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PROPHYLAXIS, DIAGNOSIS AND TREATMENT OF PROSTHETIC JOINT INFECTIONS

Tese de Candidatura ao grau de Doutor em Ciências Médicas submetida ao Instituto de Ciências Biomédicas Abel Salazar da Universidade do Porto.

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Real knowledge is to know the extent of one's ignorance

Confucius

This work was performed in the Orthopedic Department of the Centro Hospitalar do Porto
with the cooperation of several other departments within the same institution.

Publicações

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- **Sousa R**, Massada M, Pereira A, Fontes F, Amorim I, Oliveira A. [Diagnostic accuracy of combined 99mTc-sulesomab and 99mTc-nanocolloid bone marrow imaging in detecting prosthetic joint infection.](#) *Nucl Med Commun* 2011;32-9:834-9.
- **Sousa R**, Munoz-Mahamud E, Quayle J, Dias da Costa L, Casals C, Scott P, Leite P, Vilanova P, Garcia S, Ramos MH, Dias J, Soriano A, Guyot A. [Is asymptomatic bacteriuria a risk factor for prosthetic joint infection?](#) *Clin Infect Dis* 2014;59-1:41-7.
- **Sousa R**, Soriano A, Guyot A. [Reply to Uckay et al.](#) *Clin Infect Dis* 2014;59-10:1507-8.
- **Sousa R**, Barreira P, Leite P, Santos AC, Ramos MH, Oliveira A. [Preoperative *Staphylococcus aureus* Screening/Decolonization Protocol Before Total Joint Arthroplasty: Results of a Small Prospective Randomized Trial.](#) *J Arthroplasty* 2016; 31-1:234-9.
- **Sousa R**, Serrano P, Dias J, Oliveira JC, Oliveira A. [Improving synovial fluid accuracy for the diagnosis of prosthetic joint infection with simple and inexpensive biomarkers: C-reactive protein and Adenosine deaminase.](#) *Bone Joint J.* 2017; 99-B:351-7.
- **Sousa R**, Silva M, Sousa A, Esteves J, Neves P, Seabra Lopes, Oliveira A. [Prosthetic Joint Infections Treatment with Debridement and Implant Retention: results of prospectively applying a predetermined protocol.](#) *Rev Port Ort Traum.* in press.
- **Sousa R**, Esteves J, Sousa A, Silva M, Ramos J, Seabra Lopes, Oliveira A. [Treatment of Prosthetic Joint Infections with Two-stage Exchange Surgery - results of a prospective study with a management protocol.](#) *Rev Port Ort Traum.* in press.

Preface

Those who know me the longest, know that my interest in prosthetic joint infections was born many years ago when I was still taking my first steps as an orthopedic resident. As many things in life, I think it happened by accident...

I was confronted with a series of patients suffering with infected total joint replacements and I witnessed my colleagues struggling hard to try and treat them and not often succeeding. Then I operated on D. Natalia, a very nice but extremely obese patient that I followed on the outpatient clinic after her total knee replacement. She presented persistent wound leakage and despite being prescribed antibiotic therapy she progressively worsened. I closely witnessed as she went through a long calvary of surgical debridements and prolonged periods of IV antibiotics followed by removal of the implant, a few more debridements and then ultimately a knee fusion! This patient really opened my eyes to this problem as I witnessed her downfall from being an active working women to a disabled woman struggling to walk with crutches...

I started reading and researching and I reached a point where I was able to identify a lot of common mistakes that were being made on a daily basis.

In order to systematically address this problem, I retrospectively looked at our institution's experience in dealing with prosthetic joint infections between 2001 and 2007. Out of 69 cases, only 30 were successfully treated! I undertook an extensive literature review and proposed a number of changes to our practice. I was lucky enough to see my work acknowledged and I continued to make clinical research on this topic throughout the years.

When I finished my residency, I had already set the scene for continued clinical research and transforming it into a PhD dissertation was but a natural event. My only condition was that I wanted it to be all about clinical research. At the end of the day, what I am really interested about is what can I do to improve the outcome of patients afflicted by prosthetic joint infections.

Now that it ends, I am sure the work must continue. There are still a lot of gray or even black areas in our current knowledge. Much of this needed understanding will certainly be born out of present and future cooperation with basic science researchers. Whereas our diagnostic accuracy and treatment results improved significantly in the past few years, the search for reliable diagnostic and treatment alternatives while providing a more comfortable and less disturbing experience to the patient is the next priority.

Acknowledgments

Naturally, a work of this span would not have been feasible without the help of many people that I must thank.

First and foremost, I would like to thank Professor António Oliveira. Long before I was even considering a PhD he had the vision to acknowledge me. I imagine it was not easy for a Head of Department to have a “kid” point out to an existing problem in such a sturdy way. I always felt encouraged to question the status quo and pursue the search for further know-how even if it meant leaving abroad. If there are conditions in our department to advance scientific research regardless of classic beliefs and traditions, it is greatly thanks to him. I also think I could not have made a better choice for my supervisor. I thank him deeply for helping me keep things in perspective whenever I got lost in the fine print. Lastly, I cannot thank him enough for all the times he proved his belief in me and my work and for all the occasions he helped promote it.

I would also like to deeply thank Professor Alex Soriano. We have come a long way since we met in 2010 and I had the chance to learn a lot about PJI management visiting his Bone and Joint Infection Unit. Not only is he a never-ending source of knowledge regarding prosthetic joint infections but he is also always glad to share his love for scientific research in this field. Thank you for greatly contributing for the success of the work we have been performing.

To Professor Maria Pia Ferraz I would like to thank her for introducing me to the world of basic science research, especially in the field of infection resistant implant surfaces. I hope we can further improve our cooperation and bring new developments to the clinical setting.

I also need to thank all those within my department that have endured me throughout the years. To Dr. Seabra Lopes a special thank you for always believing and trusting me and my work. I know he was fearful of taking on this endeavor within his group, because tradition implied these were difficult to treat cases that one would be better of avoiding. He always knew how to give me just the right amount of autonomy while always being there for support when I needed. To Dr. Costa e Castro for being a most helpful reviewer of all my papers since the beginning. Thank you for your always pertinent comments and insights.

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To all other colleagues that were kind enough to cooperate and accommodate my requests as well as those who trusted me to treat their cases. Without them I could not have gained much needed experience.

To all my junior colleagues that so willingly helped me collect, organize and process data. Without their help, it would not have been possible to perform the same amount of scientific output over the last few years.

To all the nurses of the Orthopedic Department, especially those in our outpatient clinic, for gladly embracing the added work load with a smile.

Although the main focus of this work was in the Orthopedic Department, it would not have been possible without the cooperation of several others.

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I would also like to sincerely thank Dra Joana Dias for all her statistical work over the years. If it wasn't for her support, know-how, thoroughness, patience, perseverance, and most of all endless hours spend with this research, our findings would certainly not have been as respectable.

Last but certainly not least, a few words to my loving family. I could not have made it here without their great sacrifice over the years. Thank you for everything! To my brother, a friend for every occasion. To my mother who never ceases to take care of me even when I am at my worst. To my father: Wherever you are, I am sure you can be proud of me now...

They say behind every great man there's a great woman and I am sure that whatever degree of greatness there might be in me, I owe it all to the women in my life. Ana, I cannot thank you enough for patience, encouragement, help, understanding, etc. In a word, love! Thank you, Clara, Joana and Teresa for being the sunshine of my life!

Abstract

Prosthetic joint infection is probably the most dreadful complication after total joint arthroplasty. It is indisputably a source of significant deleterious impact on a patient's health status and quality of life.

Prophylaxis is challenging because the implant greatly reduces the number of bacteria needed to cause a clinically relevant infection. There is no single measure able to completely eradicate it. Despite modern operating room environment and rigorous aseptic procedures there is still a growing rate of infection after elective total hip or knee arthroplasty. The patient itself as a source of bacterial endogenous contamination has become focus of attention recently. A positive co-relation between being *S. aureus* carrier and risk of infection as well as a positive impact of preoperative decolonization has been shown in different fields of surgery. Less information is available about asymptomatic bacteriuria and its possible influence on surgical site infection rates. We further studied these questions by analyzing the real impact in reducing prosthetic joint infection rates of preoperatively screening and treating *S. aureus* carriers and/or patients with asymptomatic bacteriuria.

Regardless of every progress made on prophylaxis, there will always be a small proportion of total joint arthroplasties that will need revision surgery. Distinguishing between septic and aseptic prosthesis failure is often difficult. There is no 100% accurate diagnostic modality. Definitive diagnosis relies on the combined interpretation of several different parameters and often it may only become clear after surgery. Notwithstanding, correct preoperative diagnosis is critical as treatment differs significantly. Despite its known limitations, arthrocentesis and subsequent synovial fluid examination is probably the most informative test currently available. We proposed to further refine the diagnostic accuracy of preoperative joint aspiration by more exhaustively studying synovial fluid biomarkers. In addition to leukocyte count and differential, we focused on simple, readily available and inexpensive molecules that could easily make the transition into clinical practice such as synovial C-reactive protein and Adenosine Deaminase. Once a proper diagnosis is reached, correct treatment is mandatory. Managing prosthetic joint infections is fastidious and often unrewarding as the results have been traditionally unfavorable. Although some centers of excellence are able to show reasonably satisfying success rates, that is not often true in day-to-day practice of many other institutions as was previously our own case. We sought to validate a rational and evidence-based approach by treating infected cases strictly according to a predetermined protocol that proved to offer significant improvements in treatment success rates.

Resumo

A infecção é provavelmente a complicação mais terrível após a realização de uma artroplastia. É indiscutivelmente fonte de significativo impacto sobre o estado de saúde do doente e sua qualidade de vida.

A profilaxia é um desafio porque a presença do implante reduz significativamente o número de bactérias necessário para causar infecção clinicamente relevante. Não existe nenhuma medida isolada capaz de erradicá-la completamente. Apesar do moderno ambiente do bloco e procedimentos de assepsia rigorosos, existe ainda uma taxa crescente de infecção após artroplastia eletiva da anca ou joelho. O próprio doente como fonte de contaminação bacteriana endógena tornou-se foco de redobrada atenção recentemente. Uma correlação positiva entre ser portador de *S. aureus* e risco de infecção, bem como um impacto positivo da descolonização pré-operatória tem sido demonstrada em diferentes campos cirúrgicos. Menos informação está disponível sobre bacteriúria assintomática e sua possível influência nas taxas de infecção do local cirúrgico. Estudamos estas questões, analisando o impacto real na redução das taxas de infecção protésica do rastreio e tratamento pré-operatório de portadores de *S. aureus* e/ou doentes com bacteriúria assintomática.

Independentemente do progresso feito na profilaxia, haverá sempre uma pequena proporção de próteses que necessitarão de cirurgia de revisão. Distinguir entre falência séptica e asséptica é muitas vezes difícil. Não há nenhuma modalidade de diagnóstico 100% exata. O diagnóstico definitivo baseia-se na interpretação conjunta de vários diferentes parâmetros e muitas vezes só após a cirurgia de revisão fica claro. Não obstante, o correto diagnóstico pré-operatório é fundamental, uma vez que o tratamento é significativamente diferente. Apesar de todas as limitações conhecidas, a artrocentese e subsequente exame do líquido sinovial é provavelmente o exame mais informativo atualmente disponível. Propusemo-nos refinar ainda mais a sua capacidade diagnóstica, estudando exaustivamente os biomarcadores existentes no líquido sinovial. Além da contagem diferencial de leucócitos, concentramo-nos em moléculas simples, generalizadamente disponíveis e baratas que poderiam facilmente fazer a transição para a prática clínica, como a proteína C-reativa sinovial e a Adenosina-deaminase.

Uma vez feito o diagnóstico, é necessário passar ao tratamento. Lidar com infecções periprotésicas é trabalhoso e muitas vezes pouco gratificante dado que os resultados têm sido tradicionalmente desfavoráveis. Embora alguns centros de excelência sejam capazes de mostrar taxas de sucesso razoavelmente satisfatórias, isso não é frequentemente o caso na prática quotidiana de muitas outras instituições como era anteriormente o nosso próprio caso. Procuramos validar uma abordagem racional e baseada na evidência, tratando os casos infectados estritamente de acordo com um protocolo pré-determinado que provou oferecer melhorias significativas nas taxas de sucesso do tratamento.

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Table I.F International Consensus Meeting Definition of Periprosthetic Joint Infection.

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Abbreviations

AAOS	American Academy of Orthopedic Surgeons	KSS	Knee Society Scores
AFB	Acid-fast bacillus	LE	Leucocyte esterase
ALBC	Antibiotic loaded bone cement	MoM	Metal-on-metal
ALVAL	Aseptic lymphocytic vasculitis - associated lesions	MRI	Magnetic resonance imaging
ADA	Adenosine Deaminase	MRSA	Methicillin-resistant <i>Staphylococcus aureus</i>
ASA	American Society of Anesthesiologists	MSSA	Methicillin-sensitive <i>Staphylococcus aureus</i>
ASB	Asymptomatic bacteriuria	MSIS	Musculoskeletal Infection Society
AUD	Australian dollars	NARA	Nordic Arthroplasty Register Association
BMI	Body mass index	NPV	Negative predictive value
CDC	Center for Disease Control	OR	Operating room
CFU	Colony forming units	PCR	Polymerase Chain Reaction
CI	Confidence interval	PCT	Procalcitonin
CoN	Coagulase negative	PET	Positron Emission Tomography
CRP	C-reactive protein	PJI	Prosthetic joint infection
CT	Computerized tomography	PMMA	Polymethylmethacrylate
DAIR	Debridement and Irrigation with Implant Retention	PMN	Polymorphonuclear neutrophil
DNA	Deoxyribonucleic acid	PPV	Positive predictive value
EBJIS	European Bone and Joint Infection Society	RBC	Red blood cells
ELISA	Enzyme-linked immunosorbent assay	SF-12	Short Form Health Survey 12
ESR	Erythrocyte sedimentation rate	SF-36	Short Form Health Survey 36
FDG	Fluorodeoxyglucose	SPET-CT	Single Photon Emission Computed Tomography
HOOS	Hip disability and Osteoarthritis Outcome Score	SSI	Surgical site infection
HIV	Human Immunodeficiency Virus	UK	United Kingdom
HPF	High power field	USA	United States of America
ICD-9-CM	International Classification of Diseases, 9 th Revision, Clinical Modification	USD	United States dollars
ICM	International Consensus Meeting	UTI	Urinary tract infection
IDSA	Infectious Diseases Society of America	THA	Total hip arthroplasty
IL	Interleukin	TJA	Total joint arthroplasty
IgG	Immunoglobulin G	TKA	TKA
IgM	Immunoglobulin M	UV	UV
KOOS	Knee injury and Osteoarthritis Outcome Score	WBC	WBC
		WHO	WHO
		WOMAC	WOMAC
		α2M	α2M

BACKGROUND

Burden of Infection

Prosthetic joint infection (PJI) widely acknowledged as the most feared complication after total joint replacement. In addition to significant medical implications for the patient it is also the source of substantial burden for the health care systems.

Epidemiology

PJI is fortunately, a relatively uncommon event. Despite all the attention that has been dedicated to this topic over the last few years, it is still very challenging to offer an undisputable estimate of its real incidence. Traditionally, contemporary PJI rates vary between 1-3% for primary total hip (THA) or knee arthroplasty (TKA) and higher, around 3-6% for revision surgery¹. The rate of surgical site infection after joint replacement is of course, highly variable and institution specific. Since 2009, we established a prospective department surgical site infection (SSI) surveillance program focusing on infection rate after primary total hip or knee arthroplasty (Fig. 1).

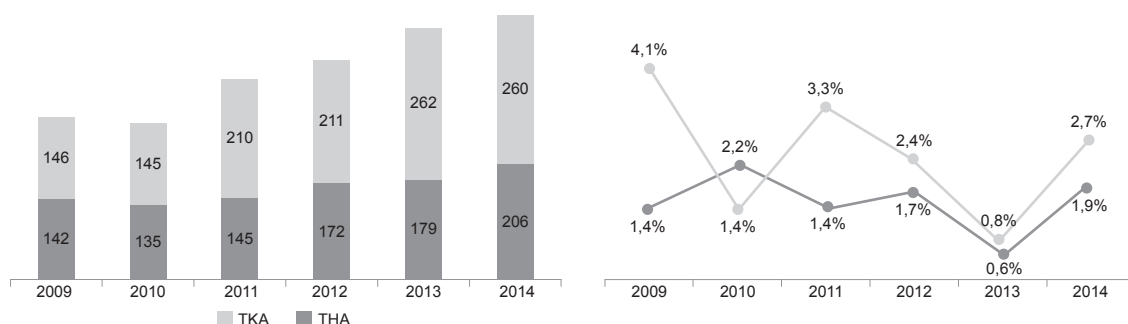


Fig. 1 Volume of primary arthroplasties (THA and TKA) and one year infection rate of our institution between 2009 and 2014.

We adopted the Center for Disease Control (CDC) recommendation to extend the surveillance period to 365 days following procedures that involve implantation of prosthesis to define our surgical site infection rate. We registered a trend towards increasing number of primary total joint arthroplasties (TJA) being performed each year and found that the overall infection rate during this six years' time period was 2.0% (44/2213). THA presented a somewhat lower infection rate compared to TKA, 1.5% (15/979) and 2.4% (29/1234) respectively. Revision

arthroplasty infection rate was calculated for the 2012-2014 period, and it was 6.4% (6/98) overall. Interestingly, revision THA infection rate was higher than revision TKA, 7.8% (5/64) vs. 2.9% (1/34) respectively. None of these differences reached statistical significance.

Conventional institutional surgical site infection surveillance, focuses chiefly on infections detected at the hospital where the operation was performed. Infections diagnosed and treated elsewhere can consequently be missed. A paper by Yokoe et al.² determined a statewide PJI infection rate using data submitted from every acute care hospitals in California. Out of a total of 91,121 THA and 121,640 TKA procedures, and using ICD-9-CM diagnosis codes predictive of SSI, they found 2214 (2.3%) THA and 2465 (2.0%) TKA presented with infection in the first postoperative year. They further found that seventeen percent of SSI would have been missed by operative hospital surveillance alone². Registries might theoretically be a way to more accurately report infection rates but that does not seem to be the case³⁻⁵. In a recent study from Denmark by Gundtoft et al.³ the authors' found that using several available data sources, the estimated "true" 1- and 5-year incidence of PJI following primary THA was 0.86% and 1.03% respectively. They found that based solely on national registries, incidence of infection was consistently 40% lower.

Notwithstanding these limitations and despite the increased awareness and prophylaxis efforts, the incidence of infection seems to be on the rise. On a study based on the Nordic Arthroplasty Register Association (NARA) dataset of 432,168 primary THA from 1995 to 2009, Dale et al.⁶ found an increasing risk of revision due to infection over time that could not be explained by change in registered risk factors. On the American side, the same phenomenon seems to be happening. Kurtz et al.⁷ found 159,360 procedures for infected hip (54,292) and knee (105,068) replacements in United States (US) hospitals between 2001 and 2009. They confirmed there was a significant year-to-year increase in the risk of both hip and knee infection over the study period even after adjusting for patient demographic factors.

In addition, it is well established that prosthetic joints are at risk for infection during their entire lifespan. Late infections occurring many years after index surgery are becoming more common as the number of people living with some kind of total joint arthroplasty is on the rise. Ong et al.⁸ determined the risk of PJI in a cohort of 39,929 primary total hip arthroplasty patients identified between 1997 and 2006. The incidence of infection was 1.6% within 2 years and 0.6% between 2 and 10 years. A recent Finnish study by Huotari et al.⁹ including 112,708 primary hip and knee replacements, found that the rate of late infections (i.e. occurring over 24 months after index surgery) was approximately 0.1% per prosthesis-year. Moreover, the incidence rate of late and very late PJI also seems to be increasing over time⁹.

As the requirements for total joint arthroplasty have been and are expected to continue steadily increasing so will the burden of infection^{10,11}. Even though infection rate is relatively low, the increasing prevalence of population living with some kind of total joint arthroplasty equates to a sizeable number of infections.

Patient Quality of Life

PJI is traditionally depicted as a devastating complication, that may potentially inflict significant morbidity in the patient's quality of life or even cause death in some instances. There is however scarce information in the literature regarding quantity and quality of life in these patients.

Berend et al.¹² studied 205 infected THA treated with a two-stage protocol. They found that despite a high rate of infection control there was a high mortality rate. Fourteen patients (7%) died before reimplantation and two (1%) were not candidates because of medical comorbidities. The 90-day mortality rate after the first-stage was 4% (eight patients). Overall, 91 patients (48%) died during the study period that extended between 1996 and 2009. Choi et al.¹³ investigated mortality rates after revision total hip arthroplasty in 93 infected patients and 93 matched control patients. They found the mortality rate was 33% (31/93) in the septic group and 22% (20/93) in the aseptic group at 5- and 6-year follow-up, respectively. The same authors performed a similar study focusing on 88 infected TKA patients and controls¹⁴. They found the overall mortality after revision TKA was 10.7% at a median of 4 years of follow-up. Most importantly, mortality after septic revision (18% - 16/88) was six times higher than that of aseptic revision (3% - 3/88)¹⁴. In a study by Zmistowski et al.¹⁵ the authors compared the outcome of 436 PJI patients with 2342 patients undergoing revision arthroplasty for aseptic failure and aimed to determine the effect of periprosthetic joint infection on mortality. PJI was associated with a fivefold increase in mortality even after controlling for other variables. Mortality in the PJI cohort was 3.7% at ninety days, 10.6% at one year and 25.9% at five years.

These figures compare unfavorably to some of the most frequently dreaded cancers such as female breast and uterus and male prostate cancer¹⁶. Of course, this increased risk of mortality is not only due to direct adverse effect of infection and treatment, but also the fact that PJI often reflects decreased health status. Nevertheless, these figures should raise awareness among surgeons to the systemic impact of infection and the need to address PJI in two dimensions that are tightly interconnected: infection eradication and general health status.

There is extensive evidence that successful total joint arthroplasty greatly increases the patients' quality of life regarding function, pain and mobility¹⁷. However, quality of life studies after PJI are surprisingly scant in the literature. Cahill et al.¹⁸ were among the first to address this issue. They compared 62 uncomplicated TJA with 34 PJI cases and naturally, found that infection reduces patient satisfaction and seriously impairs functional health status and health-related quality of life. Unfortunately, no information regarding infection control status was given. Helwig et al.¹⁹ were able to evaluate 58 patients with PJI and applied the Short Form Health Survey 12 (SF-12) as to their overall quality of life. They did find a significant disadvantage in the physical scale but not the mental scale in this cohort compared to the general German population. Surprisingly they found no significant difference in either scale when comparing successful vs. unsuccessful therapy¹⁹. The authors did not differentiate between those treated with debridement and implant retention and one- and two-stage revision protocols. Patil et al.²⁰ compared clinical outcomes and patient satisfaction rates of aseptic (30) versus septic (15) revision TKA. Interestingly, patients operated for infection had

better post-operative Knee Society Scores (KSS), Function Scores and SF-36 Mental Scores than aseptic group but there were no significant differences in the satisfaction rates. Just recently, Aboltins et al.²¹ prospectively collected pre- and post-arthroplasty data of 2,134 TJA patients, of which PJI occurred in 41. PJI cases treated with debridement and retention had a similar improvement from pre-arthroplasty to 12-months post-arthroplasty as patients without PJI in quality of life according to the SF-12 survey. The analysis however did not evaluate the potential influence of the infecting pathogen. Núñez et al.²² evaluated 24 patients who underwent debridement and retention of the prosthesis due to an acute knee PJI and were in remission after 12 months' follow-up. Health-related quality of life was measured using WOMAC and SF-36 at baseline (before TKA), 12 and 24 months after antibiotic treatment discontinuation. There was a significant improvement in all items from baseline to 48 months except for patients infected by *Staphylococcus aureus* who had significantly worse outcomes.

Our own experience reflects these observations. In a retrospective case-control study we focused on patients that underwent debridement with implant retention for suspected acute postoperative infection of total hip or knee arthroplasty between 2010-2014. Using validated patient reported outcome measures, Hip disability and Osteoarthritis Outcome Score (HOOS) or Knee injury and Osteoarthritis Outcome Score (KOOS), that include a joint related quality of life subscale, we were able to show no difference between 19 successfully treated cases and 38 uncomplicated TJA controls available for functional evaluation after 12 months' minimum follow-up. Regarding revision surgery, we studied 11 patients undergoing TKA two-stage exchange for infection and also found that function and quality of life as measured by the KOOS questionnaire was not inferior to a control group of five one-stage revisions for aseptic failures and four complex primary TKA using the same condylar constrained prosthesis. However, our own previously published paper on recalcitrant TKA infection salvage procedures shows inferior results in all KOOS sub-scales including quality-of-life²³.

Although more studies are needed to fully clarify the extent of the impact of PJI on patients' quality of life it is undeniable that it must be a concern for surgeons. It would seem that early detection of infection and successful treatment with debridement and implant retention is perhaps the more advantageous course of treatment. Revision surgery (regardless of the cause of failure) seems to have a more significant impact. Failure in eradicating infection or salvage procedures naturally leads to more deleterious effect on health-related quality of life.

Economics

In addition to the clinical implications, PJI management also represents a substantial economic burden for hospitals, health-care systems and most importantly, patients. Infection is consistently one of the leading causes for total joint revision surgery all over the world²⁴⁻³². It is often the first or second most common indication for revision total knee arthroplasty^{24,28,29,31} and the third most common in revision total hip arthroplasty after aseptic loosening and dislocation^{27,29,33,34}. It is also a leading cause for failure of other prosthesis, specifically shoulder, elbow and ankle^{33,35}.

The real cost of treating an infected joint is not easy to ascertain. Naturally, it depends on a lot of variables such as the specific type of treatment, patient co-morbidities and even bacteria related factors such as antibiotic susceptibility profile. The full spectrum of economic impact comprises the more commonly reported direct in-hospital costs, but also outpatient direct costs (follow-up visits, rehabilitation, pharmacy, etc.) and even indirect costs that are virtually impossible to accurately assess such as productivity loss and absenteeism from work of the patient or even his caregivers.

