tracts can be used for culture, but they are often contaminated whereas cultures of aspirated synovial fluid are superior identifying the causative pathogen. Intraoperative specimens should consist of at least three periprosthetic tissue samples, swabs are obsolete due to low sensitivity. Cultures of periprosthetic tissue are often used as reference standard for diagnosis of PJI. Any antimicrobial therapy has to be interrupted 2 weeks before the specimens for culture are collected. Removed prosthesis also can be cultured in enrichment broth. Sonication of implants can improve the sensitivity of the culture [24,21].

As biofilms adhere strongly to the surfaces of prosthesis cultural isolation of bacterial cells can be difficult. Sonication of removed implants should expel the bacteria of the colonized surface to isolate them for subsequent microbiological cultures. Several surveys provide evidence for the increased sensitivity of sonication fluid cultures compared to periprosthetic tissue cultures. Sonication enhances the detection of pathogens and provides more rapid diagnoses [14,25,16,26].

There is some evidence that multiplex PCR of sonicate fluid can reliably detect pathogens of PJI, even in patients with prior antibiotic therapy when culture is difficult [9,27]. Ryu et al. expected PCR to be more rapid and more sensitive than microbiological cultures and to detect organisms that cannot be cultured. Especially, in cases when the prosthesis is received and sonication of implants is not possible, multiplex tissue PCR could be a promising alternative technique for PJI dianosis. However, it was found that multiplex tissue PCR is much less sensitive than tissue culture, synovial fluid culture, sonicate fluid culture, and sonicate fluid PCR, whereas specificity

is similar. But the authors argue that biofilms and the bacteria therein grow at the prosthesis surface and are not evenly spread over the surrounding tissue so the small volume of tissue samples may have prevent the detection with tissue PCR. Further research on this issue is demanded [28]. Zegaer., *et al*. [18] found that the universal 16S rDNA PCR technique is not helpful to identify bacteria. Whereas it could detect DNA of bacteria in the samples with agreement with periprosthetic tissue culture, it failed to identify the DNA product after sequencing, perhaps because of the coexistence of other microorganisms in the sample. The specific PCR, too, showed discrepancies for sensitivity and specificity. Thus the authors explain that DNA PCR isn't a reliable and appropriate method for diagnosing PJI but they suggest RNA PCR as a promising diagnostic tool.In contrast Suda., *et al*. [29] could provide evidence that 16S rDNA PCR of biofilms, scratched from prosthetic surfaces by surgical knife, could reliably identify the causative pathogen of PJI and detect additive pathogens. They state that this method should be part of an ideal standard algorithm for diagnosis of PJI because it is easy to realise and an useful addition to the standard diagnostic assessment of PJI.

It can be supposed that the effect of PCR depends on the used sample (sonication fluid, tissue, biofilm) and the number of pathogens in a sample. Further research on these issues is needed.

Treatment

The treatment of PJI is still challenging due to difficult surgery, increasing development of resistances against antibiotics and, not least, the presence of biofilms in PJI. Biofilms built by bacteria causing PJI make an infection difficult to treat because the biofilm prevents a complete eradication. Time is a contributing factor for the building of a biofilm: the longer it has been grown the more difficult it is to eradicate [30]. Thus, not only an appropriate surgical management is necessary but also an adequate antimicrobial regimen is absolutely required, to get a complete eradication of infection and therefore a pain-free, functional joint.

Surgical management

Surgical treatment of PJI includes the exchange of prosthesis either in a one- or two-stage exchange, debridement with retention of prosthesis, arthrodesis and amputation. Debridement with retention involves removal of all necrotic and infected tissue and bone, exchange of liners and joint lavage [21,30,31]. Early PJI can successfully be treated by surgical debridement, exchange of mobile parts, retention of prosthesis and biofilm-active antibiotics, function and quality of life after treatment are comparable to patients without PJI [32]. A recent study showed evidence that gram-negative bacilli PJI could successfully be treated with debridement and prosthesis retention in combination with an intravenous antibiotic therapy followed by an oral antibiotic regimen including fluoroquinolones assumed that organisms are susceptible to fluoroquinolones. Although in general only one debridement surgery is conducted the authors of this study propose that repeated debridements to eradicate biofilms are one reason for good outcomes in their study, but further research into this issue is demanded [33].