Kurtz et al.⁷ including over 150,000 PJI cases, found that the average total hospital costs for infected hip revision were \$72,700 United States dollars (USD) in 2001 and \$93,600 USD in 2009. The average charges for infected knee revision were \$58 700 USD in 2001 and \$74 900 USD in 2009. More recent studies from the US include not only inpatient but also outpatient services costs. In 2014, Kapadia et al.³⁶ identified 21 infected TKA and matched them to 21 non-infected patients who underwent uncomplicated primary surgery. Naturally, patients with PJI had significantly longer hospitalizations, more readmissions and more clinic visits. The mean total episode cost (fixed- and variable-direct costs) for patients with a surgical site infection was \$116,383 USD (range, \$44,416 to \$269,914) which was significantly higher than a mean \$28,249 USD (range, \$20,454 to \$47,957) in the matched group. Just recently the same authors, studied 16 consecutive infected THA and matched them to 32 non-infected patients. Similarly, the mean episode cost was significantly higher in the infected group, \$88,623 USD (range, \$44,043-\$158,202) when compared to the matched cohort, \$25,659 USD (range, \$13,595-\$48,631). Naturally, specific cost varies dramatically from one setting to another depending on the type of healthcare system and the corresponding economic standards. Fernandez-Fairen et al.³⁷ performed a systematic review of the literature and found huge discrepancies in absolute values between publications according to its country of origin. Nonetheless, the cost for septic revision was consistently around 2-4 times more expensive than primary surgery. It was also 1.5-3 times more expensive than aseptic revision surgery. Early acute and hematogenous PJI cases can be treated effectively without revision surgery. An Australian study by Peel et al.³⁸, aimed specifically to calculate the cost associated with debridement and implant retention treatment. For that, they focused on 21 prosthetic joint infections (12 THA and 9 TKA) and matched them to 42 control patients with uneventful primary joint replacements. For patients with infection the total cost, including index operation and costs of PJI management was 3.1 times the cost of primary arthroplasty. The mean cost for cases was Australian dollars (AUD) \$69,414 compared with \$22,085.

We performed a similar economic analysis in our own institution, focusing exclusively on inpatient costs. Variables included were Hospital Bed costs, Pharmacy including antibiotics, Laboratory, Radiology, Blood products, etc. and Operating Room costs including orthopedic, anesthesia and nursing personnel as well as costs with implants, medications, surgical supplies and post-operative recovery bed. Unfortunately, we were not able to collect data for outpatient and emergency department visits as well as other outpatient direct and indirect costs. During the study period (January/2014 – December/2015), our mean total cost on uneventful 459 TKA and 256 THA was 3,618€ and 3,230€ respectively. Debridement and implant retention was the chosen method of treatment in 16 patients (8 TKA, 8THA) and their mean cost was 4,009€ and 5,431€ respectively which is around 2-2.5 times higher when compared to uneventful knee and hip joint replacement.

We also determined the mean cost for aseptic revision and compared it to two-stage revision for infected joints. Overall aseptic hip revision mean costs were 6,324€. Aseptic partial hip revisions were performed in 17 cases and averaged 5,994€ and total (both components) revision was performed in 4 cases with a mean cost of 7,730€. There were 13 aseptic total knee revision cases costing a mean 7,985€ each. Two stage revision is the preferred method in our department and it was performed in eight infected TKA and six infected THA during the study period. Taking into account both admissions, the overall mean cost was 12.551€ for knees and 11.415€ for hips. These costs are around 3.5 times higher than primary uneventful arthroplasty and 1.5 times the cost of revision for causes other than infection. To the best of our knowledge this is the only such study performed on the cost of PJI treatment in the Portuguese National Health System.

Biofilm and its Implications

Lastly, it is not possible to discuss all the nuances and difficulties surrounding prosthetic joint infections without first examining the role of microbial biofilms. In order to comprehend implant-related infections, one has to acknowledge a new microbiology paradigm. The classical view that bacteria grow as rapidly replicating free-floating individuals in a planktonic form causing vigorous host inflammatory response does not apply. It has been extensively shown that in most environments, including the human body, microbes grow predominantly in biofilms. Over 65% of all human infections are estimated to be biofilm-related³⁹. Although bacterial growth on surfaces has been described earlier, it was not until the extensive research performed by J.W. Costerton that it gained prominence in the scientific community³⁹. More than three decades ago, Gristina & Costerton⁴⁰ promoted the idea that microbial biofilms were responsible for increased susceptibility to infection in the presence of biomaterials and constitute a significant factor in the persistence of such infections until the removal of the prosthetic device. Since then, a considerable amount of research has supported this concept⁴¹.

Biofilms are highly structured usually adherent communities of microbial cells (of one or several different species) that express different phenotypes than its planktonic counterparts. They further produce extracellular matrices consisting mainly of exopolysaccharides, proteins, teichoic acids and lipids that surround them allowing for cell-to-cell communication and creating a protected environment⁴². In their fully mature form, biofilms act almost as multicellular organisms with each cell assuming a specific role and communicating with each other - the so called “quorum sensing” - thus combining efforts to protect themselves against the hostile environment around them⁴³.

Accordingly, the development of a biofilm onto an orthopedic implant can be described as a four stage process⁴⁴: 1) *cell adhesion* - starts immediately during surgery with the bacteria reaching the implant surface. This process is mediated by factors such as implant surface charge, hydrophobicity and topography as well as interaction between bacterial and host proteins; 2) *cellular aggregation* - in this stage, there is bacterial proliferation as well as cell-to-cell adhesion that ultimately lead to the formation of bacterial micro colonies. These organized structures are then surrounded by self-produced extracellular matrix or slime. At this point, the biofilm is still relatively unstable and susceptible to eradication; 3) *biofilm maturation* - during the maturation process, physiologic changes occur within the biofilm and bacteria express altered phenotypes beneficial to microbial survival with distinct gene expression patterns and metabolic activity according to its specific location within the biofilm structure. When the biofilm is mature, it assumes a sessile form which is more resistant to eradication; and 4) *cellular detachment* - large mature biofilms may release planktonic forms (or small pieces of biofilm) of their surfaces which then disperse to cause further local invasion or seeding to distant sites. The presence of microbial biofilms in orthopedic implants are a real game-changer and understanding this microbial biofilm paradigm is critical in developing an accurate PJI management concept.

Prophylaxis

Prevention remains the best way to avoid the dire health-related and economic consequences of infection after TJA. Still, there is no isolated preventive measure that can fully eradicate PJI. The presence of the implant greatly reduces the minimal inoculum of bacteria required to cause relevant infection and as such, effective prophylaxis must rely on the combined action of numerous strategies. Various different events that ultimately lead to clinically relevant infections such as surgical field contamination, adhesion and proliferation of bacteria on the implant and host-pathogen interaction need to be addressed. The operating theatre is the primordial moment along this process but prevention of PJI must start before and continues well after.

Reviewing the whole body of literature concerning the prevention of surgical site infection is perhaps beyond the scope of this thesis. We will focus on current and relevant evidence and try to provide concise clinical practice oriented information on various preoperative, intraoperative and postoperative factors regarding the prevention of PJI specifically.

Ultimately, it is not possible for the orthopedic surgeon to manage all these variables on its own, patients should be advised and a multidisciplinary team should seek to optimize conditions before elective joint replacement surgery. It has been proven that such a team is able to implement strategies that effectively reduce PJI rates⁴⁵. Meanwhile, every surgeon must keep in mind that despite all the recent progresses in prophylaxis, there is no substitute for careful surgical technique.

Preoperative Considerations

The first step towards effective prevention of PJI is preoperative risk stratification. Knowing each patient's specific risk of infection would be ideal in terms of preoperative decision making and counselling. Several epidemiological and intrinsic patient factors closely relate to the risk of infection. Males for instances have been shown to be at greater risk in a recent meta-analysis⁴⁶.

Revision surgery or simply previous joint surgery (e.g. posttraumatic situations), previous history of joint infection, prior steroid injection into the joint or history of bone cancer are also known risk factors that are simply not influenced⁴⁷⁻⁵¹. While it is not possible to sway such factors, they are helpful in establishing a specific risk of infection for each patient that ultimately allows for better preoperative decision making, resource allocation, and enable more effective patient counselling^{52,53}.

Prevention efforts should focus on those known yet modifiable patient risk factors. Some are straightforward such as treating active or potential septic focus (e.g. pneumonia, infected leg ulcers) before surgery, but others require considerable commitment such as nutritional optimization and management of medical comorbidities. Screening for potential sources for endogenous contamination such as *Staphylococcus aureus* colonization or unrecognized bacteriuria has also been advocated. We will further elaborate on these topics elsewhere as they were the subject of our research.

MEDICAL RISK FACTORS

Countless patient-related factors have been implicated in the increased risk of PJI. Associated chronic co-morbidities such as heart failure, pulmonary disease, renal or liver disease, coagulopathies, rheumatologic arthropathy, etc. cannot be eliminated preoperatively but can and should be optimized in order to mitigate the risk of postoperative complications^{47,54-56}. There is strong evidence that overall health status and greater illness severity is an independent risk factor for infection^{46,55,57}.

Diabetes

It is well-established that diabetic patients often present delayed wound-healing and a disordered inflammatory/immune response. It is therefore not surprising that they are at increased risk for infection after TJA^{48,54,55}. Recently, it has been shown that the current status of glycemic control is more predictive than simply having a diabetes diagnosis. Marchant et al.⁵⁸ found not only a twofold greater risk of infection in patients with uncontrolled diabetes compared with nondiabetics but more interestingly an identical risk of infection between patients with controlled diabetes compared to the nondiabetic population.

Ideally one should strive to reach a good consistent glycemic control as measured by glycated hemoglobin below 7-8%. Several papers have confirmed the increased risk of infection above that threshold⁵⁸⁻⁶³. Nevertheless, in clinical practice some patients are simply unable to reach such a good control⁵⁹ and a risk-benefit decision should be made on an individual basis. As will be discussed ahead, proper close postoperative glucose control may be just as important and should not be disregarded especially in diabetic patients. Perioperative hyperglycemia is also associated with increased risk for infection even in patients without diabetes^{61,62}.

Obesity

Although it is not easily influenced, obesity is very common in total joint arthroplasty candidates and some considerations are mandatory. Not only has it been repeatedly found to be an independent risk factor for infection^{48,49,54-57,64} but it is also associated with increased risk of other comorbid conditions such as diabetes and cardiovascular disease. A somewhat linear relation seems to exist between increased body mass index (BMI) and the risk of infection. A few papers have shown, that more elevated BMI categories seem to have increasingly higher risk of PJI^{46,48,55,65}. Lubbeke et al.⁶⁶ clearly illustrate this trend. In their recent study including over 9,000 primary hip and knee arthroplasties, infection rates were similar in the first three

BMI categories (<35), but they were twice as high with BMI 35-39.9 and four times higher with BMI ≥ 40 ⁶⁶.

It therefore seems logical that patients should be strongly advised to lose weight before TJA. There are some reports showing more favorable outcomes if bariatric surgery is performed before TJA, especially if more than two years have passed⁶⁷⁻⁶⁹. Notwithstanding, there is no clear evidence to support or refute the use of bariatric surgery prior to arthroplasty has a positive effect on postoperative complications such as PJI or even on the long-term clinical outcome and quality of life is yet to be proven⁷⁰. Naturally it is important that both the patient and the surgeon discuss infection as a possible outcome when weight loss is not feasible.

Malnutrition

From a nutritional perspective, it is desirable that patients presenting for total joint arthroplasty have a lymphocyte count of >1500 cells/mL, an albumin level of >3.5 g/dL and a transferrin level of >200 mg/dL. The negative influence of preoperative malnutrition below these thresholds has long been recognized^{71,72}. There is enough evidence to show multiple nutrient-enhanced formulas can be used to prevent surgical site infections in adult patients undergoing major surgery⁷³. However, the use of enhanced nutrition support is expensive and requires additional expertise from nutritionist and/or pharmacists. Except for elderly patients with femoral neck fractures, such debilitated patients are extremely rare in the total joint arthroplasty setting.

Preoperative anemia is also often associated with poor nutritional status and it has also been shown to be an independent risk factor for infection^{54,56}. Prior studies have also shown that these patients are more likely to require blood transfusions postoperatively^{74,75} which are associated with an increased risk of infection as will be discussed later. Although prospective studies are still missing to confirm the real benefit of improving hemoglobin before surgery we believe it is a reasonable recommendation.

Tobacco use

Cigarette smoking increases the risk for perioperative complications, soft-tissue and wound-healing complications and ultimately musculoskeletal infection⁷⁶. Singh et al.⁷⁷ analyzed data from over 33,000 patients who underwent elective primary lower limb joint replacement. They found that current smokers at the time of elective surgery were more likely to have postoperative complications, especially surgical site infections and pneumonia and suggested preoperative smoking cessation programs should be considered. Although cessation is easier said than done, the effects of smoking on the skeleton may be (at least partially) reversible and that should encourage patients. Immune function appears to recover after two to six weeks of abstinence and wound-healing after three to four weeks^{76,78,79}. The benefits of preoperative smoking cessation interventions in reducing postoperative complications have been well established with each week of cessation prior to surgery increasing the magnitude of effect⁸⁰⁻⁸². Moller et al.⁸³ conducted a randomized trial specifically before hip and knee replacement. They found a decrease in overall complication rate, especially wound-related complications after a preoperative 6-8 weeks smoking cessation intervention⁸³.

Alcohol Abuse

Patients who consume alcohol on a frequent basis may have a significantly increased risk for postoperative complications after arthroplasty⁸⁴. Although the benefit of alcohol cessation programs before surgery is not well established in the literature, it is reasonable to expect patients to reduce alcohol consumption prior to surgery and to delay elective arthroplasty in alcoholic patients until the issue has been addressed⁸⁵.

Immunosuppression

Immunosuppressive therapy is becoming increasingly common among TJA candidates. End stage inflammatory arthritis (rheumatoid arthritis being the most frequent) is a common indication for joint replacement. These patients are fundamentally different from osteoarthritis in terms of pathogenesis and it is therefore natural to expect these patients would have increased infection rates. In fact, many have found rheumatologic disease to be an independent risk factor for PJI for both the THA and TKA^{46,54,56,86,87}. Organ transplant recipients are also becoming more common candidates to TJA due to degenerative osteoarthritis or osteoporotic-related disease (e.g. hip fractures) as survival rates after transplant surgery are improving. Naturally these patients have increased risk of infection and other perioperative complications due to inherent medical co-morbidities and immunosuppressive medication^{51,53,88}. This risk however seems to be much more significant in knees rather than hips although the reason for such a discrepancy remains unclear⁸⁸.

Immunosuppressive medical therapy with corticosteroids, disease-modifying anti-rheumatic drugs and other drug(s) are often blamed for this risk. Still, evidence regarding the benefits of therapy discontinuation before surgery is conflicting^{89,90} and recommendations are also contradictory. Considering the scarce evidence to support discontinuation of treatment and even potential harm it may cause such as the risk of flare-up of the underlying condition, recently issued World Health Organization (WHO) guidelines on preoperative measures for surgical site infection prevention state immunosuppressive medication should not be discontinued routinely⁷³. On the other hand, the International Consensus Meeting (ICM) on PJI advocates disease-modifying agents should be stopped prior to elective joint replacement⁸⁵. Decision to discontinue immunosuppressive medication should be made on an individual basis and involve the prescribing physician.

Human Immunodeficiency Virus (HIV) carriers constitute another group of patients with compromised immune system that, given their increasing long-term survival and high rates of osteonecrosis are increasingly being considered for TJA as symptom relief and functional outcome seem to overlap those found in general population⁹¹. As HIV medical management, together with educational strategies continues to improve, the risk of PJI seems to be much lower than earlier studies stated. More recent studies suggest that HIV-positive patients without medical comorbidities or other risk factors (e.g. intravenous drug users or hemophiliacs) may have postoperative complication rates similar or only slightly higher than uninfected patients⁹¹⁻⁹⁴. Appropriate candidates must have CD4 T lymphocytes counts greater than 400 cells/ml and undetectable viral load⁸⁵.

Oral Hygiene

Although it is well established that seeding from a remote source of infection can lead to PJI there is still much debate regarding the use of active preoperative screening and treatment of dental pathology to ensure adequate oral hygiene as an effective measure to prevent postoperative bacteremia and PJI in all patients undergoing TJA. Barrington et al.⁹⁵ showed 23% of TJA candidates had dental issues requiring treatment preoperatively. However, there is no evidence to support routine screening and treating all patients for every dental abnormality. Still, signs and symptoms of active dental infection should be sought and treated before elective joint replacements⁸⁵.

STAPHYLOCOCCUS AUREUS SCREENING

Staphylococcus aureus is a major pathogen implicated in PJI all over the world. In our own experience it was involved in around half the cases⁹⁶. About 20-30% of the general orthopedic population is *S. aureus* carrier and the anterior nasal cavity is the main site of colonization^{97,98}. It has been extensively shown that patients who carry it in their nasal flora are at increased risk for infection in a multitude of clinical scenarios including orthopedic surgery^{97,99-103}. There is also evidence that among carriers who develop *S. aureus* surgical site infection there is great individual concordance between nose and surgical site isolates confirming for the importance of the endogenous contamination pathway¹⁰³. This apparently modifiable risk factor has driven a recent trend on preoperatively screening and treating carriers to potentially reduce infection rates also in total joint arthroplasty surgery. Although there is convincing data favoring this approach in overall SSI, data on arthroplasty surgery specifically is not so convincing¹⁰⁴.

In a paramount prospective randomized controlled study by Bode et al.¹⁰⁵, the number of *S. aureus* deep SSI was significantly lower in the treatment than in the placebo group. Still, further analysis of Bode et al. paper shows only 172 out of 808 surgical patients were orthopedics and no information is given regarding how many of those were total joint replacements. In this specific subgroup of patients there was no significant difference regarding *S. aureus* infections between treated and untreated carriers. In 2010, Kim and co-workers¹⁰⁶ enrolled over 7,000 patients before elective orthopedic surgery including arthroplasty but also spine and sports medicine cases. Non-carriers showed the lowest infection rate and MRSA carriers showed a significantly higher infection rate. MSSA carriers showed a not significant difference compared to non-carriers. Unfortunately, also in this paper, no information regarding specifically total joint replacement patients was given. A year later, Rao et al.¹⁰⁷ reported their results on a cohort study of 3,724 total joint arthroplasty patients. Infection rate in the carriers group was reported to be 0.0% and the authors conclude preoperative screening/selective decolonization was associated with fewer SSI after elective TJA. However, more detailed scrutiny shows there were 17 cases of PJI among the 1,440 patients of the intervention group and 19 infections in the concurrent control group of 2,284 patients operated by non-participating surgeons¹⁰⁷. Only when assuming that all infections of the control group occurred in the subgroup of expected to be *S. aureus* nasal carriers could the authors find a significant reduction of infection between treated and untreated carriers. This raises methodological issues that hamper this paper's

conclusions as it is incorrect to assume that non-carriers in the control group would have zero infections. A major multicenter study performed in American hospitals involving over 30,000 hip or knee arthroplasties was published in 2015¹⁰⁸. Patients were screened in the outpatient setting and carriers were treated using intranasal mupirocin twice daily and bathed with chlorhexidine gluconate once daily for up to 5 days immediately before their operations. A statistically significant decrease in *S. aureus* infections among hip or knee arthroplasties was found (difference per 10,000 operations, -17 [95% CI, -39 to 0]; RR, 0.48 [95% CI, 0.29 to 0.80])¹⁰⁸. However, patients during the intervention period were younger, had lower Charlson comorbidity index scores, and were less likely to have a history of MRSA carriage (all of which known risk factors for infection) than those during the pre-intervention period. Furthermore, and perhaps the major limitation of this finding is that patients were followed up for no more than 90 days after their operations which is admittedly a short period for PJI. Although the endogenous route of contamination in nasal carriers is clearly supported by the evidence, the exogenous *S. aureus* contamination pathway may still be preponderant in some settings. A French multicenter study including almost 4,000 joint replacements found that most cases of *S. aureus* surgical site infections, either an endogenous origin could not be demonstrated or preoperative nasal colonization retrieved a strain that was different from the infecting pathogen¹⁰². Of the 22 documented *S. aureus* infections, 13 occurred in patients classified as nasal non-carriers and nine in nasal carriers. Among nine carriers that developed infection, six were due to similar strains and three were different.

This controversy has lead us to perform research on this topic and detailed results will be presented ahead in this dissertation. We found a significant proportion of methicilin-sensitive *S. aureus* carriers (22%) but MRSA colonization was under 1%¹⁰⁹.



Fig. 2 Example of patient being screened for *S. aureus* colonization.

There was a higher infection rate among carriers but no clear benefit of the preoperative treatment protocol could be demonstrated¹⁰⁹. We also showed that patients carrying *S. aureus* are significantly different from non-carriers regarding other variables that admittedly influence infection rates such as the presence of inflammatory arthritis¹⁰⁹. Maoz et al.⁴⁹ analyzing data from 3,672 primary and 406 revision hip arthroplasties, also found *S. aureus* colonization to be associated with higher infection rate but it was not proven to be an independent risk factor as it was not significant in multivariate analysis. Although treating known nasal carriers with intranasal applications of mupirocin 2% ointment with or without a combination of chlorhexidine gluconate body wash is currently recommended to prevent surgical site infection by the WHO⁷³, the ICM on PJI did not recommend universal screening of all patients undergoing joint arthroplasty⁸⁵.

URINE SCREENING

Concern with the genitourinary tract as a possible source of hematogenous seeding has been present as far back as the 1970's when a few case reports¹¹⁰⁻¹¹² and a retrospective study¹¹³ found a relation between patients with deep joint infection and perioperative urinary tract infection (UTI). Although there seems to be enough evidence supporting a relation between postoperative symptomatic UTI and PJI^{47,57,113-115}, literature studying the correlation between asymptomatic bacteriuria (ASB) and surgical site infection after joint arthroplasty is scarce¹¹⁵⁻¹¹⁹. Nevertheless urine screening before total joint replacement has found its way into clinical practice among the orthopedic community. A recent survey in the United Kingdom revealed that two-thirds of surgeons would treat ASB prior to knee arthroplasty, although 70% would not have any evidence to cite evidence in favor of this practice¹²⁰.

This controversy has lead us to perform research on this topic. The hypothesis was that a preoperative screening and treatment program of ASB would potentially have an impact on prosthetic joint infection rates. Our results will be presented with further detail ahead in this dissertation. We found a significant proportion of elective total joint arthroplasty candidates present with ASB¹²¹. While ASB proved to be an independent risk factor for infection, the organisms found in the urine preoperatively were different from those causing PJI¹²¹. Furthermore, preoperative antibiotic treatment of ASB did not show any benefit¹²¹.

As such, testing for and treating asymptomatic urinary tract colonization before joint replacement is unwarranted⁸⁵. This statement should be interpreted cautiously and it should not be extrapolated for those showing signs and symptoms of active urinary tract infection. It is reasonable to treat symptomatic UTI before surgery⁸⁵.

Perioperative Considerations

Before surgery, every patient should be educated about the importance of skin problems and a thorough examination should be performed at admission. If any skin irregularity over the surgical site or the lower leg is present, a thorough assessment should be made regarding potential wound healing complications. Such skin problems may include simple conditions such as abrasions, scratches from pets, contact dermatitis, eczema, psoriasis, skin ulcers or even cellulitis and postponing surgery may be indicated (Fig. 3).



Fig. 3 Examples of patients presenting for total joint arthroplasty with skin problems that had surgery postponed. A: second toe diabetic foot ulcer

PATIENT PREPARATION

Preoperative bathing is recommended in order to wash gross contamination and reduce bacterial load. Chlorhexidine is commonly used although there is no evidence to show a clear benefit for preoperative showering or bathing with chlorhexidine over other wash products^{73,122}. Chlorhexidine gluconate-impregnated cloths have also been advocated as a possible improvement over simple bathing. They are used by the patient at home during the morning of or the evening prior to surgery. There are scarce yet favorable results including a small prospective randomized trial, suggesting they are effective in decreasing the rate of infection in lower extremity TJA and surgeons may wish to consider using them¹²³⁻¹²⁵.

Hair removal is also a classic concern. Although theoretically the patient's hair may be a source of contamination, it has been shown that there is no difference in infection rate among patients who have had hair removed prior to surgery and those who have not^{73,126}. Therefore, removing hair is not necessary unless the hair at or around the incision site will interfere with the operation, dressings or wound care. When hair removal is performed, concern over shaving has been raised because abrasions formed from the shaving process can become sites of bacterial growth. In fact, clipping as opposed to shaving, is the preferred method for hair removal as it has been shown to lead to inferior infection rates^{73,126}. It is also consensual that hair removal should be performed as close to the time of the surgical procedure as possible^{73,85}.

SKIN DISINFECTION

The human skin is home to a large number of resident bacteria. Although a small proportion are restricted to deeper layers and hair follicles and are not accessible to standard antiseptic formulations, most bacteria are located in superficial layers¹²⁷. The aim of skin disinfection is to reduce the microbial load as much as possible before surgery both within the patient's own skin and the medical staff hands.

Surgical Site Skin Preparation

To date, no clear difference between various skin preparation agents has been established regarding the prevention of deep infection in total joint arthroplasty. Directly comparing chlorhexidine to povidone-iodine regarding skin antisepsis and rate of surgical site infection offers conflicting evidence. Darouiche et al.¹²⁸ showed that chlorhexidine-alcohol was significantly more protective than povidone-iodine against both superficial and deep infections after clean-contaminated surgery. However, iodine preparation used in this study was aqueous and not alcohol based. This is a major issue as evidence suggests that combining alcohol with antiseptics may be critical. Two recent meta-analysis, showed that alcohol-based antiseptic solutions are more effective than aqueous solutions in reducing the risk of surgical site infection^{73,129}. Swenson et al.¹³⁰ found that when alcohol was used (either as a solvent or a scrub following iodine paint), iodophor-based compounds may be superior to chlorhexidine. Other studies were unable to show a clear advantage of one agent over the other^{131,132}. Theoretically chlorhexidine would be more advantageous in a long-lasting surgery such as total joint arthroplasty, since its bactericidal effect is sustained over a longer period of time than iodophor-based compounds^{133,134}. A recent prospective randomized trial comparing chlorhexidine–alcohol combination to iodine-alcohol combination skin antisepsis before cesarean delivery confirmed this theoretical advantage¹³⁵. With almost 600 patients in each arm, surgical site infections were significantly lower in the chlorhexidine-alcohol group¹³⁵. In fact, current recommendations are to use alcohol-based chlorhexidine gluconate antiseptic solutions as pooled results seem to suggest it is more effective than povidone-iodine^{73,129}.

Staff should be trained and informed about the potential harms of alcohol-based solutions. They should not come into contact with mucosa and caution should be exercised to allow time for adequate drying as operating room fire is a real possibility.

As a final part of the surgical skin preparation, plastic adhesive drapes have been advocated as a way to protect the wound from organisms that may be present on the skin surrounding the incision. A recent Cochrane review¹³⁶ showed a significantly higher proportion of patients in the adhesive drape group developed a surgical site infection when compared with no drapes. Even the newer iodine-impregnated adhesive drapes had no effect on the surgical site infection rate¹³⁶. As such their use is not recommended⁷³.

Surgical Team Hand Wash

Surgical team hand preparation is of vital importance to minimize surgical field contamination especially in the case of glove puncture that is not uncommon in arthroplasty surgery. However, much as for patient skin preparation, no consensus exists as to the optimum agent

or duration of the wash. A 1997 study by Pereira et al.¹³⁷ showed chlorhexidine and povidone-iodine aqueous scrubs to be equally effective in reducing skin contamination. The same study offered evidence that alcohol-based antiseptics could be just as effective¹³⁷. A subsequent large, prospective multicenter equivalence-cluster, randomized crossover study showed similar findings. Traditional (5 minutes) scrubbing methods with aqueous agents (4% chlorhexidine or 4% povidone-iodine) were equally effective at reducing the incidence of infection compared to a single hand wash for 1 min with non-antiseptic soap at the start of the day followed by alcohol-only rubs¹³⁸. A Cochrane systematic review¹³⁹ found that chlorhexidine gluconate scrubs may reduce the number of colony forming units (CFU) on hands compared with povidone iodine scrubs. They also found that alcohol rubs with additional antiseptic ingredients may reduce CFU compared with aqueous scrubs¹³⁹. However, just how much clinical relevance this surrogate endpoint is at predicting surgical site infection is unknown and no firm evidence that one type of hand antisepsis is better than another. In their systematic review, Allegranzi et al.⁷³ found a limited number of studies with surgical site infection as primary outcome and they were also unable to find a difference between the use of alcohol-based solutions and povidone-iodine or chlorhexidine gluconate antimicrobial soap.

As such, alcohol hand rubs are effective and no more damaging to the skin than more time-consuming, conventional methods using detergent-based antiseptic wash. Although no evidence exists regarding this specific topic, we believe alcohol hand wash seems to ensure more adequate compliance. Despite the variability present in the literature a reasonable recommendation is to perform either a scrub or soap-and-water wash for the first case of the day (or whenever there is gross contamination) followed by surgical hand antisepsis using an alcohol based product for a minimum of 2 minutes before each case.

PROPHYLACTIC ANTIBIOTICS

Surgical prophylactic antibiotic therapy refers to administering antimicrobial drug(s) to the operative site in effective concentrations to lessen the consequences of bacterial contamination thus reducing the number of clinically relevant infections. Its efficacy is currently indisputable and it is widely endorsed as one of the most powerful tools used to reduce infection rate after TJA^{73,85,140,141}.

Systemic Antibiotics

The goal is to reach optimal surgical site tissue concentrations of antibiotic(s) when the procedure begins. Therefore, it is usually recommended that they should be given within 60 minutes of the incision or the use of a tourniquet^{85,141}. There is evidence proving the administration of antibiotics after incision is associated with a significantly higher incidence of infection compared with administering them before incision^{73,142}. There is also enough evidence to support that administration earlier than 120 minutes is less effective⁷³. In a large multicenter collaborative study, Steinberg et al.¹⁴³ found that infection risk increased as the time interval between antibiotic infusion and the incision increased. They found a not quite significant trend towards reduced infection rate when antibiotics were infused within 30 minutes of incision (1.6%) compared to 31-60 minutes (2.4%). A Dutch multicenter study found a similar

non-significant trend to reduced infection rates when prophylaxis was given in the preceding 30 minutes¹⁴². However, the authors of a recent systematic review did not find significant differences in time intervals under 120 minutes⁷³. They do however recommend administration should occur closer to the incision time (<60 minutes) for antibiotics with a short half-life such as commonly used cephalosporins⁷³. When a tourniquet is used, it should be inflated at least 5-10 minutes after antibiotic infusion in order to allow for adequate tissue concentrations^{85,144}. It has also been suggested that giving prophylactic antibiotics before tourniquet deflation may be just as effective¹⁴⁵.

In some circumstances, there is the need for repeat antibiotic dosing during surgery. The goal is to maintain adequate antibiotic concentrations throughout the procedure and redosing is indicated if the procedure lasts longer than two half-life of the chosen drug(s) or when there is increased blood loss and/or fluid resuscitation (>2,000 mL)^{73,85,141}. It is also agreed upon that the duration of antibiotic prophylaxis should not exceed twenty-four hours postoperatively and there is extensive evidence that a single preoperative dose (and possible additional intraoperative redosing) might not be inferior^{85,141,146-148}. Longer regimens offer no added benefit and are associated with increased risk of development of resistance, increased risk of toxicity and even higher costs¹⁴¹. There is also no evidence to support continuing therapy while urinary catheter or surgical drains are in place⁸⁵.

While proof of its worth is overwhelming, specific antibiotic(s) regimen selection remains controversial. Level I evidence studies in this setting are difficult to perform. For example, to demonstrate a reduction in infection rate from 2% to 1% with a power of 90%, at the 95% confidence interval, a study would need over 3,000 patients per group. For that reason, it is not a surprise that no hard evidence favoring any drug(s) over another exists and therefore many different regimens may be adopted^{141,149}. Prophylactic antibiotics need to be effective against the most common organisms responsible for PJI. Given the varying levels of antibiotic resistance between institutions, it is often imperative to customize prophylaxis based on local trends. They should also have adequate pharmacokinetics and (ideally) reduced toxicity and side effects profile.

Cephalosporins (first or second generation) are still widely recommended as first choice in orthopedic surgery and TJA specifically^{85,141,148}. This is due to their safety profile, broad spectrum and good tissue penetration, low cost and proven effectiveness. Cefazolin tissue distribution reduces with increasing body weight and is lower in morbidly obese patients¹⁵⁰. Dose adjustments are therefore required and doses up to 3g in patients over 120 kg are recommended¹⁵¹. In patients with documented or suspected allergy, clindamycin is a good choice. It has good bioavailability, and shortly after infusion reaches effective bactericidal bone concentrations¹⁵². A 900mg dose is recommended¹⁴¹ but it should be noted that clindamycin has no activity against Gram negative bacilli.

Vancomycin is another alternative in patients with documented beta-lactam allergy but the lack of activity against Gram negative bacilli should also be acknowledged. There is increasing interest in vancomycin and other drugs effective against MRSA such as teicoplanin due to its significant prevalence in PJI also in Europe^{96,153}. In this regard, it has been shown that the

standard 1g dose may lead to suboptimal concentrations in a significant proportion of patients, thus recommending adopting a 15mg/kg weight base dose¹⁵⁴. A small trial focusing on total joint replacement specifically with little over 100 patients in each group in an institution, where MRSA and methicillin-resistant *S. epidermidis* prevalence exceeds 25% of orthopedic infections showed no advantage of vancomycin compared to cefuroxime or fusidic acid¹⁵⁵. Merrer et al.¹⁵⁶ conducted a prospective observational study comparing the incidence of infection after vancomycin or cefazolin prophylaxis in femoral neck fracture and found no significant difference. Finkelstein et al.¹⁵⁷ in a study with slightly over 800 patients who underwent cardiac surgery requiring sternotomy, showed an overall surgical site infection rate similar in both groups. There was a not significant trend towards lower proportion of MRSA in the vancomycin group¹⁵⁷. In contrast, surgical site infections caused by methicillin-susceptible staphylococci were significantly more common in the vancomycin group¹⁵⁷. Smith et al.¹⁵⁸ retrospectively analyzed data comparing two historical cohorts after switching routine prophylaxis before TJA from cefazolin to vancomycin. Overall infection rate dropped from 1% (23/2221 primary TJA) during the earlier 29-months cefazolin period, to 0.5% (14/2815 primary TJA) during the later 31-months vancomycin period¹⁵⁸. The most significant improvement seen was a decrease in the number of coagulase-negative staphylococci infections. MRSA infections also decreased but the difference was not statistically significant. There was also a not significant increase in the number of methicillin-sensitive *S. aureus* and *Streptococcus* species infections¹⁵⁸. Of course, the historical control group introduces a major bias in interpreting these results. In order to try and overcome this apparent limitation and also the lack of Gram negative coverage, dual antibiotic regimens have been investigated^{159,160}.

Table I Common antibiotics used for total joint arthroplasty prophylaxis.

Drug	Recommended Initial Dose	Redosing Schedule
Cefazolin	1g (<80 kg body weight)	2-5 hours
	2g (80-120 kg body weight)	
	3g (>120 kg body weight)	
Cefuroxime	1.5g	3-4 hours
Clindamycin	600-900mg	3-6 hours
Vancomycin	1g or 10-15mg/kg	6-12 hours
Teicoplanin	600-800mg or 10mg/kg	none*

* very long half-life precludes the need for redosing during surgery.

Sewick et al.¹⁶⁰ compared dual prophylaxis with cefazolin and vancomycin versus cefazolin alone. In their retrospective analysis of 1,828 primary THA/TKA, with 1-year follow-up, the authors found that the rates of infection did not significantly differ (1.1% and 1.4% respectively). Although the prevalence of MRSA infections was significantly lower in the dual-antibiotic group (0.02% and 0.08% respectively), these infections were very rare and therefore, the number needed to treat to prevent one MRSA infection was very high¹⁶⁰. Courtney et al.¹⁵⁹ on the other hand looked at 500 primary THA/TKA performed with cefazolin prophylaxis and 1,328 with cefazolin and vancomycin and found patients receiving dual antibiotics were more likely to develop acute kidney injury¹⁵⁹. The lack of clear evidence of efficacy and safety along with the concern of promoting bacterial vancomycin resistance advises against routine vancomycin

use. In the United States of America, there seems to be an increasing frequency of vancomycin-intermediate and resistant *Staphylococcus aureus* isolates identified in clinical practice¹⁶¹ but the problem is already present also in Europe with the first case being recently identified in Portugal¹⁶².

As such, vancomycin prophylaxis is best reserved for cases of documented MRSA colonization or previous infection⁸⁵ or other cases with increased risk of methicillin-resistant infections such as institutionalized patients, healthcare workers or revision surgery^{85,163}. In addition, vancomycin administration is more cumbersome than other antibiotics. If administered too rapidly, vancomycin can cause histamine release, resulting in hypotension and a skin reaction called red man syndrome; therefore, infusion of vancomycin should take place over a longer period of time (60 to 120 minutes)¹⁴¹. Teicoplanin is an alternative that offers high and rapid soft tissue and bone penetration and is more easy and practical to administer than vancomycin. There are some favorable reports on the use of teicoplanin in total joint replacement showing that teicoplanin is at least as effective as traditional prophylaxis with the added advantage of addressing MRSA¹⁶⁴⁻¹⁶⁶. Nevertheless, like vancomycin, the lack of Gram negatives activity is also a limitation with the use of teicoplanin. Recently, Tornero et al.¹⁶⁷ compared dual prophylaxis with cefuroxime and teicoplanin versus cefuroxime alone in patients undergoing primary lower limb arthroplasty. A significantly lower PJI rate was found in the dual-antibiotic group than in patients in the cefuroxime group, 1.3% (10/791) and 3.5% (35/995) respectively¹⁶⁷. There was also a significant reduction of *S. aureus* infections with no cases of *S. aureus* PJI in the combined prophylaxis group¹⁶⁷.

Antibiotic-loaded Bone Cement

Routine use of local antibiotic prophylaxis using antibiotic-loaded bone cement (ALBC) is still a matter of open debate. Classical evidence of its efficacy come from large studies of the Scandinavian hip registries^{168,169}. Malchau et al.¹⁶⁹ reported on 92,675 THA from the Swedish database performed from 1978 to 1990. They found significantly decreased rates of revision for infection with the use of gentamicin-containing cement¹⁶⁹. Engesaeter et al.¹⁶⁸ presented the results of 22,170 THA procedures out of the Norwegian registry. They showed lower revision rates when antibiotic prophylaxis was given both systemically and in cement versus systemic or cement alone¹⁶⁸. Information regarding total knee arthroplasty (TKA) is meagre and not as compelling. Earlier studies that suggest its efficacy are clearly underpowered^{170,171}. More recent studies by Namba et al.¹⁷² and Hinarejos et al.¹⁷³ involving 2030 and 2948 total knee replacements performed with ALBC respectively, failed to demonstrate superiority in reducing infection rates. This lack of effectiveness regarding infection as an endpoint is also shown by Bohm et al.¹⁷⁴ in a larger retrospective study including 20,016 TKA with plane cement and 16,665 with ALBC from the Canadian registry. Notwithstanding, they did find a significantly higher proportion of revision for aseptic loosening in the non- ALBC group¹⁷⁴. Tayton et al.⁵⁰ recently presented the results of 64,566 TKA from the New Zealand joint registry. At the 12 months' follow-up, there was no advantage in the infection rate among the 42,038 patients where ALBC was used (0.29%) compared to the 22,528 cases where plane cement as used (0.25%)⁵⁰. Currently no conclusive evidence exists regarding the real efficacy of routinely using ALBC in preventing PJI after primary total joint replacement¹⁷⁵⁻¹⁷⁷.

There are also questions regarding mechanical issues. A classical concern is that adding antibiotic(s) to bone cement may have a negative impact on its mechanical strength. However, it has been proven that the doses required for prophylaxis (< 2 g antibiotic per 40g cement) do not compromise fixation which is critical to achieve a functional and painless joint¹⁷⁷. This statement is further reinforced by the fact that a lower incidence of aseptic loosening is consistently found using ALBC^{168,174}. A more relevant concern is that routine use of ALBC may select for antibiotic-resistant microorganisms' infections. An *in vitro* study by Thomes et al.¹⁷⁸ showed a lower overall rate of infection in the gentamicin-loaded cement group, but also a significantly higher rate of gentamicin-resistant microorganisms in this group. Hope et al.¹⁷⁹ on a study of 91 patients with deep infection of a cemented total hip arthroplasty demonstrated the use of gentamicin-loaded cement was significantly associated with the higher prevalence of gentamicin-resistant coagulase-negative staphylococci. This concern is further reinforced by recent clinical studies that have found an increasing prevalence of gentamicin resistant microorganisms, especially coagulase-negative staphylococci^{180,181}. It is only logical to expect such a phenomenon. Gentamicin loaded bone cement is by far the most widely used and while it is effectively preventing infections by gentamicin-sensitive microorganisms, the relative weight but not necessarily the absolute numbers of gentamicin-resistant infections grows.

To this date, data on the use of ABLC in primary uncomplicated arthroplasty is mostly retrospective and it is possible surgeons are using it in patients with higher baseline risk of infection. It is not entirely clear whether a potential advantage of using ABLC outweighs the potential disadvantage of its routine use such as selecting resistant microorganisms. Therefore, a clear recommendation for or against its use in the general population cannot be made. One common recommendation is to use it only in patients with a high risk of infection in primary arthroplasty (e.g. patients with diabetes mellitus, morbid obesity, prior history of PJI) and whenever cemented fixation is used for revision surgery^{85,141}.

OPERATING ROOM CONDITIONS

Despite all the recent advances in surgical site infection prophylaxis, respecting the rules of good conduit in the operating room (OR) may never be disregarded. Traffic in and out the OR increases air bacterial counts by two methods, bacterial shedding from the additional personnel and air exchange between the OR and the hallway. Unwarranted traffic should therefore be avoided and doors should be kept closed throughout surgery^{85,182,183}. Optimizing OR conditions should be considered a team work including the surgeon as well as the rest of the surgical team and even hospital administrations whenever necessary.

Surgical Team Equipment

Over the years, surgical attire has remained relatively unchanged. This uniform has traditionally been thought to play two roles: to protect scrubbed personnel from exposure to body fluids and to maintain the sterile surgical field. Health care personnel is admittedly one of the major sources of bacterial contamination. However, many of our time-honored practices have limited literature support.

The use of scrubs, masks and some kind of head covering has become universally recommended. Despite the absence of clear evidence-based proofs of efficacy, wearing them should be considered in the best interest of both patients and medical staff pending evidence of advantage to not wearing them. Sterilized surgical gowns are demonstrably relevant and impervious gowns seem to be superior although no clear advantage of disposable non-woven versus reusable woven gowns has been shown^{146,184}. The use of sterilized gloves is absolutely critical and its introduction resulted in a dramatic reduction of surgical site infections¹⁸⁴. Many orthopedic surgeons prefer double gloving, but there is no direct evidence that additional glove protection reduces surgical site infections^{184,185}. Nevertheless, the addition of a second pair of surgical gloves significantly reduces perforations to innermost gloves and blood stains on the skin, indicating a decrease in percutaneous exposure incidents¹⁸⁵. In addition to perforation, gloves are also at risk for bacterial contamination during the procedure. It is recommended that they are changed whenever they are perforated, before prosthesis implantation, after handling bone cement as it has been shown to affect permeability or at least every 90 minutes in longer surgeries⁸⁵.

In order to minimize bacterial shedding, body exhaust suits were initially described and popularized by Sir John Charnley in the 1970's¹⁸⁶. Despite the initial enthusiasm around these suits in arthroplasty, their use remains controversial. In fact, modern day's data shows that compared with conventional clothing, the use of body exhaust suits could not be proven to provide more protection against microbial contamination^{187,188}. Recent data out of the New Zealand Joint Registry by Hooper et al.¹⁸⁹ also calls into question its efficacy. Their retrospective review included more than 50,000 primary THA and 30,000 primary TKA and showed that the use of space suits was actually associated with a significant increased rate of surgical site infections compared with traditional head coverings regardless of the type of operating-room ventilation for both THA and TKA¹⁸⁹. As such their use in routine joint replacement seems to be unjustified especially considering the added costs they represent.

Laminar Air Flow and Ultraviolet Lighting

Laminar air flow was also first introduced in THA surgery by Sir John Charnley¹⁸⁶. In his paramount study, the use of laminar air flow and body exhaust suits showed an impressive (9% to 1%) reduction in the rate of infection. However, this study was undertaken before the implementation of routine antibiotic prophylaxis.

More recent studies question the real value of this methodology, especially considering its high cost. The first indication that antibiotic prophylaxis could reduce the impact of laminar air flow is brought by Lidwell et al.¹⁹⁰. Although the infection rate in rooms with laminar air flow was 0.6% as opposed to 1.5% in rooms without it, they also found a significantly lower rate of infection (0.6%) in patients with preoperative antibiotics regardless of the laminar air flow. More recent data, reflecting modern OR air filtration and routine antibiotic prophylaxis is not able to show an advantage in the use of laminar air flow. A study including over 8,000 total knee replacements in over 250 hospitals in the United States showed no significant advantage in laminar air flow¹⁹¹. Another major multicenter German study involving almost 100,000 surgeries and controlling for many patient and hospital-based confounders, also found a lack of benefit in OR ventilation with laminar airflow¹⁹². They found it was even associated with a significantly

higher risk for severe infection after hip prosthesis¹⁹². The same deleterious impact was noted by Tayton et al.⁵⁰ in their analysis of 64,566 primary TKA recorded on the New Zealand joint registry between 1999 and 2012. This seemingly paradoxical effect may be explained by several factors that influence air flow such as specific architectonic OR characteristics, equipment positioning, pressure and ventilation conditions or even lack of adequate protective clothing (i.e. body exhaust suits). As such, current recommendations state that laminar air flow should not be used to reduce infection rate in TJA surgery¹⁴⁶.

An alternative to laminar air flow could be the use of ultra-violet (UV) lighting. Ritter et al.¹⁹³ found a statistically significant reduction of infection in total joint arthroplasty with and without UV light. In their study with almost 6,000 joint replacements, the infection rate with the use of laminar airflow and no UV lighting was 1.8%, and the infection rate with UV lighting only was 0.6%. Although the costs of its use are 100 times lower than laminar air flow, UV lighting throughout surgery is not without dangers that ultimately limit its use. It requires appropriate safety precautions and staff protective equipment to minimize the risk of cutaneous and ocular injuries that may still occur.

PATIENT HOMEOSTASIS

Despite the indisputable importance of enhancing operating room background, optimizing the host environment must not be overlooked. Patient homeostasis in the intraoperative and immediate postoperative period is also critical to reduce the risk of infection and surgeons must articulate with anesthesia staff and other operating room personnel.

Supplemental oxygen should be provided both intraoperatively and for 2-6 hours in the immediate postoperative period¹⁴⁶. Tissue oxygenation benefits are maximized when normothermia and normovolaemia are also maintained¹⁴⁶. Warming devices should be used to avoid hypothermia that commonly occurs in prolonged surgical procedures because of impairment of thermoregulation by anesthesia combined with body exposure to the cold environment in the operating room¹⁴⁶. Adequate intravascular volume is an essential part of tissue perfusion and subsequent oxygenation. Intraoperative goal-directed fluid therapy has also been shown to reduce the risk of surgical site infection¹⁴⁶.

DURATION OF SURGERY

Prolonged surgical time is consistently associated with increased risk of infection and there seems to be a direct linear association^{47,49,57,64,121,172}. Naturally some surgeries are particularly complex and will require more time to perform. Still, some time-consuming variables are modifiable and staff education in how to operate efficiently and follow systematically defined and predictable steps might decrease the risk of PJI. It is also important to stress the need for antibiotic re-dosing when the surgery prolongs for more than two times the half-life of the prophylactic antibiotic administered before surgery as was discussed earlier.

Postoperative Considerations

It is thought that most surgical site infections occur as a consequence of intraoperative surgical field contamination. However, some may occur in the immediate or even in the late postoperative period and there are a number of contributing factors that can be influenced.

DRAINS AND BLOOD MANAGEMENT

Surgical wound drains are a widespread tradition after orthopedic surgery and total joint arthroplasty specifically. The rationale behind its use is to reduce the formation of hematoma and subsequent need for re-intervention or over infection. However, several studies have demonstrated they can be colonized by bacteria¹⁹⁴. The risk of bacterial colonization is directly time related and increases dramatically after the first 24 hours^{195,196}. It has also been suggested that the use of a surgical drain for more than one day may be associated with MRSA infection¹⁹⁷. As such when choosing to use a drain in uncomplicated primary TJA the authors believe it should be discontinued in the first 24 hours. Notwithstanding, the main controversy is whether to use drains at all. Two recent meta-analysis on orthopedic surgery¹⁹⁸ and total joint replacement specifically¹⁹⁹ both reached the same conclusion. No significant difference between the wounds treated with a drain and those treated without a drain was found with respect to the occurrence of wound infection, wound hematoma or reoperations for wound complications. On the other hand, a drained wound was significantly associated with a greater need for blood transfusion^{198,199}.

Moreover there is increasing evidence that allogeneic blood transfusions, though required in some circumstances after joint replacement surgery, are not innocuous²⁰⁰. A retrospective 1999 study²⁰¹, found transfusion of allogeneic blood after total joint replacement was significantly associated with infection, fluid overload and increased duration of hospitalization. These findings have consistently been confirmed in more recent studies^{57,202-204}. Although the clear etiology is not fully understood it seems that some kind of adverse immunomodulation occurs. On one hand, autologous blood transfusion does not seem to increase the risk so clearly⁸⁵. Friedman et al.²⁰² looked at data from more than 12,000 patients after primary total hip or knee arthroplasty. Most of them received no transfusion (n=6,313) and among those requiring it, most received allogeneic blood (n=3,962) and some received autologous blood only (n=1,902). Infection rates in patients receiving no transfusion or autologous blood transfusion were similar. All kinds of infections, including wound infection, were significantly higher in patients receiving allogeneic blood transfusion²⁰². On the other hand, allogeneic blood seems to be associated with a lower infection rate when it is depleted of leukocytes prior to transfusion although the real value of such practice in the total joint arthroplasty setting has not been established²⁰⁵.

As such, orthopedic surgeons should make an effort to reduce the need for perioperative allogeneic blood transfusions during total knee and total hip joint arthroplasty. A more restrictive hemoglobin threshold strategy is currently advisable with no evidence that it impacts mortality or morbidity after elective surgery²⁰⁶. Decision should be based on clinical and not just

laboratory criteria. A discussion regarding preoperative hemoglobin optimization, cell salvage technology, the use of tranexamic acid or other strategies is beyond the scope of this paper but surgeons should be aware of this predicament when deciding whether or not to implement them or even whether or not to use a drain.

WOUND CARE

Careful hemostasis and meticulous closure of the joint capsule and subcutaneous tissue at the end of the procedure to avoid dead space is crucial in obtaining good wound healing. Persistent wound drainage or wound dehiscence has been shown to be a significant risk factor for PJI^{55,207,208}. Antimicrobial, specifically triclosan-coated sutures seem to be effectively protective against infection¹⁴⁶.