Exchange surgery contains resection of the infected prosthesis, debridement and re-implantation of a new prosthesis either during the same procedure (one-stage exchange) or delayed in a second surgery (two-stage exchange). In case of two-stage exchange, which is the traditional and most common treatment approach, in first surgery usually an antibiotic-loaded spacer is inserted [21,30]. Ilchmann., *et al*. [34] analyzed in a recently published observational cohort study data of 39 patients suitable for one-stage exchange and they report good outcomes for one-stage surgery in all patients. However, as there is still a lack of controlled trials surgical strategies differ between individual surgeons and centers. Trampuz and Zimmerli [24] propose a surgical treatment algorithm based on factors such as onset of infection, individual risk factors, type of pathogen or damaging of tissue. According to Zimmerli and Moser [35] all surgical procedures lead to a similarly good outcome (cure rates > 80%), if the algorithms conditions are considered.

Medical treatment

Medical treatment is based on antibiotics effective against biofilm-building organisms. For example, the penetration of rifampicin, clindamycin, and macrolides is not affected by biofilms whatincreases susceptibility of bacteria embedded in biofilms [12]. Antibiotic regimen usually starts with intravenous beta-lactams, glycopetides, or daptomycin to decrease the bacterial load previous to oral therapy. Thus the emergence of resistance during initial therapy can be avoided [35]. Antimicrobial therapy without surgery is only reasonable when surgery is contraindicated for patients [21].

Evidence for antimicrobial effects of oral antibiotics is rare except of rifampicin. Rifampicin has a good antimicrobial effect against biofilm-forming staphylococci but it has absolutely to be combined with another antimicrobial to avoid the development of rifampicin-resistant staphylococci. Typically used in combination with rifampicin are fluoroquinolones particularly levofloxacin or ciprofloxacin [30,36]. For treatment of fluoroquinolone-resistant staphylococci daptomycin seems to be effective in combination with rifampicin [37]. For the eradication of gram-negative bacilli oral fluoroquinolones, particularly ciprofloxacin, show evidence. In case of Pseudomonas or Acinetobacter infections the concurrent treatment with anti-pseudomonas beta-lactams (such as piperacillin/tazobactam, meropenem or ceftazidim) seems to be useful to avoid the development of ciprofloxacin resistance. Only few data exist for treatment of PJI caused by enterococci or streptococci:There is some evidence for intravenous beta-lactams for susceptible strains and a combination of penicillin with ceftriaxone in event of enterococci has been successful in some patients. For penicillin-resistant enterococci intravenous vancomycin-therapy can be orally continued with linezolid. For streptococci, the combination of penicillin or amoxicillin and rifampicin is proposed, other experts suggested clindamycin [30].

Much more research is needed having regard to biofilm-active agents, optimal duration of antibiotic therapy, and treatment of uncommon microorganisms.

RSA as screening method for implant loosening

PJI involves implant loosening: An early infection causing inflammatory reaction and subsequent bone resorption reduces initial fixation and leads to long-term implant instability [38]. Furthermore, later infection can result in motion of initially stable implants [39]. Radiostereometric analysis (RSA), rather than conventional radiographs, can detect these migrations with a superior accuracy varying from 0.05 to 0.5 mm for translational movements and from 0.15° to 1.15° for rotation [40]. RSA uses tantalum markers inserted into bone during joint replacement surgery as fixed points to which the relative motion of prosthesis will be calculated [41]. Currently, RSA is typically used for detection ofaseptic implant failure: RSA studies are conducted for evaluation of new joint implants, implant components and fixation techniques to get information about early micromotion which can predict implant failure [42-45]. RSA examinations over a relatively short period after surgery can predict the clinical outcome in the long term [46,47]. Furthermore, different types of implants can be compared by RSA concerning their stability [39,48]. Although RSA is currently not used to detect septic implant loosening, it could be a valuable support for detection as it is able to quantify elementary micromotions of implants.

Outlook

Future methods for *in-vivo* detection of PJI

It is worked on development of new methods for *in-vivo* detection of biofilms. One approach focuses on optical analysis of biofilms and the development of sensors which can detect different surfaces despite nearly similar indices of refraction. For pre-examinations, a model of an artificial biofilm would be established consisting of agarose beads before biofilms on removed implants would be analyzed. Different optical procedures as for example low-coherence interferometry and optical coherence tomography should help to identify typical characteristics of biofilms.