The goal of wound dressings applied after closure is to provide physical support, protection and absorb exudate. The traditional approach to wound care after TJA consists of gauze bandages that are usually removed after 1 or 2 days with the idea that the wound re-epithelializes during that time and can then be left with a simple dressing. There is nonetheless no evidence that early removal of dressings (<48h) has detrimental effect on outcomes²⁰⁹. In a further effort to prevent surgical site infection, commercial dressings have been developed to optimize wound healing, seal wound drainage and have antimicrobial properties. Occlusive dressings with hydrofiber have shown favorable results after total joint arthroplasty and its use was recommended in the latest ICM on PJI⁸⁵. Ravenscroft et al.²¹⁰ in prospective randomized trial compared it against an absorbent perforated dressing and found that new hydrofiber occlusive dressing was 5.8 times more likely to result in a wound with no complications. A similar advantage regarding skin blisters, wound leakage and number of dressing changes has been repeatedly noted since^{211,212}. More recently, Cai et al.²¹³ retrospectively looked at a single institution experience of 903 consecutive total joint arthroplasty cases who received the occlusive hydrofiber dressing and 875 consecutive cases who received standard gauze dressing. The incidence of infection was significantly lower in the new dressing group and multivariate analysis showed it was an independent protective. Grosso et al.²¹⁴ also confirmed the favorable impact of such dressings. Analyzing the charts of more than 1,100 patients, they found a 4-fold decrease in acute PJI with the use of occlusive silver-impregnated hydrofiber dressing. Body of evidence is not enough to make a strong recommendation regarding the additive value of silver and aspects such as costs should be taken into consideration²¹⁵. The addition of topical antibiotics is also probably beneficial in reducing the risk of infection in surgical wounds healing by primary intention compared with no topical antibiotic, although the specific role of different antibiotic(s) or even its role in promoting antibiotic resistance or possible adverse reactions such as contact dermatitis are unclear²¹⁶.

URINARY CATHETER

Indwelling urinary catheterization is often used to facilitate patient care in the first postoperative hours and days after TJA and it has been shown to reduce the incidence of urinary retention²¹⁷. However, urinary tract infection is a frequent minor complication after TJA especially in older

females²¹⁸ and, as previously discussed postoperative symptomatic UTI is an established risk factor for PJI^{57,119,121}.

Wald et al.²¹⁹ confirmed the empirical awareness that prolonged catheterization increases the risk of UTI and defined a threshold at two days. As such, surgeons must keep in mind that urinary catheterization is not without risks and efforts should be made to avoid it or minimize its length of stay. Stephan et al.²²⁰ showed that a multifaceted prevention strategy can dramatically decrease both the frequency and duration of urinary catheterization thus decreasing urinary tract infection after surgery.

DURATION OF HOSPITAL STAY

Prolonged hospital stay is an important risk factor for the occurrence of infection after hip replacement^{8,49,57,64}. Not only do these patients tend to have more medical comorbidities as they are also more exposed to nosocomial usually more virulent microorganisms. Decreasing the duration of hospital stay depends on many factors. Of course preoperative optimization of patient comorbidities is paramount but also proper patient education, optimal pain management, blood-sparing strategies, adequate anticoagulation and early ambulation collectively known as “fast-track” surgery seems to play a major role in diminishing length of stay without increasing complications²²¹.

PREVENTION OF LATE HEMATOGENOUS INFECTIONS

Even after successful procedures with uneventful wound healing and rehabilitation, patients with any kind of joint arthroplasty are at risk of developing late infections^{8,9}. They most often arise as a result of bacteremia episodes and should be distinguished from those that result of intraoperative contamination.

The strongest evidence for an extra-articular source of PJI would be to culture the same pathogen both in the joint and the extra-articular site. Notwithstanding, that is not possible in a significant proportion of cases and presumed etiology is therefore assumed²²². Most late hematogenous infections are sequelae of *Staphylococcus aureus* sepsis, skin infection, or urosepsis²²³⁻²²⁶. It has been shown that the risk of developing PJI after a documented *S. aureus* bacteremia may be as high as 30-40%^{224,225}. Naturally, other conditions such as infective endocarditis, pneumonia, gastrointestinal system inflammatory conditions, IV drug users and even dental abscesses have also been implicated^{47,227-229}. Any active bacterial infections in a patient bearing prosthetic joint(s) should be promptly diagnosed and treated to prevent bacterial seeding. Extra-articular sources that contribute to late PJI should be identified by obtaining clinical history and performing a thorough physical exam, laboratory testing, adequate imaging, and examination by specialists whenever required.

Although cases described in the literature are exceptional, it is hypothetically believable that a small portion of these cases are caused by transient bacteremia during invasive medical procedures. The question whether patients undergoing such procedures (e.g. dental, urologic

or gastrointestinal) should undergo specific antibiotic prophylaxis is still matter of open debate. The recent ICM on PJI⁸⁵ acknowledged the conflicting evidence available and recommended the use of antibiotic prophylaxis on an individual basis, according to patient risk factors and the type and invasiveness of the procedure to be performed⁸⁵. The risk of bacteremia is, of course, directly related to the invasiveness of the procedure. Techniques such as dental extraction or scaling²³⁰, esophageal dilation or variceal sclerotherapy²³¹ and transurethral prostate resection²³² or transrectal prostate biopsy²³³ pose higher risks than simple endodontic treatment, flexible colonoscopies, esophagogastroduodenoscopies or simple cystoscopy. Regarding dental procedures, the consensus recommends one dose of antibiotics be given about one hour prior to the procedure in all patients within the first two years after surgery⁸⁵.

High risk patients (e.g. previous prosthetic joint infection, inflammatory arthropathies, immunosuppression, diabetes, etc.) should consider doing it during their entire lifetime⁸⁵. In gastrointestinal endoscopic procedures, prophylaxis is recommended routinely especially in high-risk patients⁸⁵. The same is true for genito-urinary procedures, especially in patients with bacteriuria that has been shown to significantly increase the risk of bacteraemia²³⁴.

However, this recommendation is not consensual and this is not surprising given the paucity of strong clinical evidence. The lack of clear evidence and the potential risks of antibiotic use such as toxicity, allergy and the promotion of microbial resistance have lead other experts to advise against routine antibiotic prophylaxis^{235,236}. Ultimately the decision relies on clinical judgment of the treating physician taking into consideration an individual patient risk/benefit analysis.

Diagnosis

From an abstract standpoint, PJI is somewhat plainly defined as failure of the implant caused by pathogenic microorganisms (most often bacteria). This definition is however sometimes very difficult to translate into clinical practice.

As the improvement of microorganism detection methods continues, more and more bacteria are being found at or around failed implants. Not only that, but such improvements are consistently finding bacteria traditionally considered to be nonpathogenic. The findings of two independent research groups clearly illustrate this. In addition to finding that culture of the sonication fluid of the explanted prosthesis increased sensitivity over traditional tissue cultures, Portillo et al.²³⁷ also determined that multiplex polymerase chain reaction (PCR) of sonication fluid further increased sensitivity. In a larger cohort of patients that included with 272 knee and 162 hip prostheses, Cazanave et al.²³⁸ also determined that a PCR panel performed on implant sonicate fluid is more sensitive and more rapid than tissue culture for the diagnosis of PJI. Both these studies demonstrate using more powerful microbial investigation tools allowed for some cases who would otherwise be classified as aseptic failures to be classified as infections. Furthermore, they also reiterate that there is a significant proportion of cases that are ultimately classified as aseptic failures where some kind of bacterial positivity was found (though not sufficient to safely classified them as infections according to current accepted criteria). These advances are blurring the frontiers between PJI and aseptic failures making a bullet proof diagnosis of absence of infection extremely hard.

Another hint to the same phenomenon can be found in ALBC studies. While searching for the additional effectiveness of adding ALBC to the standard systemic antibiotic prophylaxis regimen, researchers from the Norwegian Arthroplasty Register came across an interesting finding. In their 2003 study comprising over 22,000 primary hip replacements, Engesaeter et al.²³⁹ found not only a decreased risk of revision for infection when ALBC was used, but also a significantly decreased risk of revision for aseptic loosening. More recently, Bohm et al.²⁴⁰ in large retrospective study including 20,016 primary total knee arthroplasties with non-ALBC and 16,665 with ALBC, were unable to show an advantage in using ALBC with respect to infection rates but found significantly more revisions for aseptic loosening in the group treated with non-ALBC. These figures raise the question of whether some so-called aseptic loosening cases are really misdiagnosed subclinical low grade infections that are being prevented by the use of ALBC.

These recent advances in our knowledge tend to challenge the traditional limits between clinically relevant infection, bacterial contamination and unquestionable aseptic loosening. It is becoming harder to determine where microorganisms are truly the cause of the failed implant or just happen to be found around it by increasingly sensitive methodologies and are really not causing an adverse reaction.

It is therefore no surprise that up until recently, there was no universally adopted clinical definition of PJI. There is a multitude of several different definitions that have been proposed over time. In 2011, during the annual meeting of the American Musculoskeletal Infection Society (MSIS) a first attempt at creating a “gold standard” definition for PJI was made²⁴¹. A couple of years later, an international consensus meeting, promoted by Dr. Javad Parvizi and Dr. Thorsten Gehrke was held and this worldwide collective effort resulted in a further refinement of the previously proposed definition⁸⁵. One of the major changes was the elimination of purulence as a diagnostic criterion. This was due to the recognition that despite intraoperative purulence is commonly encountered in patients with PJI, the presence of purulent-appearing or turbid synovial fluid is also frequently reported in non-infected prosthetic joints^{242,243}.

Table II ICM definition of Periprosthetic Joint Infection⁸⁵.

1) Two positive periprosthetic cultures with phenotypically identical organisms, or
2) A sinus tract communicating with the joint, or
3) Having three of the following minor criteria:
Elevated serum CRP and ESR
Elevated synovial fluid WBC count OR ++ change on leukocyte esterase test strip
Elevated synovial fluid PMN percentage
A single positive culture
Positive histological analysis of periprosthetic tissue

CRP C-reactive protein; **ESR** erythrocyte sedimentation rate, **WBC** white blood cell; **PMN** polymorphonuclear neutrophil.

Currently, in the absence of a perfect gold standard, PJI diagnosis must rely on a combination of microbiological and non-microbiological PJI criterion (see table II). However, the same document states that PJI may be present without meeting these criteria, specifically in the case of less virulent organisms thus illustrating that we have not yet reached a perfect definition⁸⁵. They also acknowledge that numerous other tests, including sonication of explanted prosthesis, synovial fluid biomarkers or molecular techniques may ultimately offer convincing results that might command modification of the proposed definition.

History, Physical Examination and X-ray

PJI can manifest itself as a myriad of different clinical scenarios. Only by understanding the previously discussed etiology and pathophysiology is one able to grasp the full spectrum of PJI presentations. Patients' symptoms may vary from acute, rapid-onset joint pain along with frank inflammatory signs and wound purulence with or without systemic features of infection, to chronic pain or discomfort, decreased range of motion with or without sinus formation and subtle discharge.

The mode of presentation relates to the pathogenesis and microbial etiology of the infection. Acute joint arthritis reflects the presence of numerous microorganisms in planktonic phase. It often occurs in the early postoperative period. In a multicenter study performed in Australia²⁴⁴ comprising PJI that occurred within 365 days of implantation, purulent discharge from surgical wound was the most common clinical finding (72%) followed by pain and erythema at the affected joint (42% each). Fever $>37.5^{\circ}\text{C}$ was present in 38% of cases. This clinical scenario is also a common presentation of late infections following hematogenous seeding of bacteria from another body site into a previously asymptomatic total joint replacement²⁴⁵. It should be emphasized that not all early infections are that manifest. They often present as delayed wound healing or persistent (macroscopically seemingly innocent) leakage. A high level of suspicion should be maintained in these cases as persistent wound drainage has been found to be a major predictor of PJI^{207,208,246}.

In contrast, chronic and more indolent symptoms reflect the presence of a lower number of adherent microorganisms (often less virulent species) in a slow growth phase, protected against host defenses by the ability to persist intracellularly or coalesce to form biofilm. It is the chronic feeble inflammatory host response at the prosthesis interface that causes pain and promotes tissue destruction that eventually leads to loosening of the prosthesis²⁴⁷. This is supported by studies that confirm the interface membrane is the best specimen for diagnosis of PJI both microbiologically (as it contains higher bacterial load) and histologically^{248,249}.

Realistically speaking, the only physical finding that is considered pathognomonic of infection is a sinus tract communicating with the joint⁸⁵. Other findings such as wound dehiscence, joint warmth, erythema or swelling should increase the clinical suspicion but are not specific for PJI. It should be stressed that a normal physical examination is not enough to dismiss infection as a possible cause of a painful TJA.

Getting to know the patients' medical history is also a crucial part of the initial exam. Chronic comorbidities that predispose patients to an immunocompromised state (e.g. diabetes mellitus, inflammatory arthropathy, malignancies) are not only known risk factors for infection as was previously discussed but also greatly influence the host's ability to fight off the infection during a hypothetical treatment. Host status is of major importance in the final outcome and unsurprisingly is taken into account in a number of PJI classification systems²⁵⁰⁻²⁵². Prior history of periprosthetic joint infection, superficial surgical site infection, recent bacteremia/infections at other body sites or even an history of multiple surgeries on the same joint should also raise the suspicion. Patients with factors that increase risk of skin barrier penetration (e.g. intravenous

drug use, poor wound conditions, psoriasis, chronic venous stasis or skin ulceration) should be considered to have a higher probability of infection.

Plain radiographs are always a first line imaging modality in orthopedics and naturally also when evaluating a painful arthroplasty. It is important to note that plain radiographs are generally normal in the setting of PJI. Nevertheless, serial radiographic evaluation over time can be very informative to detect subtle changes plus they are also important in evaluating many other possible causes of prosthesis failure and joint pain as well as allowing for planning of a possible revision surgery.

Signs of loosening of previously well fixed components, osteolysis or bone resorption around the prosthesis, especially if they occur in the first years after surgery should be considered suspicious. There is evidence that a significant proportion of cases revised for supposed aseptic loosening are found to be infected^{253,254}. There is an inverse correlation between microbiology and prosthesis-age as early loosening is more often caused by hidden PJI than late loosening²⁵⁵. Periosteal reaction with new bone formation or the presence of a transcortical sinus tract are more specific features of bone infection but are rarely present²⁴⁷.

Serology

Serological inflammatory markers, more commonly erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), are often used as an initial screening test in a variety of suspected implant related or otherwise musculoskeletal infections²⁵⁶. They are inexpensive and can be performed with minimal inconvenience.

ESR is a nonspecific hematological test routinely used as an indirect parameter of increased acute phase reactants. CRP is a major acute phase reactant that is produced by the liver in response to inflammation, infection, malignancy and tissue damage. It responds quickly to the inflammatory process²⁵⁷. As such, they are nonspecific and are affected by countless factors. They can be altered in non-infectious arthroplasty problems such as taper corrosion of modular stems or metal-on-metal bearings^{258,259} and they can be influenced by extra-articular infections, non-infectious inflammatory diseases or even underlying medications or medical conditions^{257,260}.

Despite all of its inherent limitations, ESR and CRP are widely considered to be valuable tools and are even accepted as a criterion for the diagnosis of PJI in recent consensus definitions^{85,241}. In the setting of chronic PJI (i.e. more than six weeks from the latest surgery), suggested thresholds are ESR>30mm/h and CRP> 10mg/L. Since they are traditionally used as screening tools, sensitivity was privileged over specificity. Still, these thresholds were determined somewhat arbitrarily taking into account traditionally accepted values.

In 2007, Greidanus et al.²⁶¹ tried to determine optimal cutoff values for determining infection among 151 TKA presenting for revision. They found ESR>22.5mm/h or CRP >13.5mg/L were the best performing. These results were later on confirmed by Piper et al.²⁵⁶ in their study including 297 knees (ESR>19 mm/h or CRP>14.5 mg/L). On the other hand, they also studied 221 THA and found ideal cutoff values for differentiating infected from non-infected hips to be ESR>13mm/h or CRP >10.3 mg/L. On the contrary, CRP and ESR showed poor sensitivity for the diagnosis of implant infection in their cohort of 64 shoulder arthroplasties. A similar study focusing on 479 THA presenting for revision²⁶² found different optimal cutoffs at 31 mm/h for ESR and 20.5 mg/L for CRP. More recently, using the already mentioned consensus definition of PJI, Alijanipour et al.²⁶³ reviewed 1962 patients (1203 THA and 759 TKA). For chronic cases, they found ESR >48.5 mm/h and CRP > 13.5mg/L for hips and ESR > 46.5mm/h and CRP > 23.5mg/dL for knees were the optimal values.

Another typical concern regards the specific subgroup of patients with an history of inflammatory arthropathy. Patients with this underlying condition are known to be at a higher risk for infection and although there is evidence of limited sensitivity and sensitivity of measuring inflammatory markers to monitor rheumatic disease activity²⁶⁴, theoretically elevated ESR and/or CRP may represent either disease exacerbation or PJI. Most studies exclude this subgroup of patients or do not separately analyze them. Cipriano et al.²⁶⁵, approaching this question specifically found no significant differences in the ideal cutoff or respective diagnostic performance in patients with inflammatory arthritis.

Despite the wide range of proposed thresholds illustrated previously, there are some common and relevant findings in the volume of literature^{256,259-263,265-267}: 1) “optimal” cutoffs in each paper perform very similarly to traditional thresholds in excluding infection with negative predictive values consistently around or over 95%; 2) interpreting both markers together is helpful by increasing specificity when both are positive and sensitivity when either one is elevated.

All things considered it is important to emphasize that these tests alone should not be used to rule out infection in a suspicious clinical scenario. There is a small but constant proportion of so-called seronegative PJI. There seems to be a high prevalence of low virulence pathogens in this group and in some cases, previous antibiotic therapy may be the culprit. In other cases, patients just seem to be unable to mount a sufficient immune response to be above the threshold but nevertheless treatment results seem to be comparable to patients with positive serology²⁶⁷.

BEYOND ESR AND CRP

In trying to overcome these limitations, many other serum markers have been researched for the diagnosis of PJI but they have failed to show an unequivocal superiority.

Procalcitonin (PCT) is a precursor of calcitonin and elevated levels have been noted in patients with systemic bacterial infections²⁶⁸. Bottner et al.²⁶⁹ measured serum levels of different markers including PCT, CRP and ESR in 78 subjects undergoing revision total knee or hip replacement. PCT levels >0.3 ng/mL were very specific (98%) but had a low sensitivity (33%). More recently, Glehr et al.²⁷⁰ studied 124 revision arthroplasties and found that PCT >0.35 ng/mL revealed a sensitivity of 89% and specificity of 37%. In both studies, procalcitonin was outperformed by traditional CRP measurements. Furthermore, Worthington et al.²⁷¹ as well as Drago et al.²⁷² found that PCT levels were not significantly higher among PJI subjects when compared to aseptic failures of TJA.

Interleukin(IL)-6 is another often-proposed marker for PJI that has repeatedly been shown to be significantly higher in infected cases²⁶⁹⁻²⁷². IL-6 is secreted by different immune cells, such as monocytes, macrophages, fibroblasts and T2 lymphocytes. Because IL-6 triggers the release of CRP in liver cells, it can react much faster than CRP. There is evidence that the peak and return to base levels after uncomplicated TJA surgery is even faster than CRP^{271,273}. Bottner et al.²⁶⁹ proposed that IL-6 <12 pg/mL had a 95% sensitivity and 85% specificity. Glehr et al.²⁷⁰ stated that an IL-6 <2.55 pg/mL had a sensitivity of 92% and specificity of 59%. Ettinger et al.²⁷⁴ analyzed data from 98 patients, 57 with aseptic joint failure, 20 low-grade infections and 21 high-grade infections. They found a IL-6 cutoff of 5.12 pg/mL had a sensitivity of 80% and specificity of 87.7% for predicting a low-grade infection. The classification tree method showed that the combination of CRP and IL-6 was the most suitable combination for discriminating aseptic loosening from low-grade infection. A patient with IL-6 >5.12 pg/mL and CRP >0.3 mg/dL could be categorized as very likely (high-risk) to have a low-grade infection²⁷⁴. Notwithstanding, these papers show that sensitivity gains compared to CRP are only marginal and come at the expense of decreased specificity. Focusing specifically in shoulder

arthroplasty, Grosso et al.²⁷⁵ found serum IL-6 is not an effective marker for diagnosis of infection. Additionally, laboratory requirements for IL-6 measurement is much more complex and not as widely available as CRP.

The search for a more favorable serum marker of PJI continues with other molecules such as tumor necrosis factor- α and soluble intercellular adhesion molecule-1 under scrutiny. There is already limited evidence of its ability in distinguishing PJI from aseptic failures^{269,271,272}.

For the time being, ESR and CRP are still the more practical serum markers and they should be ordered in virtually all cases of painful total joint arthroplasty requiring revision. It has been demonstrated that their use before arthrocentesis is the best diagnostic strategy for PJI (hip and knee)²⁷⁶. Whether different ESR and CRP thresholds should be adopted according to anatomic site is not completely defined. It also seems clear that joints other than hip or knee lack more extensive research as to their specific diagnostic accuracy.

Arthrocentesis

Synovial fluid analysis is most probably the best venture for preoperative diagnosis of PJI. The enormous amount of research being performed worldwide on this topic is the natural response of such a belief. Furthermore, both the 2010 American Academy of Orthopedic Surgeons (AAOS) guidelines²⁷⁷ and the 2013 ICM on PJI⁸⁵, recommend joint aspiration for synovial fluid testing when there is a clinical or laboratory suspicion of infection.

Traditionally, TKA and THA aspirations were performed to obtain fluid for direct Gram examination and bacterial culture. As results of synovial fluid leukocyte count's diagnostic accuracy for differentiating PJI from aseptic failure became known it gained increasing popularity. Nowadays, several other investigations can (and perhaps should) be performed when the joint is aspirated and fluid is available for testing as will be discussed further.

There is nevertheless a major practical limitation of such tests that is seldom discussed in the literature. It relates to the technical difficulties in performing the arthrocentesis, especially in the hip. Because of its superficial location, the knee is usually readily available for aspiration in the outpatient setting. The hip however, presents different challenges. Because of its distance from the skin, adjacent anatomic neurovascular structures, and poor probability of blindly reaching the joint space, most clinicians hesitate to attempt aspiration of the hip joint without fluoroscopic or ultrasound guidance²⁷⁸. Sometimes, even despite confirmed appropriate anatomic location within the joint at the time of aspiration, fluid is not recoverable the so called "dry tap". There is a paucity of information in the literature regarding the exact rate of "dry taps" in joint aspirations. In our empirical experience, it is more common in hips but it can also happen in TKA.

It is critical to emphasize that absence of recoverable fluid within the joint does not imply that periprosthetic joint infection is not present. Ali et al.²⁷⁹ while investigating the utility of hip aspiration in 73 patients with moderate to high risk of infection, found a dry tap to be present in 32% of THA and the volume of fluid recovered from infected (4.1mL) and aseptic (4.7mL) was nearly identical²⁷⁹. Corona et al.²⁸⁰ described a technique for percutaneous interface biopsy in dry-aspiration cases (ten hips and 14 knees) and found that 17 (71%) patients were ultimately found to be infected after revision surgery. Most studies, recommend washing these "dry" joints with saline in order to increase the chance of recovering fluid for culture. However apart from culture, most other tests deal with some kind of fluid concentration measurement and therefore this methodology would hamper the results.

One other major issue that the treating clinician must be aware in interpreting the results and deciding when to perform an arthrocentesis is the negative impact of systemic antibiotics in most synovial fluid test's accuracy. Shahi et al.²⁸¹ have shown that premature antibiotic therapy may compromise the diagnosis of PJI. The median laboratory values of 53 patients that were on antibiotics showed significantly lower serum ESR and CRP as well as synovial fluid leukocyte count, polymorphonuclear neutrophil (PMN) percentage and naturally higher rates of negative cultures and false-negative cases falling below proposed diagnostic thresholds²⁸¹.

While serum ESR and CRP are easily available for repeat measurement, joint aspiration (especially hip) is not as easy and consideration should be given to allow for an antibiotic-free period of at least two weeks before arthrocentesis is performed^{85,277}. It is critical that systemic antibiotics not be administered to the patient suspected of PJI until deep sampling has been obtained. Only risk of sepsis should supersede this axiom. Unfortunately, in clinical practice many patients are started on antibiotics before a definitive diagnosis is made.

GRAM STAINING AND CULTURE

Gram staining is a long held tradition among clinicians whenever there is a suspicion of infection. There is however extensive evidence showing that in the context of PJI specifically, the sensitivity of the test is extremely low^{282,283}. Notwithstanding, apart some reports on false positive results²⁸⁴, its overall specificity is considered extremely high^{282,283}. Although it is perhaps expendable, if performed it should never be used to rule out PJI.

Traditional cultures of aspirated joint fluid remain an important feature of preoperative diagnosis and should not be disregarded. Obtaining a causative pathogen is not only indicative of infection but it also may help guide treatment choices. If the study is used as a confirmatory test for patients with clinical and/or laboratory suspicion of infection and not as a universal screening test, the predictive value of a positive result is high. Nevertheless, it is far from being the ideal diagnostic tool to exclude infection. Many studies have demonstrated the failure of culture of the aspirated fluid to provide accurate diagnosis of PJI, especially low sensitivity^{279,285-287}.

The reason for such limitations will become obvious as the correct methodology for intra-operative microbiological sampling is discussed further ahead. As previously noted, especially in chronic low-grade infections, there are but few planktonic bacteria floating around in the synovial fluid. Multiple tissue sampling and even some kind of biofilm disruption technique of the extracted implants greatly enhances both sensitivity and specificity of cultures. Additionally, in a proportion of cases microorganisms identified in the preoperative aspiration fluid may not have a total correspondence with those ultimately identified in intraoperative samples^{288,289}. Holleyman et al.²⁸⁹ showed that only 37 out of 75 cases (49%) matched for both microorganism and antimicrobial sensitivity comparing preoperative joint sampling obtained by either aspiration or tissue biopsy and intra-operative findings.

In summary, a negative aspirate culture often represents a false-negative (especially in cases of chronic infection by low virulence microorganisms) and even culture growth may constitute a false-positive that must be interpreted in conjunction with other diagnostic tests.

LEUKOCYTE COUNT AND DIFFERENTIAL

Synovial fluid leukocyte counts and neutrophil differential has become an important tool in the past few years as different papers have consistently shown good diagnostic accuracy. Nevertheless, proposed thresholds vary significantly in the literature²⁹⁰⁻²⁹⁵ according to the definition used for PJI (see table III).

Because the hip is not as easily aspirated in the clinic, these values are more often studied in the knee. Schinsky et al.²⁹³ studied 201 total hip arthroplasties (55 infected and 146 noninfected) and found the optimal cutoff to be around 4,000 leucocyte/ μ L which is higher than most other studies that focus on TKA. However, other authors that studied THA and TKA simultaneously did not find such a significant difference.

Dinnem et al.²⁹⁰ studied a total of a total of 75 patients including 48 TKA and 27 THA. They found similar optimal cutoffs for hips (1,425 cells/ μ L) and knees (1,715 cells/ μ L). In our own cohort (results will be discussed further ahead in this thesis), we also did not detect a higher synovial fluid leukocyte count amongst infected hips.

Much as for serum inflammatory markers, there is the question of how reliable are these conventional thresholds in patients with inflammatory arthropathy. Based on limited evidence presented by Cipriano et al. (27), no change from the above thresholds are recommended⁸⁵. Their data on 871 revision joint arthroplasties (TKA and THA) including 61 cases with inflammatory arthritis found very similar optimal cutoffs in both groups. Total leucocyte counts over 3,450 cells/ μ L (91% sensitivity; 93% specificity) and PMN proportion >78% (96% sensitivity; 87% specificity) for the non-inflammatory group compared to > 3,444 cells/ μ L (88% sensitivity; 80% specificity) and PMN proportion >75% (100% sensitivity; 82% specificity) for the non-inflammatory group.

Despite this wide range of proposed thresholds for chronic infections, delegates to the ICM on PJI were able to reach a strong consensus that leukocyte counts >3,000 cells/ μ L and proportion of PMN > 80% are indicative of infection occurring later than six weeks after surgery⁸⁵. Nevertheless, some technical considerations should be regarded.

If some kind of bloody or traumatic arthrocentesis is performed, serum white blood cells (WBC) and neutrophils are introduced into the joint which can then create false-positive readings. In order to minimize such phenomenon, it is recommended that observed synovial fluid WBC count results be transformed using the synovial red blood cell (RBC), serum RBC and serum WBC concentrations to adjust for traumatic aspirations according to a previously validated formula²⁹¹: $\text{expected WBC} = (\text{WBC}_{\text{blood}} / \text{RBC}_{\text{blood}}) \times \text{RBC}_{\text{fluid}}$. The difference between the observed number of fluid leukocytes and the expected number of WBC introduced into the knee joint with the blood yields the real number of WBC present in the joint fluid before arthrocentesis: $\text{adjusted WBC} = \text{observed WBC} - \text{expected WBC}$.

Another limitation of this test relates to metal-on-metal (MoM) bearing surfaces or metal corrosion. It is well established that a hypersensitivity adverse reaction to metal debris (ARMD) with either aseptic lymphocytic vasculitis-associated lesions (ALVAL) or metallosis can occur even in the new generation metal-on-metal bearings and its clinical presentation may mimic infection²⁴³. Wyles et al.²⁹⁶ have shown that the synovial fluid in failed MoM THA, may not only be macroscopically indistinguishable from bacterial induced purulence but may also offer extremely high WBC readings.

More recently, Yi et al.²⁵⁹ published their results of revision THA with metal-on-metal bearings or metal corrosion. They found that excluding synovial fluid samples found to be inaccurate (if the laboratory technician noted the presence of metal debris, amorphous material, fragmented or degenerating cells or the presence of clots; or if the sample had some defect, for instance excessive viscosity, that prevented an automated cell count from being performed) the synovial fluid leukocyte count diagnostic accuracy was improved, setting an optimal cutoff at 4,350 cells/ μ L with 100% sensitivity and 95% specificity. Both these papers, recommend that manual synovial fluid WBC count should be requested when evaluating these samples. Although a manual count will not necessarily lead more accuracy²⁵⁹, it can alert the physician to an unreliable count.

Table III Leukocyte count and differential results.

	PJI Definition	Cell count technique	Joint	Proposed cutoff(s)	Sensitivity (95% CI)	Specificity (95% CI)
Trampuz et al. 2004 ²⁹⁴	At least one of the following: 1) growth of the same micro-organism in at least two cultures of synovial fluid or periprosthetic tissue; 2) purulence at the time of arthrocentesis or surgery; 3) acute inflammation on histopathologic examination.	Microscopic examination	TKA	1,700 cells/ μ L PMN >65%	94% (80-99) 97% (85-100)	88% (80-93) 98% (93-100)
Della Valle et al. 2007 ²⁹⁷	Same organism ≥ 2 cultures OR ≥ 2 of the following: 1) one positive culture; 2) consistent histopathology >10PMN in the 5 most cellular field; 3) gross purulence.	Not specified	TKA	3,000 cells/ μ L PMN >65%	100% 97.6%	98.1% 84.9%
Schinsky et al. 2008 ²⁹³	Two of the following: 1) positive intra-operative culture; 2) gross purulence, 3) consistent histopathological result.	Not specified	THA	4,200 cells/ μ L PMN >80%	84% (74-94) 84% (74-93)	93% (88-98) 82% (76-89)
Ghanem et al. 2008 ²⁹²	At least one of the following: 1) the presence of an abscess or sinus tract communicating with the joint; 2) positive preoperative culture of aspirate on solid medium; 3) ≥ 2 intraoperative cultures of the same organism, or one positive culture on solid medium + gross purulence or abnormal histology.	Manually with use of the Wright-Giemsa stain	TKA	1,100 cells/ μ L PMN >64%	90.7% (85.1–94.7) 95.0% (90.4–97.8)	88.1% (83.6–91.7) 94.7% (91.3–97.1)
Cipriano et al. 2012 ²⁶⁵	Same organism ≥ 2 cultures OR ≥ 2 of the following: 1) sinus tract or gross purulence; 2) one positive deep culture; 3) consistent histopathology >10PMN in the 5 most cellular field.	Not specified	THA & TKA	3,450 cells/ μ L PMN >78%	91.0% (81-94) 95.5% (94–97)	93.0% (91-95) 87.3% (85-90)
Zmistowski et al. 2012 ²⁹⁵	Three of the following: 1) positive culture from aspirate; 2) positive culture from intraoperative tissue; 3) purulence; 4) serum ESR >30 mm/h; 5) serum CRP >10 mg/L.	Automated analysis	TKA	3,000 cells/ μ L PMN >75%	93% 93%	94% 83%
Dineem et al. 2013 ²⁹⁰	At least one of the following: 1) histological examination of tissue yielding >5PMN per HPF; 2) ≥ 3 culture samples growing identical organisms; 3) frank pus >50,000 leukocyte/ μ L + growth of pathogenic organism.	Manually in a Neubauer cell counting chamber	THA & TKA	1,590 cells/ μ L PMN >65%	89.5% (78.3–99.7) 89.7% (79.5–99.9)	91.3% (82.7–99.9) 86.6% (76.1–97.1)

*TKA Total knee arthroplasty; THA total hip arthroplasty; PMN polymorphonuclear neutrophil; HPF high power field.

LEUKOCYTE ESTERASE

Leucocyte esterase (LE) is an enzyme secreted by neutrophils that have been recruited to the site of an infection. A rapid colorimetric strip test for this enzyme has long been used to diagnose urinary tract infections, especially as a rule out test²⁹⁸.

Parvizi *et al.*²⁹⁹ were the first to recognize the potential of this simple test and ascertain its role in the diagnosis of PJI. Since then, others have found similar results³⁰⁰⁻³⁰³ (see table IV). Given its simplicity and wide availability it may be easily used as a fast test in the office when performing diagnostic aspirations or it can even be used as an adjunct to intraoperative decision making.

There are however some important practical limitations. Firstly, sometimes it is not possible to gather enough synovial fluid to perform an LE test in addition to all other examinations (i.e. leukocyte count, culture, etc.). Secondly, often there is some blood or debris in the aspirate that preclude a decent test reading. In this regard, it has been proposed that a centrifugation protocol with the use of the supernatant for colorimetric strip testing is simple and does not affect the accuracy of the test³⁰⁴. Finally, it is also important to emphasize that most studies do not specifically mention certain sub-group of patients such as those with inflammatory arthropathy, metallosis or those with previous antibiotic therapy. As such, its role in the presence of these confounding variables is yet to be established.

Table IV Leukocyte esterase test results.

	Joint	Definition of infection	Positivity criteria	Sensitivity (95% CI)	Specificity (95% CI)	Observations
Parvizi <i>et al.</i> ²⁹⁹ 2011	TKA	Criteria for PJI: 1) sinus tract or open wound communicating with the joint; 2) purulence at the time of arthrocentesis or surgery; 3) positive cultures; 4) elevated serum markers as well as elevated leukocyte count and/or PMN proportion.	++ + or ++	81% (62–92) 94% (77–99)	94% (77–99) 87% (77–93)	26% inadequate samples (i.e. too much blood or insufficient amount)
Wetters <i>et al.</i> ³⁰³ 2012	THA & TKA	WBC count >3,000 cells/μL 2 positive cultures or sinus tract	+ or ++	93% 93%	89% 77%	29% unable to be read (i.e. blood, debris or a result that could not be differentiated between positive and negative)
Tischler <i>et al.</i> ³⁰² 2014	THA & TKA	MSIS Criteria: 1) sinus tract communicating with the joint; 2) same pathogen ≥2 cultures; 3) at least three of the following: a) ESR>30 and CRP>10; b) synovial leukocyte >2,000 cells/μL; c) PMN proportion>65%; d) purulence; e) one positive culture.	++ + or ++	66% 79%	97% 81%	12% incomplete synovial fluid data (i.e. inadequate fluid sample to perform all tests or a dry tap)
Shafafy <i>et al.</i> ³⁰¹ 2015	THA & TKA	IDSA Criteria: 1) sinus tract communicating with the prosthesis; 2) acute inflammation on histopathology; 3) purulence in the absence of other etiology; 4) same pathogen ≥2 cultures.	125 WBC 70 WBC	81% 86%	93% 87%	significant agreement between LE semi-quantitative automated readings and leukocyte count

* **TKA** total knee arthroplasty; **THA** total hip arthroplasty; **PMN** polymorphonuclear neutrophil; **HPF** high power field; **MSIS** Musculoskeletal Infection Society; **ESR** erythrocyte sedimentation rate; **CRP** C-reactive protein; **IDSA** Infectious Diseases Society of America; **LE** leukocyte esterase.

OTHER BIOMARKERS

Much as the synovial fluid leukocyte count and leukocyte esterase, other biomarkers (i.e. molecules that are involved in the host response to infection) are being actively researched³⁰⁵⁻³⁰⁸. Gollwitzer et al.³⁰⁷ further demonstrated that, for the vast majority of them, analysis in the synovial fluid is more accurate than analysis of serum levels. They can broadly be divided into two categories: proinflammatory cytokines and antimicrobial peptides.

Although an exhaustive report on every molecule ever tested is perhaps not warranted, countless cytokines (e.g. IL-1b, IL-6, IL-8, IL-17, TNF- α , IFN- β , etc.) have already been shown to be substantially more elevated in the synovial fluid of patients with periprosthetic infection when compared to those patients with aseptic failures³⁰⁵⁻³⁰⁸. Of these, IL-6 is perhaps the most widely studied in clinical practice. Lenski et al.³⁰⁹, studying 69 TJA (mostly hip and knee) found an optimal threshold at 30,750 pg/ml which is much higher but also more accurate (91% sensitivity; 95% specificity) than previously described. In 2010, Deirmengian et al.³⁰⁶ found the optimal cutoff to be 13,350 pg/ml (100% sensitivity; 100% specificity); Jacovides et al.³⁰⁸ a year later proposed 4,270 pg/ml as the best threshold (87% sensitivity; 100% specificity) and Gollwitzer et al.³⁰⁷ located the ideal limit at 1,896 pg/ml (60% sensitivity; 95% specificity).

Randau et al.³¹⁰ presented their results on 120 patients (both TKA and THA) and found that adding synovial fluid IL-6 measurement might increase diagnostic accuracy as opposed to measuring it in the serum only. Nevertheless, synovial fluid IL-6 levels at >2,100 pg/ml, offered reasonable specificity (85.7%) but limited sensitivity (62.5%). Increasing the cutoff to >9,000 pg/ml naturally raised specificity to 97.6% but also significantly reduced sensitivity to 46.9%. Recently, Frangiamore et al.³¹¹ focusing specifically in total shoulder arthroplasties showed the ideal cutoff for IL-6 was 446 pg/mL (86% sensitivity; 95% specificity).

In addition to the large discrepancy between proposed cutoffs (around 2,000-4,000 pg/mL to over 30,000 pg/mL even if we consider THA/TKA findings only) and suboptimal diagnostic accuracy with limited sensitivity in most studies, there is also the topic of laboratory processing. Cytokines measurement is not easy and it requires immunoassays that are not widely available thus limiting its role in clinical practice.

Antimicrobial peptides are a large group of peptides that constitute crucial components of the innate immune system and have the capacity to directly kill or inhibit the growth of microbes³¹². Examples of such molecules that have proven its value in distinguishing infected from aseptic total joints are alpha- and β -defensins, skin-derived antileukoproteinase and cathelicidin LL-37^{305,307}. By far the most widely known and studied molecule thus far has been alpha-defensin.

In their groundbreaking initial study, Deirmengian et al.³¹³ analyzed synovial fluid samples from 149 THA/TKA cases. Of those, 37 had PJI according to the MSIS criteria. Immunoassay measurement of the synovial fluid alpha-defensin protein was optimized to operate at a cutoff value of 5.2 mg/L, providing results as a semiquantitative signal-to-cutoff ratio of 1. It was able

to correctly classify 143 of the 149 patients, corresponding to a specificity of 95.5% (95%CI, 89.9 - 98.5%) and a sensitivity of 97.3% (95%CI, 85.8 - 99.6%).

Since then, the same research group has demonstrated the value of the alpha-defensin assay in different scenarios. Based on their synovial fluid sample's bank, they were able to select 244 positive culture out of 498 alpha-defensin positive samples and showed the alpha-defensin test provides consistent results regardless of the organism type, Gram type, species or virulence of the organism³¹⁴. Studying the records of 106 patients (77 TKA and 29 THA) meeting the MSIS criteria for PJI and with a positive alpha-defensin test, they found 30 of them had received antibiotics within 2 weeks before the diagnostic workup. Although synovial fluid leukocyte counts and proportion of PMN (as well as serum CRP) were significantly lower in this sub-group of patients, alpha-defensin level was not significantly decreased, thus showing the alpha-defensin test is not affected by prior antibiotic treatment³¹⁵. Comparing alpha-defensin test to leukocyte esterase colorimetric strips they also found it to be much more accurate³¹⁶. A closer look into these findings shows that LE tests were performed at the time of sample collection without processing of the synovial fluid thus showing all the known limitations: eight out of 46 joint fluids were unreadable as a result of blood interference and defining 2+ result to be positive yielded a sensitivity of 68.8% and a specificity of 100%. Samples for alpha-defensin testing were subjected to centrifugation to separate all particulate and cellular material and the resulting supernatant was then used for the immunoassay. This specific methodology correctly diagnosed 100% of patients in this study³¹⁶.

Independent researchers have also been able to replicate these results hence underlining the great promise of this test. Bingham et al.³¹⁷ found the alpha-defensin assay to correctly diagnosed all 19 infections in their 61 hip and knee arthroplasties samples, with an overall sensitivity of 100% and specificity of 95%. Frangiamore et al.³¹⁸ showed similar results in their cohort of first- and single-stage revision THA or TKA procedures performed for aseptic loosening or suspected PJI (100% sensitivity; 98% specificity). Interestingly, they also looked at second stage revisions and in this setting it performed less well (67% sensitivity; 97% specificity). With regards to total shoulder arthroplasty, Frangiamore et al.³¹⁹ also found results to be less favorable than for THA or TKA (63% sensitivity; 95% specificity). Just recently, Bonanzinga et al.³²⁰ published their experience with the alpha-defensin assay. The major particularity of this study is that alpha-defensin measurement was performed by an independent blinded laboratory, unlike all the previously mentioned papers, which is useful in proving the reproducibility of the test. Using the ICM definition of PJI, they found the sensitivity of the alpha-defensin immunoassay to be 97% (95% CI, 92%-99%) and the specificity 97% (95% CI, 92%-99%).

There seems to be sufficient evidence that the alpha-defensin immunoassay performed in a laboratory by trained staff is a very promising diagnostic tool for PJI diagnosis. However, such laboratories are not widely available and in order to overcome that lack of practicality a quick lateral flow assay (Synovasure®, Zimmer, Warsaw, IN) has been developed. Nevertheless, there is still a paucity of information regarding this test specifically. It is possible that publication bias may exist. This is an important issue in diagnostic accuracy studies, as results

of new tests with poor sensitivity and specificity may remain unpublished. In the only published paper focusing specifically in the use of this specific lateral flow assay as a point-of-care test without laboratory sample processing, results lack behind those previously reported. Kasparek et al.³²¹ used this test intra-operatively at the time of revision surgery in 29 TKA and 11 THA. Twelve patients had confirmed PJI based on MSIS criteria. The test offered a sensitivity of only 67% (95%CI, 35%-89%) and a specificity of 93% (95%CI, 75%-99%). Just recently, Sigmund et al.³²² focusing on 50 revision arthroplasty surgeries, showed 69% sensitivity and 94% specificity. As such, care must be taken before extrapolating the alpha-defensin quantitative test results obtained in the laboratory after due processing of the synovial fluid to the lateral flow test device that is commercially available and is intended to be used as a point-of-care test. In addition to the aforementioned cytokines and antimicrobial peptides that require complex laboratory methodologies that are not widely available in routine daily practice and/or expensive tests (in Portugal the Synovasure® test costs around 400€), other simpler and inexpensive biomarkers can be tested.

In their initial study, Jacovides et al.³⁰⁸ screened 46 inflammatory proteins and cytokines and found synovial CRP and α 2-macroglobulin to be among the five most accurate biomarkers. In recent years, numerous papers (see table V) have demonstrated the potential use of synovial CRP to differentiate between infected and non-infected total joint arthroplasties despite some variability in proposed cutoffs³²³⁻³²⁹. Moreover, in their seminal paper on alpha-defensin, Deirmengian et al.³¹³ found that a 3.0 mg/L threshold for synovial CRP offered a 97.3% sensitivity and 78.6% specificity. They further demonstrated that applying this test to every alpha-defensin positive test correctly reversed all five false-positive alpha-defensin results to true-negatives but did not erroneously reverse any true-positive alpha-defensin results.

Synovial CRP may be measured using different methodologies including complex ELISA assays but also the more common high sensitivity nephelometry test. This test is already routinely performed in many laboratories as it is commonly used to stratify cardiovascular risk³³⁰. An exploration of table V shows this nephelometry method failed to measure samples with very high viscosity as is often the case in synovial fluids^{324,328,329}. As will be discussed further ahead we were able to overcome this limitation by diluting samples in solution of hyaluronidase.

Our research aimed to focus on a specific list of biomarkers that could perhaps make a difference in routine daily clinical decision making. As such, alongside leukocyte count we chose to focus on C-reactive protein, adenosine deaminase, alpha-2-macroglobulin and procalcitonin. These tests are not only inexpensive (they cost around 8€, 9€, 6€ and 14€ respectively) but were already being routinely performed in our own institution laboratory (and widely available in most other laboratories).

Table V Synovial C-reactive protein results.

	Definition of infection	Laboratory technique	Proposed cutoffs	Sensitivity (95% CI)	Specificity (95% CI)	Observations
Parvizi <i>et al.</i> ³²⁵ 2012	similar to MSIS criteria	Individual ELISA (10 infected, 5 aseptic)	0.06 mg/L	70% (62-92)	100% (77-99)	66 revision TKA for septic or aseptic reasons; accuracy and diagnostic threshold highly dependent on the CRP measurement technique used.
		Multiplex ELISA (25 infected, 34 aseptic)	3.7 mg/L	84% (77-99)	97% (77-93)	
		automated turbidimetric method (25 infected, 30 aseptic)	16.5 mg/L	76% (77-99)	93.3% (77-93)	
Parvizi <i>et al.</i> ³²⁶ 2012	AAOS guidelines	automated turbidimetric method	9.5 mg/L	85%	95.2%	35 aseptic and 20 infected revision THA/TKA but also 8 primary TKA.
Vanderstappen <i>et al.</i> ³²⁹ 2013	MSIS criteria	automated immunoturbidimetric assay (detection limit 0.3 mg/L)	1.8 mg/L	100% (72-100)	84.9% (68-95)	44 TKA requiring revision surgery; 51 cases CRP assay not performed because fluid was too viscous (43) or insufficient (8)
			2.8 mg/L	90.9% (59-100)	93.9% (80-99)	
Ronde-Ostau <i>et al.</i> ³²⁷ 2014	MSIS criteria	immuno-nephelometry	2.8 mg/L	100% (69-100)	82% (48-98)	10 aseptic and 10 infected revision TKA but also 10 aseptic effusions in native knees.
			5.4 mg/L	90% (56-100)	91% (59-100)	
Treteault <i>et al.</i> ³²⁸ 2014	MSIS criteria	automated turbidimetric method	6.6 mg/L (overall)	88% (82-93)	85% (79-91)	119 THA/TKA requiring revision surgery; 22 cases CRP assay not performed because fluid was too viscous.
			8.5 mg/L (hip)	87% (78-95)	86% (78-95)	
			14.1 mg/L (knee)	82% (73-92)	93% (87-99)	
Buttaro <i>et al.</i> ³²³ 2015	MSIS criteria	high-sensitivity turbidimetry (detection limit 0.2 mg/L)	9.5 mg/L	90% (71-99)	94% (84-99)	71 THA reoperation including debridement, first or second-stage; No difference to frozen section in ability to diagnose infection.
Omar <i>et al.</i> ³²⁴ 2015	AAOS guidelines	immuno-nephelometry	2.5 mg/L	95.5% (87-100)	93.3% (84-100)	89 chronic painful THA (i.e. acute infections excluded); 9 cases excluded cause of dry tap or fluid was too viscous.

***MSIS** Musculoskeletal Infection Society; **AAOS** American Academy of Orthopedic Surgeons; **ICM** International Consensus Meeting; **TKA** total knee arthroplasty; **THA** total hip arthroplasty.

Diagnosing the Acute Infection

As it was previously mentioned the diagnosis of infection in the acute postoperative period is not always straightforward. Inflammatory signs and even wound leakage are a common finding after surgery and distinguishing aseptic from potentially infected cases is often difficult. On one hand, timely recognition and intervention may lead to successful infection eradication with preservation of the original prosthesis. On the other hand, unwarranted surgery with all its costs and potential complications must be avoided.

SEROLOGY

Diagnostic accuracy of ESR and CRP are extensively studied in the context of chronic infections to try and distinguish them from aseptic failures. In the acute postoperative infections, their role is not as clear. In the recent consensus definition⁸⁵, CRP >100mg/L in the first six weeks after surgery was considered indicative of infection but no threshold for ESR could be determined.

Two major papers specifically address the issue of laboratory diagnoses of PJI in first six weeks after surgery. Bedair et al.³³¹ focuses on TKA and Yi et al.³³² studies hip replacements. While they both found that synovial fluid white cell count was the most informative test, they reached different conclusions regarding serum inflammatory markers. ESR was significantly different between infected and non-infected cases in the hip study³³² but not in the knee setting³³¹. CRP was found to be significantly higher in infected cases in both studies and suggested cutoffs are similar at around 93 and 95mg/L for hip and knee respectively. Notwithstanding, sensitivity/specificity of these proposed thresholds was much better for THA (88%/100%) than for TKA (68%/66%)^{331,332}.

To understand the importance of these markers in the postoperative period it is essential to know their normal kinetic patterns after uncomplicated arthroplasty. As one would expect both these markers rise after surgery. The peak seems to be higher after TKA in comparison to THA^{333,334}, maybe because the bone and soft tissue trauma is higher in TKA, helping to explain the different diagnostic accuracy demonstrated by the proposed cutoff. Nonetheless, after the initial peak, these values should steadily decrease after uncomplicated arthroplasty. ESR levels usually peak around the fifth postoperative day and drop close to preoperative levels by the end of the third month after THA or even as late as the ninth to twelfth month after TKA^{333,335,336}. As one would expect, CRP respond much quicker usually peaking at the second or third day and falls swiftly by the fifth to seventh day. Return to basal levels also occur much faster than ESR, at around the sixth week although again it occurs faster in hips than in knees^{273,333,335,336}. Despite this mean trend, there are wide inter-individual variations and many cases do not follow the typical patterns. In this regard C-reactive protein has less frequent atypical temporal patterns than ESR and is therefore more useful shortly after surgery³³⁶. All the same, many patients especially after total knee replacement do have CRP values >100mg/L during the first postoperative days thus recommending caution in interpreting an isolated CRP measurement.

IL-6 seems to be an even superior marker for the acute inflammatory phase after TJA as it shows an analogous but faster pattern^{273,334}. It peaks at around the 6th postoperative hour and rapidly falls with a half-life of 15h. Return to base levels also occur faster than CRP. A slightly prolonged inflammatory course is also seen in TKR patients but the peak falls well within the first 24 hours³³⁴.

Understanding this normal pattern after uncomplicated arthroplasty is the key to better using these inflammatory parameters to our advantage in the diagnosis of early acute PJI. A sustained persistent elevation of these parameters or rebound after the initial fall (especially CRP or IL-6) should raise the suspicion of an infectious complication. Maathuis et al.³³⁷ proposed a protocol using ESR and CRP as an adjunct to clinical judgement to help dictate the need and timing for debridement in patients with persistent drainage after total joint replacement. Serial measurements of these inflammatory parameters were taken in suspicious circumstances and only decrease in ESR and CRP or a decrease in drainage could postpone or alter the decision to perform open debridement. Persistent wound leakage by the tenth day would command surgery for debridement. We have been using a similar protocol in the past few years in our institution. It allowed us to accurately detect early infection in 96% (28/29) of patients that underwent early debridement after primary hip or knee arthroplasty.