Another approach is based on oxygen consumption of biofilms due to its metabolic activity. A thin and flexible oxygen sensor foil consisting of an indicator dye doped polymer is exposed to a biofilm by an endoscope. The polymer of the sensor forms a porous structure which incorporates oxygen sensitive dyes and at the same time shows a high solubility to molecular oxygen resulting in an oxygen reservoir within the sensor foil. Covering the biofilm with the oxygen sensor foil forces the biofilm to consume the oxygen from the reservoir of the sensor and the oxygen sensitive dyes of the senor will directly report the oxygen decrease. So a decrease in sensor oxygen shows metabolic activity of microorganisms embedded in the biofilm. A similar method is used for measurement of perfusion in microvascular flaps [49]. The combination of both approaches should improve sensitivity and specificity.

Future directions

As mentioned above, septic loosening is a challenging complication in the field of arthroplasty as it is different to diagnose and treat and leads to immense discomfort for patients and surgeons. Septic implant failure is usually followed by extensive therapeutic

procedures which cannot always succeed. Just like aseptic failure, septic loosening of joint implants starts with micromotions of prosthesis, potentially before clinical symptoms or changes in conventional radiographs occur. RSA is the gold standard for detection of these early migrations to diagnose aseptic loosening but it could also provide an indication for septic loosening as it detects the earliest motions. Obviously, a differentiation between aseptic and septic loosening by RSA is not possible. However, the future technology of biofilm sensors should enable the direct in-vivo detection of biofilms on implants via arthroscopy. A new approach to diagnosis and treatment of PJI may be imaginable from these developments: RSA as a routine follow-up examination after joint replacement surgery could detect micromotions. Arthroscopic use of new sensors could identify biofilms on prosthesis in vivo and, thus, could indicate whether micromotions are caused by septic or aseptic loosening. These findings determine the following therapy: In case of septic loosening the therapy is as mentioned above, with debridement or prosthesis exchange and antibiotic therapy. But the early detection of a biofilm indicating a PJI may be an advantage because, on the one hand, an early revision surgery would allow the preservation of bone and reduction of tissue damage, so revision surgery is facilitated. On the other hand, the biofilmmay notbe already mature, what it makes it easier to eradicate [10,50]. A complete eradication of biofilm *in vivo*, for example by future in vivo sonication, may enable rescue surgery receiving the original implant instead of prosthesis exchange. Of course, these are visions nowadays and processing of new methods and further research on this issue is not only necessary but also needs time. Nonetheless it could be the future of managing periprosthetic infections.

Bibliography

1. Del Pozo., *et al.* "Infection Associated with Prosthetic Joints". *New England Journal of Medicine* 361.8 (2009): 787-94.
2. Kurtz., *et al*. "Projections of Primary and Revision Hip and Knee Arthroplasty in the United States from 2005 to 2030". *The Journal of bone and joint surgery. American volume* 89.4 (2007):780-785.
3. Trampuz A and W Zimmerli. "Prosthetic Joint Infections: Update in Diagnosis and Treatment". *Swiss Medical Weekly* 135.17-18 (2005): 243-251.
4. Kurtz., *et al*. "Future Clinical and Economic Impact of Revision Total Hip and Knee Arthroplasty". *The Journal of bone and joint surgery: American volume* 89.suppl3 (2007): 144-151.
5. Healy WL., *et al*. "Complications of Total Hip Arthroplasty: Standardized List, Definitions, and Stratification Developed by the Hip Society". *Clinical Orthopaedics Related Research* (2015).
6. Healy WL., *et al*. "Complications of Total Knee Arthroplasty: Standardized List and Definitions of the Knee Society". *Clinical Orthopaedics Related Research* 471.1 (2013): 215-220.
7. Winkler T., *et al*. "[Periprosthetic Infection after Hip Arthroplasty]". *Orthopaedics* 43.1 (2014): 70-78.
8. Portillo ME., *et al*. "Prosthesis Failure within 2 Years of Implantation Is Highly Predictive of Infection". *Clinical Orthopaedics Related Research* 471.11 (2013): 3672-3678.
9. Achermann Y., *et al*. "Improved Diagnosis of Periprosthetic Joint Infection by Multiplex Pcr of Sonication Fluid from Removed Implants". *Journal of Clinical Microbiology* 48.4 (2010): 1208-1214.
10. Cobo J and JL Del Pozo. "Prosthetic Joint Infection: Diagnosis and Management". *Expert Review of Anti Infective Therapy* 9.9 (2011): 787-802.
11. Al Mohajer., *et al*. "The Expanding Horizon of Prosthetic Joint Infections". *Journal of Applied Biomaterials & Functional Materials* 12.1 (2014): 1-12.
12. Donlan RM and JW Costerton. "Biofilms: Survival Mechanisms of Clinically Relevant Microorganisms". *Clinical Microbiology Reviews* 15.2 (2002): 167-93.
13. Trampuz A., *et al*. "Molecular and Antibiofilm Approaches to Prosthetic Joint Infection". *Clinical Orthopaedics and Related Research* 414 (2003): 69-88.
14. Trampuz A., *et al*. "Sonication of Removed Hip and Knee Prostheses for Diagnosis of Infection". *The New England Journal of Medicine: Research & Review* 357.7 (2007): 654-663.
15. Berbari Elie F., *et al*. "Risk Factors for Prosthetic Joint Infection: Case-Control Study". *Clinical Infectious Diseases* 27.5 (1998): 1247-54.