SYNOVIAL FLUID TESTING

Much as serum inflammatory markers, synovial fluid leukocyte count and differential are much more exhaustively studied in the context of chronic infection. Christensen et al.³³⁸ have assessed the natural progression of synovial fluid leukocyte counts and the percentage of PMN after primary total knee arthroplasty. They found that total leukocyte count decreases rapidly during the first three months whilst proportion of PMN continued to decrease significantly throughout the first two postoperative years. Most importantly they showed that the use of the thresholds defined for chronic infection during the first ninety postoperative days may result in a significant proportion of false-positive results.

As such, proposed thresholds for acute infections occurring in the first six weeks after surgery are much higher than for chronic infections: Leukocyte count >10,000 cells/ μ L and proportion of PMN > 90%⁸⁵. These cutoffs are based mostly on only two papers focusing on this specific clinical scenario and a closer look at their results may help to further comprehend them. Bedair et al.³³¹ studied 224 knees (1.9%) out of 11,964 primary TKAs that had arthrocentesis performed within the first 6 weeks after primary surgery. After excluding 78 aspirations for several different reasons they were left with 146 knees (19 infected and 127 aseptic) for analysis. Two potential cutoff values for the synovial fluid leukocyte count were found. With the threshold set at 10,700 cells/ μ L, acute infection could be diagnosed with a sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of 95%, 91%, 62%, and 99%, respectively. With the threshold set at 27,800 cells/ μ L the sensitivity, specificity, PPV, and NPV were 84%, 99%, 94%, and 98%, respectively. The lower leukocyte count cutoff around 10,000 cells/ μ L is helpful in excluding infection and only around 30,000 cells/ μ L is the leukocyte count a useful positive predictor of infection. Proportion of PMN >89% was found

to have sensitivity, specificity, PPV, and NPV of 84%, 69%, 29%, and 97%, respectively (i.e. good for excluding infection). Yi et al.³³² performed a similar study focusing on THA. On a consecutive series of 6033 primary THA, 122 (2%) were found to have undergone a reoperation within the first 6 weeks postoperatively. Seventy-three hips (36 infected and 37 aseptic) were available for analysis after exclusion of 49 patients. Setting the optimal cutoff at 12,800 cells/ μ L they found the sensitivity, specificity, PPV, and NPV to be 89%, 100%, 100% and 88% respectively. Proportion of PMN >89% was found to have sensitivity, specificity, PPV, and NPV of 81%, 90%, 91%, and 79% respectively. This study found a highly specific cutoff at around the lower threshold previously determined for knees.

To the best of our knowledge there is no study comparing leukocyte counts and percentage of PMN natural progression after uneventful THA and TKA. As such, one can only speculate if the higher postoperative inflammatory response after TKA previously demonstrated in serum markers is also true for synovial fluid. If that is the case perhaps using the same cutoff for both TKA and THA is not the most adequate and more studies are needed to clarify this. Meanwhile, one should be aware of this seeming difference.

Other synovial fluid biomarkers that are being studied in the chronic setting (e.g. CRP, IL-6, etc.) lack research in the acute postoperative setting and certainly no recommendation can be made at this point.

Nuclear Medicine and other Imaging Techniques

Despite substantial evidence regarding the effectiveness of nuclear imaging in the diagnosis of PJI, currently there seems to be no role for its routine use⁸⁵. Several methodologies have been proposed but they are expensive and time-consuming thus limiting their role in the work-up for PJI.

Notwithstanding, there are a few selected cases where it might be indicated. In cases where repeated attempts at joint aspiration failed to provide fluid for analysis, especially if other co-morbidities ill advise against more invasive testing or surgery, nuclear imaging may prove to be a valuable asset. In addition, such tests are often solicited in trying to identify other causes of joint pain/failure and physicians must be aware of its real value in affirming or excluding infection.

Bone scintigraphy with technetium-99m labeled diphosphonates, which is often requested to ascertain the presence of loosening, is undoubtedly the most extensively investigated nuclear medicine test for imaging total joint arthroplasties. Several different (and often contradicting) uptake patterns have been proposed to serve as better indicators of infection but regardless of how images are interpreted, its overall accuracy for diagnosing infection of lower extremity joint prostheses, at around 50-70%, is low³³⁹⁻³⁴¹. At the present time this test is used primarily for screening purposes, especially after the postoperative period where periprosthetic activity may persist for up to 12-24 months³⁴⁰. A normal study makes it very unlikely that the patient's symptoms are related to an infection.

Over the years, various techniques designed to overcome the limitations inherent to bone scintigraphy have been proposed. Gallium-67 citrate imaging is a classic and several studies were performed mostly in painful total hip prostheses with a wide range of diagnostic accuracy variability, but overall low sensitivity³⁴⁰. Over the years the use of gallium for joint replacement infection has declined, and it has been replaced in most circumstances by labeled leukocyte imaging. *In vitro* labeled leukocytes will accumulate at a site of infection but also accumulate in bone marrow, the normal distribution of which can be variable after TJA surgery thus decreasing the specificity of the test³⁴⁰. Using any periprosthetic activity regardless of intensity, as the criterion for infection greatly increases sensitivity (while naturally decreasing specificity) for PJI diagnosis. Following this test with bone marrow imaging greatly increases specificity by mapping reticuloendothelial cells of the bone marrow where labeled leukocytes will also accumulate. Several papers report diagnostic accuracy of this combined approach around or above 90%^{340,342-344}.

Positron Emission Tomography (PET) bone imaging also shows great promise in the evaluation of suspected PJI. The rationale being that activated leukocytes demonstrate increased uptake of ¹⁸F-fluorodeoxyglucose (FDG). There are numerous and conflicting results on the real accuracy of this test in diagnosing infection but a recent meta-analysis found the pooled sensitivity and specificity of FDG-PET for the detection of prosthetic hip or knee joint infection to be 82.1% and 86.6% respectively. Direct comparison with combined leukocyte/

marrow imaging³⁴⁴ or even simple three-phase bone scintigraphy³⁴¹ however, does not yet seem favorable. Adding advanced imaging that provides detailed anatomical information such as Single Photon Emission Computed Tomography (SPECT-CT) seems to have great potential. There seems to be gains in both sensitivity and specificity over plain scintigraphy in a number of fore mentioned radiopharmaceuticals^{345,346}. The advantages may extend beyond diagnosing infection. In patients with negative studies, the CT component could provide information about other causes of prosthetic failure.

Although research is underway in these more advanced nuclear imaging modalities as well as “infection-specific” molecules such as antibiotics or antimicrobial peptides currently, combined labeled leukocytes/bone marrow imaging seems to be the most accurate³⁴⁰. There are, unfortunately, disadvantages. The leukocyte labeling procedure is technically demanding and not routinely available. As such radiolabeled antigranulocyte antibodies and antibody fragments have been explored as alternatives with reported suboptimal sensitivity and specificity at around 80%³⁴⁷. Surprisingly, even though *in-vivo* labeled leukocytes accumulate in the marrow, in much the same way that *in-vitro* labeled leukocytes do, scant attention has been paid to combining these studies with bone marrow imaging. In trying to validate such an approach, that could be integrated into our own clinical practice we performed our own research³⁴⁸. We confirmed the lack of specificity of isolated leukocyte scans using sulesomab (antigranulocyte antibody). We did however confirm that a subsequent bone marrow scan and combined imaging interpretation greatly increases specificity³⁴⁸. Results will be presented in more detail ahead.

CT AND MRI

There is a paucity of data regarding the diagnostic value of other advanced imaging modalities such as CT or MRI. One paper specifically focusing on this topic found, found that CT scan soft tissues findings such as joint distention, fluid-filled bursae and fluid collection in muscles and perimuscular fat were accurate in diagnosing infection around THA³⁴⁹. However, these findings cannot be extrapolated to other joints and confirmation in similar studies is missing. Despite known technical difficulties in performing MRI around prosthesis, metal artifact reduction sequences have been developed and some reports state it may be helpful in distinguishing qualitative differences in the appearance of the synovium in TKA between particle-induced synovitis, infection and nonspecific synovitis³⁵⁰. Nonetheless, it is not presently recommended to use CT or MRI to evaluate for a potential PJI⁸⁵.

Microbiological Investigation

Obtaining precise microbiological information is obviously a crucial part of prosthetic joint infection management. It is widely considered a definite evidence of infection if the same undistinguishable organism grows in two separate samples and, if only a single sample shows growth, it is viewed as a minor criterion that must be framed together with other laboratory findings^{244,302,340}.

Aside sustaining diagnosis, it is also a vital piece of information that allows for adequate antibiotic treatment thus surrendering the best chance for success. That being said, it is natural to conclude that considerable efforts must be undertaken to avoid cases where no isolation of microorganisms can be achieved, the so-called culture-negative PJI. Furthermore, if a standardized sample gathering protocol is implemented in every TJA revision case, there is a consistent proportion of cases that will ultimately reveal themselves to have an infection that was previously unrecognized^{255,351,352}.

PREOPERATIVE SAMPLING

In the face of a possible PJI, most patients will have had some kind of specimen sent to culture before surgery. Limitations inherent to culture of the synovial fluid obtained by arthrocentesis have already been discussed elsewhere. These concern mainly limited sensitivity either in being able to isolate a microorganism or even being able to identify the full spectrum of microorganisms involved in a particular infection^{279,286,288}. Performing a biopsy of either the synovium or the bone-implant interface membrane seems to be helpful in increasing diagnostic accuracy^{280,353}.

Oftentimes, cultures are obtained from a draining wound in the early postoperative period or later from a sinus tract. In chronic osteomyelitis, sinus tract swabs are admittedly unreliable in predicting bone cultures isolates^{354,355}. The same seems to be true in periprosthetic infections. Treteault et al.³⁵⁶ studied the results of superficial cultures taken from 34 draining wounds in the acute postoperative period and 21 patients with chronic draining sinuses and compared them to intraoperative tissue samples. They found that superficial cultures matched the deep intra-articular cultures in less than half of patients³⁵⁶. One other study offers scarce evidence that superficial samples may have different intrinsic value in these two different clinical scenarios. Cuñe et al.³⁵⁷ evaluated the relationship between superficial swab and deep intraoperative cultures in 56 patients (30 hip and 26 knee) exclusively among patients with acute postoperative PJI. They found the overall concordance between superficial and deep samples was 80.3%. Superficial swabs were especially accurate when Gram negative bacilli or *S. aureus* were isolated but performed poorly for other Gram positive microorganisms³⁵⁷.

Notwithstanding, intraoperative samples should always be considered mandatory and withholding administration of antibiotics until deep samples are obtained is recommended whenever possible.

INTRAOPERATIVE TISSUE SAMPLING

Adequate deep tissue sampling obtained during revision surgery is still the gold standard for the microbiological diagnosis of PJI. There are however a few simple principles that must be met in order to achieve satisfactory results.

There is a worldwide agreement that numerous perioperative samples are needed to diagnose PJI. In 1998, Atkins et al.³⁵⁸ recommended that five or six specimens should be sent in order to increase diagnostic accuracy. Multiple samples increase the chance of growing a pathogen (i.e. sensitivity) and it also allows more correct interpretation in cases where a skin flora organism such as coagulase negative staphylococci is grown. Specificity is increased by interpreting the number of samples in which such species is grown. If more than one sample grows the same indistinguishable organism it is likely that it is indeed a pathogen and not dismissed as a contaminant. Otherwise, it would be very difficult to interpret such findings if such commensal bacteria grew in an isolated sample.

Recent guidelines recommend at least three but no more than six distinct intraoperative tissue samples should be sent for aerobic and anaerobic culture^{85,359}. Obtaining intraoperative culture specimens by using swab cultures should be discouraged. It has been repeatedly shown that they perform significantly worse than tissue cultures³⁶⁰⁻³⁶². Tissue sampling should be obtained from different sites within the joint and it has been recommended that in order to reduce the risk of cross contamination, they must be taken with different set of instruments and sent to the laboratory separately^{358,363}. It has also been shown that they should be immediately transferred directly to a sterile container or bottle after being taken from the joint. The samples should not be placed on the OR table for the duration of the surgical procedure as a significant proportion of false positives may arise³⁶⁴. The exact location of each biopsy is naturally determined by the treating surgeon but generally, any suspicious looking material should be biopsied. A special consideration should be paid to obtaining samples from the bone-implant membrane interface^{248,249,365}. Although some authors do recommend obtaining more samples in cases of suspected less virulent organisms or in patients with recent antibiotic therapy, there is a consensus that culture specificity should not be compromised by taking more than five samples⁸⁵. In such cases, other techniques (e.g. increased incubation time, molecular techniques or sonication) may be more helpful. The adoption of this kind of standardized procedures carries a definite positive impact on clinical care³⁶³.

Another typical concern regards to timing of prophylactic antibiotics administration in revision arthroplasty. Previous antibiotic therapy is a well-established risk factor for negative cultures^{281,366}. With this fact in mind, many over the years have advocated withholding perioperative prophylactic antibiotics until deep samples are collected as there is concern that occult infection may be present. In recent years, there has been sufficient evidence that such a distress is not called for³⁶⁷⁻³⁶⁹. In a multicenter randomized trial including 37 TKA and 28 THA with known PJI, Treteault et al.³⁶⁹ were able to show there was no effect on the results of cultures obtained intraoperatively when prophylactic antibiotics were administered before skin incision or after intraoperative cultures were obtained. Intraoperative cultures yielded the same

organisms as preoperative cultures in around 80% of cases in both groups³⁶⁹. More recently, Bedencic et al.³⁶⁷ prospectively collected three paired tissue samples before and after the administration of prophylactic antibiotics in 29 THA and 11 TKA. Measured tissue concentrations of cefazolin in the second set of samples were greater than the minimum inhibitory concentration in all samples. Still, no difference was found in cultures results taken before and after administration of antimicrobial prophylaxis³⁶⁷. In cases of high suspicion of PJI especially if a low virulence pathogen is thought to be involved but has yet to be identified, the use of prophylactic antibiotics is dependent upon clinical judgment⁸⁵. Also, if antibiotic therapy is prematurely started, a minimum of two weeks' interval after cessation should be respected before surgery if the patient's clinical condition will allow it³⁵⁹.

SAMPLE PROCESSING

Laboratory processing of tissue samples gathered during surgery is naturally, a vital part of accurate diagnosis. Due to the wide spectrum of possible pathogens potentially involved in PJI, samples should be investigated for both aerobic and anaerobic bacteria. Although fungal^{370,371} and even mycobacterial^{372,373} prosthetic joint infections have been described often, there is a generalized consensus that acid-fast bacillus (AFB) and fungal testing should not be routine but rather reserved for patients at high risk for such infections or when other traditional pathogens have not been identified and clinical suspicion persists^{374,375}.

The orthopedic surgeon is obviously not the more qualified physician to appreciate all the variables involved in processing microbiology specimens but he should nevertheless be able to accurately convey his needs to the laboratory personnel.

There a number of techniques increase the diagnostic ability of microbiological detection. Extending incubation time is one of them. Traditional cultures are maintained for about seven days and indeed, most common infecting organisms can be isolated within a few days. However, there is evidence that extending cultures for up to 14 days significantly increases sensitivity (especially increased detection of fastidious organisms such as *Propionibacterium acnes*) while not increasing the risk of contaminants^{376,377}. In cases of suspected PJI with low virulence organisms or if preoperative cultures have failed to show bacterial growth and the clinical picture is consistent with PJI, extending periprosthetic cultures, significantly increases sensitivity while not increasing the risk of contaminants³⁷⁸.

Different culture media naturally yield different diagnostic sensitivity³⁷⁹. There is increasing amount of evidence that blood culture bottles may be advantageous not only for joint aspirate but also for periprosthetic tissues^{360,361,380,381}. Extrapolating from previous studies on native septic arthritis, Font-Vizcarra et al.³⁶⁰ compared the frequency of positive synovial fluid cultures inoculated into aerobic and anaerobic blood culture flasks with the results of periprosthetic tissue and swab samples cultured in standard media. They found synovial fluid inoculated in blood culture flasks had greater sensitivity, specificity and positive and negative predictive values than swabs or even standard tissue samples³⁶⁰. Others have replicated these findings suggesting that blood culture bottles should become standard methodology for synovial fluid

culturing³⁶¹. More recently, Peel et al.³⁸⁰ extended this concept into tissue specimens. They compared inoculation of periprosthetic tissue samples into blood culture bottles with standard agar and thioglycolate broth culture. Not only did they find increased sensitivity but also faster time to microorganism detection using the automated blood culture bottles system (both aerobic and anaerobic) than with standard media³⁸⁰.

All these demands dramatically increase the number of samples to be processed by bacteriology laboratories, with a major impact on both the staff work load as well as increased costs. A recent French prospective multicenter study tried to determine a cost-effective protocol for the microbiological diagnosis of PJI taking into account these novel developments³⁸². Their study included 264 suspected cases with 215 confirmed PJI out of seven different centers. They were able to show that taking four samples instead of five had no impact on diagnosis effectiveness. Although they did not confirm the superiority of interface membranes over other samples, they argue that it seems preferable to privilege tissue in contact with the material and the joint fluid. Joint fluid should be seeded directly into a blood culture bottle by the surgeon in the operating room. As to the amount of culture media necessary, they determined that a combination of a blood culture bottle, a chocolate agar plate and Schaedler broth offered similar results as those obtained with four or five culture media³⁸².

SONICATION AND OTHER BIOFILM-DISRUPTION TECHNIQUES

Even before the advent of sonication, there were attempts on removing the bacterial biofilm of the explanted prosthesis by simply scraping it with a scalpel. Although there are anecdotal evidence that this simple technique may be superior than traditional tissue cultures³⁸³ it soon became apparent that scraping is not an efficient technique for dislodgement of biofilm bacteria³⁸⁴.

In 2007, Trampuz et al.³⁸⁵ published a landmark paper on sonication. They studied the effectiveness of a sonication protocol of 331 explanted total knee or hip prosthesis for aseptic failure or presumed infection and compared it to conventional fluid and tissue sampling. They found that sonicate fluid culture was significantly more sensitive (78.5%) than tissue cultures (60.8%) in general. However, further analysis on their results show the sensitivity of tissue culture increased from 50.0% to 54.1% to 66.7% to 72.7% as the number of specimens collected increased from two or three to four or five or more respectively. Furthermore, the authors acknowledge this a time-consuming laboratory process and the equipment to perform sonication is not widely available. Nevertheless, many have since then showed that sonication increases the likelihood of isolating pathogens without increasing the rate of contaminants in revision arthroplasty of the hip, knee, shoulder and elbow^{249,381,386-391}. Sensitivity of sonicate fluid cultures can be even higher if molecular detection methods^{237,238} are used or simply by inoculating it into blood culture bottles^{381,392} which is much more simple and widely available.

In 2010 we were able to publish a retrospective analysis of 75 hip or knee prosthetic joint infections and described our microbiological results. We found an upsetting 18% proportion of culture-negative cases⁹⁶. Several common mistakes were identified such as insufficient

intraoperative sampling (many cases with a single fluid sample), antibiotics were often and unjustifiably started before surgery, etc. Working alongside the microbiology department to change and improve methodologies (including sonication) and also by educating surgeons we were able to change the scenario. A recent analysis of our experience, confirmed the benefits of this collective effort. In a total of 93 patients with PJI treated between 2009 and 2013, there were only three cases (3.2%) in which we failed to isolate any microorganism. Sonication was used in 52 cases. Interestingly, although sonication enabled us to find the infecting pathogen in four cases in which tissue cultures were negative (all of them chronic infections with previous attempts at debridement and implant retention and antibiotic therapy), it did not grow an organism in 22 cases with positive tissue cultures (mostly acute postoperative and hematogenous infections). In the remaining 25 patients (27 microorganisms) there was complete correspondence between the findings of sonication and traditional tissue culture. As such, we currently view sonication not as a surrogate for traditional tissue sampling but rather as supplemental tool that increases overall sensitivity (especially in cases of chronic infections with previous antibiotic therapy) and can perhaps reduce the ideal number of tissue samples to be collected. Recent results from the Oxford Bone Infection Unit in the United Kingdom, presented at the 35th Annual Meeting of the European Bone and Joint Infection Society allow a similar conclusion. Analyzing over 200 joint prostheses (aside from many other orthopedic hardware), they found tissue culture (4-5 independent periprosthetic tissue samples) was more sensitive than sonication alone. The combination of tissue culture and sonication provided optimum sensitivity especially in chronic infections where the biofilm burden is presumably higher.

Being a time- and resource-intensive procedure, routine sonication is not routinely warranted in cases where preoperative identification of pathogen is already available. It has been demonstrated that in early or acute infections, sonication is not clearly superior to periprosthetic tissue cultures³⁹³. Its greatest advantage over standard tissue culture is appreciated when antibiotics were provided within the two weeks previous to surgery³⁸⁵. As such, the recent ICM on PJI recommends its use be limited to cases of suspected or proven PJI in which preoperative aspiration does not yield positive culture and antibiotics have been administered within the previous 2 weeks⁸⁵.

Their role in routine revision surgery for presumably aseptic failure is much more controversial since there are conflicting results. On one hand, Puig-Verdie et al.³⁹³ examining 54 THA and 98 TKA, found sonication to be significantly more sensitive than conventional tissue cultures in unsuspected septic failure (100% vs. 48.5% respectively) and in delayed implant failure (88% vs. 58% respectively). On the other, Kempthorne et al.³⁵¹ prospectively examining the role of sonication of the implants in cases of presumed aseptic loosening of 77 THA and 29 TKA, found that conventional sampling techniques provided more positive cultures than sonication.

There are other alternatives to dislodging bacteria from biofilm of implants after its removal. An Italian research group has been working with Dithiothreitol (DTT) which is a strong reducing agent commonly used in chemical laboratories. Initial *in vitro* analysis suggested that sonication and DTT treatment seem to provide reproducible results in removing bacteria from

biofilm in polyethylene and titanium discs suggesting that treatment of prostheses with DTT may be a reasonable alternative to sonication³⁹⁴. Clinical data from 80 patients undergoing removal of the prosthetic joint or cement spacer showed encouraging results with treatment with DTT displaying the same specificity of sonication but a higher sensitivity especially a higher recovery of *S. epidermidis* than sonication³⁹⁵. The same research group has developed this principle into a ready-to-use technology specifically designed to collect, transport and process explanted prosthesis that may be more practical than sonication³⁹⁶. These findings and hypothetical advantages are still lacking confirmation from larger and independent research.

MOLECULAR TECHNIQUES

The high cost and limited availability of molecular techniques such as polymerase chain reaction will probably prevent its broad application in the near foreseeable future. Nevertheless, they are worth mentioning as their findings may ultimately have an impact on how we define aseptic failure of a total joint arthroplasty.

Molecular techniques have repeatedly been shown to be more sensitive than conventional methods especially when sonicate fluid and not periprosthetic tissue is the analyzed specimen^{237,238,397}. But such an advantage is however, not universally found. In 2012, Gomez et al.³⁹⁸ focused on 366 prostheses from unique subjects. Defining PJI as (i) synovial fluid or periprosthetic purulence, (ii) sinus tract communicating with the prosthesis and (iii) periprosthetic tissue histopathology showing acute inflammation, 135 were classified as PJI and 231 as aseptic failures. These authors found broad-range PCR and culture of sonicate fluid have equivalent performance for PJI diagnosis³⁹⁸.

A main concern of such PCR techniques is their specificity. Bacterial DNA is often found in cases where current standards for defining infection are absent (i.e. aseptic failures)³⁹⁷⁻³⁹⁹. More information is needed to understand the real pathogenic value of this finding. A very recent paper clearly illustrates a major interpretation dilemma associated with research being performed on these ultra-sensitive diagnostic molecular techniques. Do these techniques lack specificity or are current definitions of infection in need of amendment? Rak et al.³⁹⁷ prospectively studied 87 patients who underwent revision operation of total knee or total hip arthroplasty. Using MSIS criteria for defining infection, aseptic failure was diagnosed in 58 cases and PJI in 29 cases. Molecular methods detected the presence of bacteria in 13 out of 58 aseptic failures. In seven of those, one additional minor criterion was fulfilled: positive culture from periprosthetic tissue in one sample (4), positive histology (2), and positive synovial fluid leukocyte count (1). Even by dismissing some cases that did not fulfill their previously determined cutoff for significance of PCR results⁴⁰⁰, the authors believe some cases were ultimately misclassified as having aseptic failure and should have been classified as having PJI. As such, molecular techniques are not currently a recommended routine diagnostic test for PJI⁸⁵.

Another customary limitation of this technology compared to traditional cultures is knowing complete antibiotic susceptibility of isolated microorganisms. Early detection of resistant genes

using PCR (e.g. *mecA* gene which is the coding gene for the most important mechanism of resistance to beta-lactams in methicillin-resistant *S. aureus*) is currently available but few clinical studies have been performed using test kits specifically designed for the diagnosis of PJI. Prieto-Borja et al.⁴⁰¹ recently published data from 88 prostheses of 68 patients using a new commercial molecular biology technique designed to detect 27 species or groups of organisms and simultaneously detect 19 resistance genes frequently involved in PJI. Interestingly, they found a very high specificity and positive predictive value with good performance in detecting antibiotic resistance when compared to traditional tissue cultures and sonication. Nine resistance mechanisms genes were detected and all of them were confirmed by standard phenotypic antimicrobial susceptibility testing. One *Staphylococcus simulans* resistance to erythromycin and clindamycin, was not detected by the system⁴⁰¹. Despite promising research being made, there are still important limitations. Low overall sensitivity is at least partially explained by the fact that some relevant microorganisms as well as some resistance mechanisms are not yet included in this technique⁴⁰¹.

Histological Analysis

Positive histological analysis is considered to be a minor criterion for the diagnosis of PJI^{85,241}. Positivity is determined by the amount of polymorphonuclear neutrophils existing in a given periprosthetic tissue sample collected during revision surgery. Tissue sampling follows much of the same rules as microbiological investigation. Multiple samples should be collected as the expression of infection may vary according to the anatomical location and the bone-implant interface membrane should be privileged²⁴⁸.

Histopathological exploration can be performed in conventional formalin-fixed, paraffin-embedded permanent sections as part of a complete diagnostic protocol to distinguish between aseptic and septic loosening^{402,403}. However, most of the times it is especially useful in cases of equivocal preoperative investigation. In this context, intra-operative frozen sections will offer a swift answer that may help decide on the more adequate treatment. There seems to be enough evidence that there is good concordance between frozen and permanent sections^{404,405}.