16. Portillo ME., *et al*. "Advantages of Sonication Fluid Culture for the Diagnosis of Prosthetic Joint Infection". *The Journal of Infection* 69.1 (2014): 35-41.
17. Piper KE., *et al*. "C-Reactive Protein, Erythrocyte Sedimentation Rate and Orthopedic Implant Infection". *PLoS One* 5.2 (2010): e9358.
18. Zegaer Batool., *et al*. "Detection of Bacteria Bearing Resistant Biofilm Forms, by Using the Universal and Specific Pcr Is Still Unhelpful in the Diagnosis of Periprosthetic Joint Infections(Pji)". *Frontiers in Medicine* 1.30 (2014).
19. Trampuz Andrej., *et al*. "Synovial Fluid Leukocyte Count and Differential for the Diagnosis of Prosthetic Knee Infection". *The American Journal of Medicine* 117.8 (2004): 556-562.
20. Morawietz L., *et al*. "Twenty-Three Neutrophil Granulocytes in 10 High-Power Fields Is the Best Histopathological Threshold to Differentiate between Aseptic and Septic Endoprosthesis Loosening". *Histopathology* 54.7 (2009): 847-853.
21. Zimmerli Werner Andrej Trampuz and Peter E Ochsner. "Prosthetic-Joint Infections." *New England Journal of Medicine* 351.16 (2004): 1645-1654.
22. Krenn V., *et al*. "Revised Histopathological Consensus Classification of Joint Implant Related Pathology". *Pathology Research and Practice* 210.12 (2014): 779-786.
23. Peel Trisha N., *et al*. "Prosthetic Joint Infection: Challenges of Diagnosis and Treatment". *ANZ Journal of Surgery* 81.1.2 (2011): 32-39.
24. Trampuz A and W Zimmerli. "Diagnosis and Treatment of Implant-Associated Septic Arthritis and Osteomyelitis." *Current Infectious Disease Reports* 10.5 (2008): 394-403.
25. Nguyen LL., *et al.* "Detecting Bacterial Colonization of Implanted Orthopaedic Devices by Ultrasonication". *Clinical Orthopaedics and Related Research* 403 (2002): 29-37.
26. Evangelopoulos DS., *et al*. "Sonication: A Valuable Technique for Diagnosis and Treatment of Periprosthetic Joint Infections". *The Scientific World Journal* (2013): 375140.
27. Gomez Eric., *et al*. "Prosthetic Joint Infection Diagnosis Using Broad-Range Pcr of Biofilms Dislodged from Knee and Hip Arthroplasty Surfaces Using Sonication". *Journal of Clinical Microbiology* 50.11 (2012): 3501-3508.
28. Ryu Seong Yeol., *et al*. "Low Sensitivity of Periprosthetic Tissue Pcr for Prosthetic Knee Infection Diagnosis". *Diagnostic Microbiology and Infectious Disease* 79.4 (2014): 448-53.
29. Suda Arnold J., *et al*. "Prosthetic Infection: Improvement of Diagnostic Procedures Using 16s Ribosomal Deoxyribonucleic Acid Polymerase Chain Reaction". *International Orthopaedics* 37.12 (2013): 2515-2521.
30. Aboltins C., *et al.* "Current Concepts in the Management of Prosthetic Joint Infection". *Internal Medicine Journal* 44.9 (2014): 834-840.
31. Peel TN., *et al*. "Diagnosis and Management of Prosthetic Joint Infection". *Current Opinion in Infectious Diseases* 25.6 (2012): 670-676.
32. Aboltins C., *et al*. "Early Prosthetic Hip Joint Infection Treated with Debridement, Prosthesis Retention and Biofilm-Active Antibiotics: Functional Outcomes, Quality of Life and Complications". *Internal Medicine Journal* 43.7 (2013): 810-815.
33. Aboltins CA., *et al*. "Gram-Negative Prosthetic Joint Infection Treated with Debridement, Prosthesis Retention and Antibiotic Regimens Including a Fluoroquinolone". *Clinical Microbiology and Infection* 17.6 (2011): 862-67.
34. Ilchmann T., *et al*. "One-Stage Revision of Infected Hip Arthroplasty: Outcome of 39 Consecutive Hips". *International Orthopaedics* (2015).
35. Zimmerli., *et al*. "Pathogenesis and Treatment Concepts of Orthopaedic Biofilm Infections". *FEMS Immunology & Medical Microbiology* 65.2 (2012): 158-168.
36. Berdal JE., *et al*. "Use of Rifampicin and Ciprofloxacin Combination Therapy after Surgical Debridement in the Treatment of Early Manifestation Prosthetic Joint Infections". *Clinical Microbiology and Infection* 11.10 (2005): 843-45.

37. Lora-TamayoJaime., *et al*. "High Doses of Daptomycin (10 Mg/Kg/D) Plus Rifampin for the Treatment of Staphylococcal Prosthetic Joint Infection Managed with Implant Retention: A Comparative Study". *Diagnostic Microbiology and Infectious Disease* 80.1 (2014): 66-71.
38. Bauer TW and J Schils. "The Pathology of Total Joint Arthroplasty.Ii. Mechanisms of Implant Failure". *Skeletal Radiology* 28.9 (1999): 483-497.
39. Pijls BG., *et al*. "The Beneficial Effect of Hydroxyapatite Lasts: A Randomized Radiostereometric Trial Comparing Hydroxyapatite-Coated, Uncoated, and Cemented Tibial Components for up to 16 Years". *Acta Orthopaedica* 83.2 (2012): 135-1341.
40. Sesselmann S., *et al*. "Radiostereometric Analysis of Hip Implants: A Critical Review of Methodology and Future Directions". *OA Musculoskeletal Medicine* 1.31 (2013).
41. Kärrholm J. "Roentgen Stereophotogrammetry. Review of Orthopedic Applications". *Acta Orthopaedica* 60.4 (1989): 491-503.
42. Sköldenberg OG., et al. "A New Uncemented Hydroxyapatite-Coated Femoral Component for the Treatment of Femoral Neck Fractures: Two-Year Radiostereometric and Bone Densitometric Evaluation in 50 Hips". *Journal of Bone & Joint Surgery* 93-B.5 (2011): 665-677.
43. Lazarinis S., *et al*. "A Prospective Cohort Study on the Short Collum Femoris-Preserving (Cfp) Stem Using Rsa and Dxa. Primary Stability but No Prevention of Proximal Bone Loss in 27 Patients Followed for 2 Years". *Acta Orthopaedica* 84.1 (2013): 32-39.
44. Wierer T., *et al*. "Radiostereometric Migration Analysis of the Lubinus Sp Ii Hip Stem: 59 Hips Followed for 2 Years". *Biomedizinische Technik. Biomedical engineering* 58.4 (2013): 333-341.
45. Tschunko F., *et al*. "Radiostereometric Migration Analysis of the Cerafit Femoral Stem: 28 Patients Followed for 2 Years". *Biomedizinische Technik. Biomedical engineering* (2015).
46. Kärrholm Johan. "Radiostereometric Analysis of Early Implant Migration-a Valuable Tool to Ensure Proper Introduction of New Implants". *Acta Orthopaedica* 83.6 (2012): 551-552.
47. Karrholm J., *et al*. "Does Early Micromotion of Femoral Stem Prostheses Matter? 4-7-Year Stereoradiographic Follow-up of 84 Cemented Prostheses". *The Journal of Bone & Joint Surgery* 76.6 (1994): 912-917.
48. Bettinson Karen A., *et al*. "All-Polyethylene Compared with Metal-Backed Tibial Components in Total Knee Arthroplasty at Ten Years. A Prospective, Randomized Controlled Trial". *The Journal of bone and joint surgery. American* 91.7 (2009): 1587-1594.
49. Meier JK., *et al*. "Simple, Fast and Reliable Perfusion Monitoring of Microvascular Flaps". *Clinical Hemorheology and Microcirculation* 50.1-2 (2012): 13-24.
50. Costerton JW., *et al*. "Bacterial Biofilms: A Common Cause of Persistent Infections". *Science* 284.5418 (1999): 1318-22.

Volume 2 Issue 3 October 2015