Performance of intraoperative frozen sections in the diagnostic of PJI has been extensively studied over the past decades. Table VI depicts some of the most recent studies and illustrates the wide range of proposed cutoffs for interpretation that have already been proposed^{293,297,405-413}. A meta-analysis performed in 2012⁴¹⁴, found that regardless of the criteria defined by the histopathologist, frozen section analysis of periprosthetic tissue was very good at predicting culture-positive joint infection and it was moderately accurate in ruling out this diagnosis. This overall suboptimal sensitivity seems to be related to the false-negative results when the infection is due to low-virulence microorganisms. Bori et al.⁴¹⁵ analyzing the results of 38 resection arthroplasty of infected hips found the percentage of positive histology in documented infections due to coagulase-negative staphylococci was significantly lower than in infections due to other microorganisms. They further reviewed available data on the relationship between histology and microbiology from previous papers and found the same significant difference. Positive histology was significantly less prevalent among coagulase-negative staphylococci infections (71%-39/55) when compared to all other microorganisms (89%-66/74)⁴¹⁵. The vast majority of publications deal with either revision THA or TKA but the same principles seem to hold true into other joints. Ahmadi et al.⁴¹⁶ reviewed 296 consecutive revision elbow procedures. With a positive histology when any single high-power field contained at least five neutrophils they found frozen sections to display high specificity (93%) and low sensitivity (51%).

A very recent paper by Kwiecien et al.⁴¹⁰ accurately condenses current knowledge. They assessed the value of intraoperative histology in a study that included 100 TKA and 100 THA with complete information to diagnose or exclude PJI as defined by the MSIS criteria. Both frozen sections and permanent histology demonstrated excellent approximation of modified MSIS criteria, and there were no significant between them. A very high specificity of the test was confirmed (when at least one of the samples presented at least 5 neutrophils in at least 3 high power fields) at around 99% but only a moderate sensitivity (74% overall). The authors

conclude that in the availability of experienced pathologists, frozen sections analysis is a valuable tool that can reliably guide surgeons in intraoperative planning of treatment⁴¹⁰.

Table VI Summary of recent frozen section results.

	Joint(s)	Standard for PJI definition	Sensitivity	Specificity	PPV	NPV
Positivity criteria: ≥5 PMN in >1 HPF (400x)						
Ko <i>et al.</i> ⁴⁰⁹ 2005	34 THA + 6 TKA	intraoperative culture results	67%	97%	86%	91%
Nilsdotter <i>et al.</i> ⁴¹² 2007	THA (n=85)	preoperative clinical and laboratory results or significant intraoperative culture results	81%	100%	100%	87%
Nuñez <i>et al.</i> ⁴¹³ 2007	THA (n=136)	intraoperative culture results	85%	87%	79%	91%
Positivity criteria: ≥5 PMN in ≥3 HPF (400x)						
Kwiecien <i>et al.</i> ⁴¹⁰ 2016	Overall (n=200)	MSIS criteria	74%	99%	93%	94%
	TKA (n=100)		68%	99%	93%	93%
	THA (n=100)		79%	99%	94%	94%
Positivity criteria: ≥10 PMN in ≥1 HPF (400x)						
Banit <i>et al.</i> ⁴⁰⁶ 2002	Overall (n=121)	intraoperative culture results	67%	93%	67%	93%
	TKA (n=55)		100%	96%	82%	100%
	THA (n=63)		45%	92%	55%	88%
Positivity criteria: ≥2 PMN in >10 HPF (400x)						
Tohz <i>et al.</i> ⁴⁰⁵ 2010	THA (n=64)	Same organism ≥2 cultures; sinus tract; gross purulence; consistent histopathology	87%	100%	100%	95%
Positivity criteria: ≥5 PMN in >5 HPF (400x)						
Muswso <i>et al.</i> ⁴¹¹ 2003	26 THA + 19 TKA	intraoperative culture results	50%	95%	60%	92%
Bori <i>et al.</i> ⁴⁰⁷ 2006	THA (n=61)	clinical, laboratory, nuclear medicine and culture results	50%	81%	40%	86%
Kanner <i>et al.</i> ⁴⁰⁸ 2008	137 THA +107 TKA	intraoperative culture results and other pertinent clinical data	29%	95%	40%	92%
Positivity criteria: ≥10 PMN in >5 HPF (400x)						
Della Valle <i>et al.</i> ²⁹⁷ 2007	TKA (n=105)	Same organism ≥2 cultures OR ≥2 of the following: 1) one positive culture; 2) consistent histopathology; 3) gross purulence.	88%	96%	91%	93%
Schinsky <i>et al.</i> ²⁹³ 2008	THA (n=201)	Two of the following: 1) positive intraoperative culture; 2) gross purulence, 3) consistent histopathological result.	73%	94%	82%	90%

PMN polymorphonuclear neutrophil; **HPF** high power field; **TKA** Total knee arthroplasty; **THA** Total hip arthroplasty; **MSIS** Musculoskeletal Infection Society.

The timely availability of an experienced pathologist is perhaps the major limitation of performing histological frozen section analysis intraoperatively. Not every institution will be able to accommodate this requirement. Plus, there is increasing evidence that other diagnostic tools may perform just as well with the added advantage of ease-of-use. We have already

discussed the value of leukocyte esterase test strips or alpha-defensin and these tests can be performed promptly intraoperatively^{301,321}. Even laboratory synovial fluid leukocyte count is a relatively quick procedure and can be very informative in cases where it was not performed preoperatively. Buttaro et al.³²³ directly compared the utility of synovial C-reactive protein and frozen section in 76 patients who underwent hip revision. Using MSIS criteria for PJI, and at a threshold of synovial CRP of 9.5 mg/L, sensitivity was 90% and specificity was 94% which was comparable to intraoperative frozen section.

Diagnostic Approach

Infection is known to be a major cause for revision. We have already established that it may be present without obvious signs and symptoms and is frequently found in cases thought to be aseptic, especially in the early years after surgery^{255,351,352}. As such, all patients who present with a painful or failed arthroplasty should undergo investigation to rule out infection.

Figure 4 portrays an algorithm for the diagnosis of PJI proposed in the 2013 ICM⁸⁵. Naturally, the use of this (or any other) algorithm should not outweigh clinical judgment. Nor should any one individual test as we have already discussed that all of them have limitations and there is no perfect gold standard. Moreover, preoperative aseptic diagnosis using this algorithm should not completely eliminate suspicion for PJI⁸⁵. There are also practical limitations and experiences in each institution that in some point may influence the diagnostic flow chart.

There is a wide consensus that serum inflammatory markers, with all its known limitations, should be a universal first preoperative screening test. Most of the times, arthrocentesis will follow if laboratory or clinical suspicion persists. Sometimes, in patients who have a hard time getting to our hospital for instances, we will do them simultaneously. If enough synovial fluid is gathered a number of tests should be performed: leucocyte esterase immediately in the office or after centrifugation, leukocyte count and differential, C-reactive protein, ADA and other more sophisticated markers if available such as IL-6 or alpha-defensin and of course culture (preferably in a blood culture bottle). In cases of a dry tap or equivocal results a second joint aspiration may be attempted in a later stage. We find that nuclear medicine testing (combined sulesomab/nanocolloids scan) may be a very helpful tool in these circumstances, especially if revision surgery is not being considered.

Finally, intraoperative testing with adequate microbiological sampling and eventually histological analysis offer the best chance for a definitive diagnosis and should be performed routinely in every revision arthroplasty. In dubious cases, some tests such as leukocyte esterase, alpha-defensin lateral flow test or even frozen section histology may be performed during surgery and help decide on the more adequate course of action.

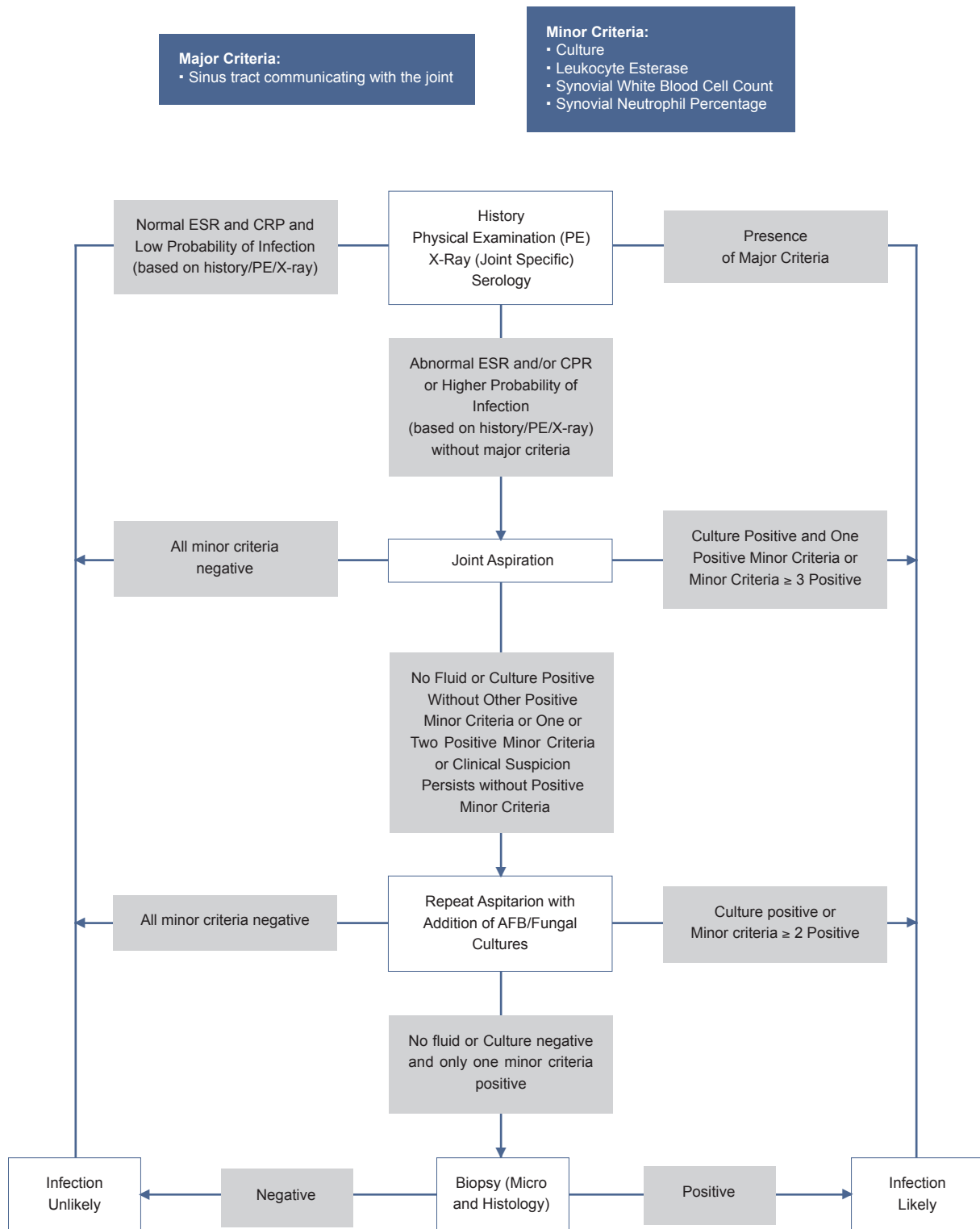


Fig. 4 International Consensus meeting algorithm for the diagnosis of prosthetic joint infection.

Treatment

Once a diagnosis of prosthetic joint infection has been reached, little treatment alternatives exist. The overwhelming majority of patients will require some form of surgical treatment, ranging from debridement with implant retention to revision arthroplasty (be it a one or two-stage exchange), followed by adequate antibiotic therapy with curative intent. In selected cases, the host medical condition is so dismal that it precludes these often very demanding treatments. In such cases, salvage procedures or even chronic suppressive antibiotic therapy may be the best palliative care options.

Classification of Infection

Ideally, the first step in ascertaining the best treatment alternative would be to accurately classify each case using some kind of helpful classification system. Infections can be broadly classified according to the route of acquisition as perioperative or hematogenous depending on whether the bacteria gained direct access to the joint during surgery or via the blood stream at a later stage. Infections reaching the joint through contiguity by progression of an adjacent infectious focus are also possible. This classical criterion offers no therapeutic guidance.

In 1996, Tsukayama et al.⁴¹⁷ defined four different clinical settings for THA infection and made treatment recommendations for each one. *Early postoperative infections* were defined as wound infection that developed less than one month after the operation. *Acute hematogenous infections* were those associated with a documented or suspected antecedent bacteremia and were characterized by an acute onset of symptoms in the affected prosthetic joint. Both of these settings would undergo debridement with implant retention. *Late chronic infections* developed a month or more after the index operation and had an insidious clinical course. These should be dealt with revision surgery. A final type was *Positive intraoperative cultures* and it was assumed when at least two specimens taken during revision surgery for supposedly aseptic loosening with no obvious clinical infection were positive on culture and they should be treated with antibiotics. The same model was also later on adopted for infection after TKA⁴¹⁸.

In 2004, Zimmerli et al.²⁴⁷ proposed a different system in which infections were classified as *Early* (those that develop less than 3 months after surgery), *Delayed* (3 to 24 months after surgery) or *Late* (more than 24 months after surgery). According to these authors, early and delayed infections are usually acquired during implantation of the prosthesis, whereas late

infections are predominantly acquired by hematogenous seeding. Still, there seems to be a gap between their classification system and treatment recommendations. It is clear that acute hematogenous infection can occur several years after surgery (in which case they would be classified as late infections) and early infections (up to three months after surgery) may exceed the three weeks' duration of symptoms they recommend as the threshold for choosing debridement with retention over exchange arthroplasty. More recently, Senneville et al.⁴¹⁹ sought to refine this classification. They defined time to infection or "joint age" using the same criteria but added a new criterion based on the duration of symptoms which was critical in selecting treatment modality. Acute or chronic PJI was defined as time from initiation of symptoms of infection to diagnosis lasting for less or more than one month respectively.

Although they can serve as rough guides to selecting appropriate treatment (debridement with implant retention vs. revision surgery), none of these classification systems takes into account other variables that greatly influence the outcome such as host and microorganism factors. The concept of stratifying bone and joint infections according to the host's condition has been in place for many years in the context of adult osteomyelitis⁴²⁰ and its extrapolation into PJI seems to hold prognostic value⁴²¹. McPherson et al.^{251,252} also acknowledge the importance of systemic compromising factors but further introduce local wound compromising factors such as multiple incisions, soft tissue loss or sinus tract, or even previous radiation therapy or vascular insufficiency into their three-parts staging system for PJI that includes infection type, systemic host grade and local extremity grade.

Romano et al.⁴²² tried to devise a comprehensive classification proposal for bone and joint infections in adults that also includes PJI. Their so-called Seven-Item Comprehensive Classification System includes clinical presentation, etiopathogenesis, host systemic and local (both bone and soft tissue) features. Interestingly, they are the first to take into consideration microorganisms characteristics. This is however a very complex system which is hardly applicable to clinical practice and according to the authors' own admission this proposal is intended for didactic and scientific purposes⁴²².

As such, although numerous classification systems exist for PJI, a flawless classification system is still lacking. In our Institution, we follow the simple classification system originally proposed by Tsukayama et al. as we believe in its intrinsic therapeutic guidance.

Debridement and Irrigation with Implant Retention

Debridement and Irrigation with Implant Retention (DAIR) is an appealing treatment alternative. It is less demanding than revision surgery both for the surgeon and the patient. It is less time consuming and technically easier to perform than revision surgery and it represents a reduced physiologic insult making it easier to recover from. It has been shown that successful DAIR procedures lead to equivalent outcomes to uninfected controls with regards to function and quality of life⁴²³. There is however extensive controversy in the literature regarding its real worth with success rates ranging from 0% to over 90%, and averaging at around 50% both for knees and hips⁴²⁴⁻⁴²⁶.

INDICATIONS AND RISK FACTORS FOR FAILURE

Despite the wide variability of recommendations present in the literature, it is indisputable that such an attempt should only be made when facing a well-fixed, well positioned and stable prosthesis (i.e. one worth saving) and when there is a good soft tissue envelope to cover the prosthesis. Also, DAIR should not be viewed as an emergent procedure except in patients with overt generalized sepsis. Whenever possible, all efforts should be made to optimize the patient's comorbidities to reduce the risk of medical complications, which can ultimately prove to be fatal.

Several variables have been implicated in likelihood of success of this procedure. Some of them such as the actual technique of the procedure and the antibiotic regimen are under the direct control of the medical team, others such as time since presentation, host medical status or even the causative pathogen are not, but may serve as selection criteria to find the best indication for treatment with implant retention.

DURATION OF SYMPTOMS

Duration of symptoms is a major factor implicated in the prognosis of DAIR. In interpreting the literature, it is important to emphasize the difference between duration of symptoms (i.e. time since infection manifests itself and treatment) and the "joint age" (or time from implant/index surgery to presentation). The recent consensus meeting suggests that DAIR may be performed in early postoperative infections that occur within 3 months of index primary arthroplasty or in late hematogenous infection that occur within 3 weeks of an inciting event with less than 3 weeks of symptoms in either case⁸⁵. There seems to be no difference in outcome between acute postoperative and hematogenous infections^{427,428}. In other words, it would seem duration of infection and not "joint age" is the decisive factor.

The problem in clinical practice is how to be sure that a hematogenous infection is really an acute infection and not an exacerbation of a chronic infection. In fact, not all patients report long lasting symptoms prior to their presentation with a chronic infection. Despite the large amount of evidence describing the importance of symptom duration, there are many discrepancies concerning the best threshold for optimal outcomes (see table VII). Nevertheless,

the three weeks limit that was proposed by Zimmerli et al.²⁴⁷ in their original treatment algorithm was adopted by the consensus group and finds support in the current literature although many authors extend the ideal time frame up to four weeks⁴²⁹⁻⁴³⁵.

Table VII Summary of selected findings that increase risk of failure after DAIR.

	Joint(s)	Country of Origin	Success Rate	Duration of Symptoms	Microorganism(s)	Host Status
Byren <i>et al.</i> ⁴³⁰ 2009	52 THA + 51 TKA + 9 other joints	UK	81%	>14 days from presentation to debridement	<i>S. aureus</i> PJI	Presence of co-morbidity
Azzam <i>et al.</i> ⁴²⁷ 2010	53 THA + 53 TKA	USA	44%	Duration of symptoms failed to predict outcome	Staphylococci PJI; frank purulence	ASA score III/IV
Peel <i>et al.</i> ⁴³⁶ 2012	118 THA + 29 TKA	Australia	71%	Only included PJI within 90 days of implantation	Gram negative PJI	Previous septic exchange; hypotension at presentation;
Buller <i>et al.</i> ⁴²⁹ 2012	62 THA + 247 TKA	USA	52%	>21 days duration of symptoms	Staphylococci PJI; VR Enterococci	Previous joint infection; higher ESR at presentation;
Kuiper <i>et al.</i> ⁴³³ 2013	62 THA + 29 TKA	Netherlands	66%	> 7 days before the start of treatment	CoN Staphylococci PJI	Rheumatoid Arthritis; ESR>60mm/h at presentation
Fehring <i>et al.</i> ⁴³² 2013	40 THA + 46 TKA	USA	47%	31-90 days worse than <30 days (joint age)	Type of microorganism failed to predict outcome	Charlson Comorbidity Index failed to predict outcome
Tornero <i>et al.</i> ⁴³⁴ 2015	85 THA + 137 TKA	Spain	77%	Only included PJI with duration of symptoms <21 days	All cultures positive during debridement	Chronic renal failure; liver cirrhosis; revision surgery or cemented prosthesis; CRP >11.5mg/dL;

DAIR Debridement and Irrigation with Implant Retention; **TKA** Total knee arthroplasty; **THA** Total hip arthroplasty; **UK** United Kingdom; **USA** United States of America; **PJI** Prosthetic Joint Infection; **VR** Vancomycin-resistant; **CoN** coagulase negative; **ASA** American Society of Anesthesiologists; **ESR** Erythrocyte sedimentation rate; **CRP** C-reactive protein.

Host Status

Overall health status and medical comorbidities of the patient afflicted by any kind of infection and of course also PJI is of chief importance^{251,252,427,430,433,434}. It plays a major role in the patient's ability to overcome infection but also has a significant impact on the patient's vital prognosis as we have discussed earlier. Other patient-related factors such as elevated BMI, past history of joint infection or revision arthroplasty have been implicated in worse outcomes^{429,430,436,437}.

Interestingly, clinical presentation features such as hypotension at presentation⁴³⁶, higher blood inflammatory markers (ESR or CRP)^{429,433,434} or even intraoperative findings such as frank purulence around the prosthesis⁴²⁷ or positivity of all cultures obtained during surgery^{434,438} may also have inherent prognostic value. Presumably, these represent more severe infection with higher bacterial load and consequent greater risk of treatment failure.

Type of Microorganism

It is only natural to expect that the specific pathogen involved in each PJI case to be of importance on the final outcome.

Indeed, staphylococci infections have frequently been implicated in unfavorable results after DAIR^{427,429,430,439,440}. Methicillin-resistant *S. aureus* (MRSA) specifically, are traditionally considered to be a major risk for failure of debridement with component retention even in acute infections⁴⁴¹⁻⁴⁴³. Bradbury et al.⁴⁴³ have even proposed that if MRSA is encountered, subsequent treatment with exchange arthroplasty should be considered. Joulie et al.⁴⁴⁴ analyzed which variables were associated with treatment failure in 93 PJI caused by *S. aureus*. Although they found that exchange arthroplasty offered a better probability of success than debridement alone, they did not find the healing rate to be influenced by methicillin resistance⁴⁴⁴. In a more recent large retrospective, multicenter, observational study of cases of *S. aureus* PJI that were managed with DAIR, the authors found no difference in failure rates in MRSA compared to methicillin sensitive cases⁴⁴⁵. Nevertheless, both these papers showed DAIR was able to save only about 55-57% of *S. aureus* infections^{444,445}.

Gram negative microorganisms are also a classic concern as they have traditionally been implicated in worse outcomes with implant retention surgery^{436,446}. Nevertheless, it seems that if fundamental principles such as short duration of symptoms and anti-biofilm antibiotic therapy are upheld, success of DAIR procedure can be just as good in this group of patients⁴⁴⁷⁻⁴⁵⁰. The key problem in managing Gram negative PJI is the growing antibiotic resistance pattern, especially in the European Mediterranean region⁴⁵¹. It has been shown that the prognosis after DAIR is dramatically decreased when fluoroquinolone resistance is found⁴⁴⁸. Nevertheless, even more serious problems such as combined resistance to third-generation cephalosporin, fluoroquinolones and aminoglycosides are often encountered greatly reducing antibiotic treatment alternatives⁴⁵¹. Carbapenemase-producing *Enterobacteriaceae* are also on the horizon and have already been implicated in PJI with dire consequences⁴⁵².

Enterococcus sp. infections although uncommon, are also of special concern as they are implicated in poor outcomes with overall success rates of around 50%⁴⁵³⁻⁴⁵⁵. This is particularly true when enterococci infection occurs in a polymicrobial setting or exhibits vancomycin resistance^{429,453}. A major European multicenter study including data from 18 hospitals of six different countries focused exclusively in PJI due to *Enterococcus* sp.⁴⁵⁵. They found an overall success rate of 56% (100/178) among patients with at least one year follow-up after surgery. Implant removal showed a higher remission rate than DAIR but this reached statistical significance only in those patients with more than two years from arthroplasty to infection⁴⁵⁵. A recent American multicenter study confirms these findings as their overall success rate was also low at 52% (45/87)⁴⁵³. In this study, success rate after DAIR was only 39% (13/33) which was significantly lower than results after two-stage exchange. Notwithstanding, it has been shown that a standardized DAIR protocol for treatment of early infections can lead to slightly superior results. Duijf et al.⁴⁵⁶ reported on 44 patients with early Enterococci infections (35 polymicrobial). Debridement was performed at an average of 15 days after the index implantation and patients were treated with teicoplanin, rifampicin, vancomycin or amoxicillin

or a combination of these antibiotics for 3 months postoperatively. The prosthesis could successfully be retained in 29 patients (66%) which is nevertheless worse than with other microorganisms⁴⁵⁶.

Streptococcal infections on the other hand seem to have a more favorable prognosis^{439,457}. Depending on the specific microorganisms involved, polymicrobial infections potentially accumulate many of the limitations aforementioned and it is natural that they are often implicated in limited success rates after DAIR^{458,459}.

Technical Aspects of the Procedure (including Mobile Parts Exchange)

The main goal of surgical debridement is to lower as much as possible the bacterial load within the joint. In that regard debridement, must be thorough and meticulous and all devitalized tissues must be excised. This is a major variable that is not possible to accurately assess when reviewing the results in the literature.

Nevertheless and despite the wide range of suggestions regarding on how to best perform a DAIR procedure, common ground has been reached as to what constitutes a favorable debridement⁸⁵. After preoperative optimization of the patient has been achieved, good visualization and thorough debridement should be performed, multiple culture samples should be obtained before copious irrigation (6 to 9 L) of the joint is made. Even when choosing to perform a DAIR, patients should be advised that the prosthesis may still need to be explanted if indicated (e.g. if it is found to be loose).

In our hands, we always start by excising the previous incision. If the fascial layer is still closed, we collect superficial samples for microbiology before undergoing superficial debridement. After this first step and before opening the fascial layer, we do a joint puncture to collect synovial fluid for testing. After the arthrotomy is completed, all devitalized tissues as well as a thorough synovectomy are performed both for debridement and exposure purposes while collecting representative culture samples as discussed earlier in the diagnosis chapter. All modular parts are removed. Once all suspicious tissue is excised (as well as suture remnants) a copious lavage with chlorhexidine gluconate scrub initially and normal saline subsequently is made. After all members of the surgical team change their scrubs and the extremity has been repped and redraped, a final lavage is made and using fresh instruments new mobile parts are inserted whenever possible. Usually, one deep drain is used (no irrigation-aspiration system) and all tissues are closed in layers much the same as a primary procedure.

Mobile parts exchange seems to be an important factor for success. It allows access to parts of the joint that otherwise be inaccessible plus it allows for removal of slime from the undersurface of such components, leading to better reduction of bacterial load⁸⁵. Polyethylene exchange is widely recommended and there seems to be enough evidence of its beneficial impact on outcome^{85,247,428,429,431,433,435,437,448,460-470}. In a massive retrospective study including over 16,600 PJI, the authors tried to determine risk factors for reinfection after treatment of infected TKA in the United States⁴⁶¹. They found that patients who underwent DAIR as a

first-line treatment had the highest risk of reinfection, compared to one- and two-stage revision surgery or amputation⁴⁶¹. More interestingly, they found that DAIR with liner exchange had significantly reduced risk of reinfection even after adjusting for all other available variables⁴⁶¹. Considering all of the above premises, it is natural to expect that arthroscopic debridement will not suffice. Indeed, even when a posterior portal is routinely used to enable debridement of the posterior compartment this approach is not as effective as an open debridement^{430,471,472}.

One big uncertainty concerns the reoperation decision for a draining wound and/or hematoma formation in the immediate postoperative period. Hematoma formation is a common event after TJA and they are often hard to differentiate between superficial and deep seated. The consequences of missing a possibly infected deep hematoma may be deleterious. Thus, the recent consensus states that if debridement is considered, the deep fascia should always be opened in TKA cases but only in patients with a clear fascial defect or hematoma/fluid deep to the fascia confirmed by aspiration in THA patients⁸⁵. Still, it is acknowledged that little or no guidance to this decision exists in the literature. There is scarce evidence suggesting that even in TKA, superficial complications can be safely managed conservatively⁴⁷³.

Based on our experience, we believe every reoperation in the immediate post-operative period should be regarded as a formal DAIR. Following the criteria for re-intervention previously discussed in the diagnosis section, infection was confirmed in 28 out of 29 patients that underwent early debridement after primary hip or knee arthroplasty. This assertive approach lead to an 86% success rate in eradicating infection without any medical complications related to the additional procedure or negative impact on the functional outcome of these patients when compared to a matched control population of uneventful primary arthroplasties.

Adjuvant(s) of Debridement

Although they should not be considered surrogates for adequate surgical debridement, some adjuvant therapies have been advocated as useful during the procedure. By far the most commonly used is to irrigate the joint with copious amounts of normal saline. Although there is the concern that high-pressure pulsatile lavage systems may cause iatrogenic bacterial seeding into deeper tissue layers⁴⁷⁴, both low-pressure or high-pressure lavage can be used and no significant difference as been shown to exist in clinical practice⁴⁷⁵. Some authors argue that adding some kind of chemical to the irrigation liquid could help in reducing bacterial load.

In that regard detergents, antiseptics or even antibiotics have been proposed but there is very limited evidence of its real efficacy in clinical practice and most findings originate from *in vitro* studies. Simply adding antibiotics to the lavage fluid, as appealing as it may be, has been shown to be no better than normal saline alone^{476,477}. In light of our current knowledge about the pathogenesis of PJI, it is natural to expect that some kind of “anti-biofilm” agent would perform better. In fact, there is evidence that detergents such as castile soap or benzalkonium chloride are more effective in disrupting biofilm from metal surfaces than normal saline alone^{476,478}. More recently, chlorhexidine gluconate scrub (antiseptic and detergent) was shown to be the most effective option at decreasing bacterial colony counts when compared to normal saline, povi-

done iodine scrub or castile soap^{479,480}. An interesting alternative may be acetic acid, commonly known as vinegar. It has been shown *in vitro* to be highly effective against both Gram positive and Gram negative biofilms⁴⁸¹. There is also limited clinical evidence of the efficacy and safety profile of a 20 minutes' soak of 3% acetic acid solution in the debridement of infected TKA⁴⁸².

A different approach is to try and complement surgical debridement by delivering local antibiotics in extremely high concentrations that are able to help eradicate biofilm remnants. Two different ways of achieving this goal have been pursued although there is insufficient evidence to definitively support the use of either until now. Direct continuous intra-articular delivery of antibiotics into the joint was initially promoted by Whiteside as an additional treatment in exchange revision surgery^{483,484}. Fukugawa et al.⁴⁶⁷ were the first to apply this concept after DAIR. They reported on a small series of six infected primary TKA, one revision TKA and five tumor mega-prosthesis. There were four recurrences, all of them occurring in the mega-prosthesis group⁴⁶⁷. There are some potential concerns associated with this practice, including drug reactions or possible re-infection through the catheters used to infuse the antibiotic and the need for an additional surgery (to remove the Hickman catheter necessary for the intra-articular infusion) and the available evidence is not enough to state that intra-articular delivery of antibiotics into the joint is an independent success factor.

Another way to deliver local antibiotics that has been explored, is to use some kind of antibiotic-impregnated conduit (PMMA beads, calcium sulphate pellets, collagen fleece, etc.). Antibiotic impregnated PMMA beads have a long tradition in bone septic surgery and there are some papers exploring its use after DAIR in total joint infections^{431,433,468,485}. They do however force a second surgery for its removal and this has moved the focus on to resorbable material such as collagen fleece or calcium sulphate pellets^{433,468,485}. Although small series have shown encouraging results, there are no randomized, controlled studies to clearly demonstrate that the use of these materials enhances the outcome of a properly performed procedure. Furthermore, resorbable antibiotic carriers are not without problems such as increased cost, local reactions and increased/persistent wound drainage.

Repeated Debridement

There is a lot of controversy and conflicting results surrounding the decision whether or not to perform repeat debridements. The ICM on PJI recommends the surgeon should give consideration to implant removal following the failure of a single DAIR⁸⁵. There is some evidence to support this recommendation. Vilchez et al.⁴⁸⁶ found the need for a second debridement was associated with failure in their series of 53 early post-operative PJI due to *Staphylococcus aureus*. These results were confirmed in a large, retrospective multicenter study of *S. aureus* PJI (n=345) where the need of a second debridement was an independent variable associated with failure⁴⁴⁵.

A potential alternative strategy is to standardize a debridement every 48-72h in order to reduce the bacterial load. There is a lot of controversy and conflicting results surrounding this protocol. Peel et al.⁴⁶⁹ performed multiple debridements, in keeping with established protocols,

and found the optimal number to be two or three as there was significantly higher risk of failure in patients with either a single or at least four surgical debridements. More recently, Moojen et al.⁴⁸⁷ compared two different strategies in the treatment of acute THA infection. In the first group consisting of 33 patients, each one received a single surgical debridement and only additional surgery if infectious symptoms persisted. In the second group (35 cases), patients always received multiple surgical debridements. Although it was not statistically significant, they did find an increased failure rate in the second group (10/35) as compared to the first group (4/33)⁴⁸⁷. Additionally, in the second group new and more resistant microorganisms were found in subsequent debridements suggesting every time the wound is opened there is a risk for further contamination⁴⁸⁷.

Notwithstanding, there are a number of papers that did not find the need for more than one unplanned debridement to be associated with worse outcomes^{430,433,468}. Even so, the maximum number of reasonable attempts seems to be three as more than that is unlikely to improve the odds of successful treatment^{468,469,488}.

ANTIBIOTIC TREATMENT

Following adequate debridement, correct antibiotic therapy is critical in achieving infection eradication. Most of the times, DAIR procedures will take place without previous knowledge of the responsible pathogen and effective empiric antibiotic therapy must be initiated while waiting for intraoperative culture results.

Initial therapy

In the early phase of acute PJI, planktonic bacteria predominate and so treatment usually starts with intravenous (IV) therapy. After the initial debulking of bacterial load caused by surgery and IV antibiotics the switch to regimens with high oral bioavailability and anti-biofilm activity can be made thus avoiding prolonged hospital stay and related complications. Traditionally, 2-6 weeks of intravenous antimicrobial therapy has been recommended³⁵⁹ but there is growing evidence that shortening IV therapy before switching to oral therapy is probably not detrimental⁴⁸⁹.

Analyzing our own findings back in 2010, we recommended initiating therapy with vancomycin in combination with carbapenem immediately after surgery⁹⁶. Given the worldwide concern of emerging carbapenem-resistance we have since adapted our protocol based on a retrospective analysis of 93 consecutive PJI cases treated in our institution between 2009-2014. We found a persistent high prevalence of methicillin-resistant staphylococci but also an increasing trend in the proportion of Gram negative infections that were now present in almost 30% of all PJI isolates. Among Gram negatives, resistance to piperacillin/tazobactam (7%) was the lowest even when compared to meropenem (11%), aminoglycosides (14%) or third-generation cephalosporins (18%). As such our current protocol is to initiate IV vancomycin in combination with piperacillin/tazobactam even if there is a known pathogen before surgery. It has been shown that only about half of the preoperative isolates fully match both microorganism and antimicrobial sensitivity when compared to final intraoperative samples²⁸⁹. As soon as

definitive microbiology results are available, antibiotic therapy is scaled down according to isolated pathogen(s) and antibiotic susceptibility pattern.

Continuation Therapy

The heterogeneous nature of PJI concerning both the microorganisms and the host, results in a huge diversity of clinical scenarios that make it impossible to offer universal solutions. Every case must be considered on an individual basis and multidisciplinary cooperation is critical. There are however some helpful guidelines available for consultation^{247,359}.

Notwithstanding, antibiotic therapy after DAIR procedures holds some peculiarities that must be observed. Unlike revision surgery where the implant is removed, it is natural to expect the presence of biofilm remnants in the prosthesis even after surgical debridement. As such, selected antibiotics should ideally have anti-biofilm activity. In this regard, ever since the pioneer work by Zimmerli⁴⁹⁰ et al., rifampicin has gained an indisputable role in biofilm-related staphylococci infections^{247,428,437,469,470,486,489,491,492}. Interestingly, it has also been suggested that rifampin in combination with other antibiotics may also lead to lower rate of failure in early *Enterococcus* sp. infections treated with DAIR⁴⁵⁵. It is important to stress that, because bacteria rapidly develop antimicrobial resistance, rifampicin should never be administered alone but rather always in combination therapy²⁴⁷. Plus, it should only be used after the bulk of bacterial load has been eliminated and never in persistently draining wounds⁴⁹³. Acherman et al.⁴⁹³ have found that rifampicin therapy with inadequate surgical debridement or less than two weeks of intravenous treatment was independently associated with emergence of rifampicin resistance.

An analogous declaration of importance can be made regarding the use of quinolones in Gram negative infections. There is good evidence to recommend the use of quinolones when facing adequately sensitive Gram negative microorganisms^{447,448,489,494}. In a recent large multicenter study including 242 Gram negative PJI, ciprofloxacin therapy exhibited an independent protective effect⁴⁴⁸. In patients with ciprofloxacin-susceptible GN-PJI treated with ciprofloxacin, success was 79% (98/124). In ciprofloxacin-resistant cases, the efficacy of DAIR management was at 41% (14/34). In those with susceptible isolates not treated with ciprofloxacin success rate was similar at 40% (6/15) suggesting lack of ciprofloxacin use and not resistance pattern is responsible for the negative impact.

The effectiveness of ciprofloxacin in these patients is probably attributable to its acceptable oral bioavailability, optimal diffusion into synovial fluid and bone, and activity against biofilm⁴⁹⁶. Although choosing the correct antibiotic regimen may prove to be a hassle for the orthopedic surgeon, this is a critical part of therapy.

Table VIII Summary of selected recent findings regarding antibiotic regimen after DAIR .

	Joint(s)	Country of Origin	Overall Success Rate	Major finding(s)
Aboltins <i>et al.</i> ⁴⁴⁷ 2011	15 THA + 2 TKA	Australia	94% at the 2-years follow-up	- Exclusively GN PJI - oral ciprofloxacin in 14 cases and amoxicillin/clavulanic acid in three cases. - Median duration of oral antibiotic treatment was 12 months.
Vilchez <i>et al.</i> ⁴⁸⁶ 2011	18 THA + 35 TKA	Spain	75% minimum two-year follow-up	- Exclusively <i>S. aureus</i> PJI - rifampin combination therapy in 91% of the patients. Only 4 MRSA. - Duration of antibiotic therapy >90days did not improve outcome.
Puhto <i>et al.</i> ⁴⁷⁰ 2012	55 THA + 77 TKA	Finland	65% at the 2-years follow-up	- Rifampin combination(s) preferred for staphylococci and quinolones preferred for GN. - Reducing duration of treatment to 3 months (vs. 6) for TKA and 2 months (vs. 3) for THA did not influence outcome.
Peel <i>et al.</i> ⁴⁶⁹ 2013	28 THA + 15 TKA	Australia	77% at the 2-years follow-up	- Exclusively MR staphylococci PJI – rifampin combination therapy in 93% of the patients. - MRSA infections and <90 days antibiotic therapy were more likely to fail.
Rodríguez-Pardo <i>et al.</i> ⁴⁴⁸ 2014	115 THA + 57 TKA + 2 other joints	Spain	68% median 25-months follow-up	- Exclusively GN PJI – 79% (98/124) success rate in ciprofloxacin-susceptible treated with it. 41% (14/34) success rate in ciprofloxacin-resistant and 40% (6/15) success rate in ciprofloxacin-susceptible not treated with it. 79% (33/42) success rate in <i>Pseudomonas</i> PJI increased to 88% (29/33) when treated with ciprofloxacin. 53% (8/15) success rate in ESBL-producing <i>Enterobacteriaceae</i> PJI. - Median antibiotic treatment duration was 70 days.
Holmberg <i>et al.</i> ⁴²⁸ 2015	145 TKA	Sweden	75% minimum one-year follow-up	- Risk of failure was 4 times higher if no rifampin used in staphylococci infections (59% vs 19%). - Failure rate was higher in polymicrobial (9/30) and Gram negative cases (2/5) - albeit not statistically significant. - Large variation in duration of antibiotic treatment.
Lora-Tamayo <i>et al.</i> ⁴⁹⁵ 2016	29 THA + 24 TKA	Spain	93% minimum one-year follow-up	- Randomized and open trial. Exclusively staphylococci acute PJI receiving rifampin-levofloxacin combination. - Cure rate in the patients who completed antibiotic treatment was 22/24 (92%) in the short (8 weeks) protocol vs. 19/20 (95%) in the long (3 and 6 months for THA and TKA respectively).
Grossi <i>et al.</i> ⁴⁹⁴ 2016	35 THA + 18 TKA + 23 Hemi hips	France	79% minimum one-year follow-up	- Exclusively GN PJI: 35 DAIR procedures -8 (22%) failed. - Failure rate was similar whether fluoroquinolones or three month IV β-lactams were used. - Median antibiotic treatment duration was 90 days.

DAIR Debridement and Irrigation with Implant Retention; **TKA** Total knee arthroplasty; **THA** Total hip arthroplasty; **MRSA** methicillin-resistant *S. aureus*; **GN** Gram negative.

A very recent paper by Tornero *et al.*⁴⁸⁹ confirms that correct antibiotic selection is the most important predictor of late failure after DAIR. In their study of 143 patients, antibiotic treatment was categorized as optimal if it included a combination of rifampicin plus rifampicin-independent antibiotic (levofloxacin, ciprofloxacin or amoxicillin) or monotherapy without rifampicin for Gram positives and when it included a fluoroquinolone for Gram negatives. It was found to be suboptimal if it included a combination of rifampicin plus rifampicin-dependent antibiotic (linezolid, co-trimoxazole or clindamycin) for Gram positives or a regimen without fluoroquinolone for Gram negatives. Receiving suboptimal antibiotic treatment proved to be the only independent predictor of failure in this study⁴⁸⁹.

The duration of antibiotic treatment after DAIR is also matter of intense controversy. Traditionally, guidelines have recommended 3 months for infections in total hip and 6 months for total knee prosthesis³⁵⁹. There are however several papers questioning this axiom.

Byren et al.⁴³⁰ have found that the risk of relapse increases after stopping antibiotics (6 weeks mean duration of intravenous and 1.5 years mean duration of oral antibiotic treatment) but increased length of treatment (>180 days) did not affect the outcome suggesting that most patients cured of PJI by DAIR are either cured early on or not and prolonging antibiotic therapy does not prevent failures but merely postpones them. Tornero et al.⁴⁸⁹ also found no relationship between failure and duration of treatment after a median duration of intravenous and oral antibiotic treatment of 8 days and 69 days respectively. A similar finding was reported by Lora-Tamayo⁴⁹⁵ et al. in a randomized clinical trial including over 60 patients with acute staphylococcal PJI managed with DAIR. Patients were randomized to receive 8 weeks of treatment (short schedule) versus a long schedule (3 months or 6 months for hip or knee prostheses, respectively) of levofloxacin plus rifampicin. They suggest that the short schedule could be just as effective as a longer standard treatment for THA but some doubt persisted over its value for TKA⁴⁹⁵. Despite some conflicting evidence, extending therapy for 3 months seems to be sufficient for the majority of cases^{469,470,486,489,494}. Although many physicians rely on C-reactive protein serial measurements to guide antibiotic discontinuation, this practice has been found to be unreliable and not predictive of failure and should therefore be discouraged^{495,497,498}.

CONTRA-INDICATIONS

Only a loose prosthesis and the inability to close the wound are considered absolute contra-indications for implant retention⁸⁵. A loose prosthesis is obviously an absolute indication for revision surgery and is therefore not amendable for DAIR. Likewise, an open wound allows for contamination and colonization of the prosthesis and will result in a chronic infection. Although it has been suggested that the presence of a sinus tract is also an absolute contra-indication⁸⁵ a detailed analysis of the literature shows apparently successful outcomes are possible after DAIR even with a sinus tract that is inherently associated with chronic infections⁴²⁷. Of course, this should be viewed as extreme cases with very low probability of success⁴⁹⁹. Additionally, all of the other risk factors for failure that were previously discussed such as PJI due to highly virulent organisms or patients with extensive comorbidities may be regarded as relative contra-indications.

In some extreme clinical conditions, simple debridement and antibiotic therapy may be indicated as a means to temporarily alleviate symptoms caused by planktonic bacteria leaving the biofilm during acute exacerbations of a chronically infected implant. It will not be able to eradicate biofilm and ensuing chronic suppressive antibiotic therapy is required but sometimes this may be the lesser of two evils in situations where the patient is not fit to undergo revision surgery.

In conclusion, some variables such as adequate patient selection, rigorous surgical procedure and correct “anti-biofilm” antibiotic therapy seem to be essential cornerstones for success and can to some degree be influenced by the treating physician. Others, such as the host medical comorbidities or past history, drug allergies or adverse reactions precluding optimal antibiotic regimens escape our control. Although it is of great consequence, specific information

about the infecting microorganism(s) and its antibiotic susceptibility is frequently not fully known when deciding whether or not to perform DAIR. Adopting specific surgical strategies to treat “difficult” microorganisms has already been proposed regarding revision surgery. Still, preoperative recommendations for selecting DAIR as treatment are yet fairly pathogen independent.

It is our belief that if appropriate minimal conditions are met (short duration of symptoms in a stable and well-fixed prosthesis with sound soft tissues and no sinus tract), debridement and irrigation with implant retention should be regarded as first-line treatment choice in the vast majority of cases. The results of this approach in our institution have been encouraging.

Revision Surgery

Exchange revision surgery is widely considered to be the gold standard treatment for PJI. It is viewed as the only meaningful alternative in chronic infections and even in some cases of acute infections where DAIR procedures are not recommended.

Presently, removing the infected implant is the only reliable way to eradicate a long-lasting mature biofilm. Still, biofilm can reside in other sites other than the implant itself. Inert foreign material such as bone cement and screws for instances, as well as dead bone (i.e. sequestrers) can also constitute a nidus for biofilm formation. The goal of surgery in this setting is to completely remove all the possibly contaminated sites thus aiming to prevent infection recurrence after the new prosthesis is put in place.

Accordingly, regardless of whether a one- or two-stage approach is encouraged, the initial treatment for the overwhelming majority of cases should be complete implant removal and exhaustive debridement^{12,85,247,500-527}. Despite this broad worldwide consensus, it has been recently suggested that partial revisions may have a role especially in treating complex THA with ingrown femoral stems or complex acetabular components that are well fixed in patients with poor bone stock in whom extracting the implant would create significant bone loss and compromise future fixation^{528,529}. Nevertheless, until or unless larger groups of patients with longer term data have been studied, this option must be considered as exceptional in extremely selected cases that do not exceed 6-7%, even in the proposing authors' experience^{528,529}.

ONE OR TWO-STAGE

In the absence of randomized controlled trials addressing this important issue, concrete indications or contra-indications for one- or two-stage revision surgery cannot be firmly established. Currently, two-stage exchange is still the most popular strategy for the surgical management of PJI particularly in North America⁴⁶¹ but also in Europe and elsewhere⁵³⁰. However, as more centers are becoming more experienced in dealing with infected arthroplasties, the one stage exchange is gaining momentum. A survey performed in the 2015 European Bone and Joint Infection Society Meeting (EBJIS) showed that single stage revision is being performed regularly according to specific selection criteria in around 40% of participants' institutions⁵³⁰.

Despite the fact that two-stage exchange is frequently considered to be the gold standard, there are no conclusive evidences of its superiority over the one-stage approach to date. A number of review and meta-analysis of the published data have been performed but they offer conflicting conclusions⁵³¹⁻⁵³⁷. Some, concerning the knee specifically clearly favor the two-stage approach stating that it offers higher rate of infection eradication^{531,532} while others reach comparable re-infection rates at around 8-10% for both hips and knees^{533,536,537}. Focusing not only at the infection eradication endpoint but also on the functional outcome⁵³⁵ or the overall risk-benefit balance⁵³⁴ some have favored the single stage exchange in infected total hips.

However, these reviews are based on publications that share certain limitations such as small numbers of patients, limited follow-up and strict exclusion criteria for the one-stage approach such as unknown or difficult to treat microorganisms, compromised soft tissues (e.g. sinus tract), significant bone loss or even relevant comorbidities. Accordingly, interpretation of the literature becomes complex and direct comparison of success rates with the two-stage approach cannot be easily (or fairly) drawn as the latter does not exclude these difficult to treat cases.

Given that a lot has changed in recent years regarding surgical and medical practice and older papers may not accurately reflect contemporary standards, tables IX and X summarize one-stage exchange latest and relevant findings. We focused on each paper's selection criteria as it greatly influences outcome. Tables XI and XII summarize recent pertinent findings regarding two-stage exchange.

Table IX Summary of selected recent findings regarding one-stage exchange for chronically infected THA.

Study	Number of cases	Selection criteria	Success rate	Follow-up Mean/ Minimum	Local Antibiotics delivery	Observations
Engesaeter <i>et al.</i> ⁵⁰⁰ 2011	86*	Retrospective registry study with indications for two-stage, one-stage or partial exchange at surgeon discretion	91%	NS /2 years	Not specified	two-stage revision success rate was 95% (155/164) in the same study period; failures not undergoing revision surgery are not reported
De Man <i>et al.</i> ⁵⁰¹ 2011	22	1) no compromised soft-tissue; 2) no difficult to treat microorganism	86%	5/2 years	Uncemented implants	two-stage revision success rate was 92% (46/50) in the same study period
Klouche <i>et al.</i> ⁵⁰² 2012	38	1) known germ before surgery; 2) minor bone loss preoperatively and after components removal	100%	NS /2 years	No ALBC even when cemented implants were used	two-stage revision success rate was 91% (42/46) in the same study period (not statistically significant)
Bori <i>et al.</i> ⁵³⁸ 2014	24	1) no fistula 2) no major soft tissue defect 3) no bone defect affecting implant stability	96%	3 years/ 2 years	Cementless stems. 7 out of 9 cemented cups with antibiotics	the only one failure was successfully treated with DAIR
Zeller <i>et al.</i> ⁵⁰³ 2014	157	1) identified organism with available culture and sensitivities (fungus and difficult to treat organisms excluded); 2) no bone grafting required; 3) <2 prior PJI treatment	94%	3.5/2 years	No ALBC even when cemented implants were used	10 patients required further revision (only one confirmed infection), there were 3 other septic episodes managed without revision
Wolf <i>et al.</i> ⁵⁰⁴ 2014	37	Retrospective study with no specific indications (Early postoperative and hematogenous infections as well as lower local extremity grade were significantly more prevalent in one-stage)	57%	NS /2 years	Not specified	two-stage revision success rate was 94% (49/52) in the same study period; if only chronic infections are considered (25% success rate of one-stage)
Jenny <i>et al.</i> ⁵⁰⁵ 2014	65	Consecutive patients including failures of previous infection treatments and cases requiring bone graft	80%	3/3 years	Gentamicin loaded bone cement	2 early deaths and 11 cases of re-infection, no analysis of failure risk factors was performed

THA total hip arthroplasty; NS not specified; ALBC antibiotic-loaded bone cement; * considering only the more recent 2002-2009 period.

Despite slight variability between different reports, there is nonetheless some agreement on some conditions that might be considered relative contra-indications to one-stage surgery

or in other words, specific circumstances where a two-stage exchange may be preferred⁸⁵. They include: 1) patients with systemic manifestations of infection (i.e. sepsis); 2) a scenario where infection appears obvious but no organism has been identified; 3) preoperative cultures identifying difficult to treat and antibiotic-resistant organisms; 4) presence of a sinus tract; and 5) inadequate and non-viable soft tissue coverage⁸⁵. Still, other criteria such as failure of two or more previous one-stage attempts and infection involving the neurovascular bundles are also acknowledged⁵⁰⁹.

Table X Summary of selected recent findings regarding one-stage exchange for chronically infected TKA.

Study	Number of cases	Selection criteria	Success rate	Follow-up Mean/ Minimum	Local Antibiotics delivery	Observations
Singer <i>et al.</i> ⁵⁰⁷ 2012	57	1) known microorganism with an antibiotic susceptibility profile (MRSA and MRSE excluded); 2) wounds that could be closed during surgery	95%	NS /2 years	ALBC according to specific susceptibility	9 patients with contraindications underwent two-stage surgery
Jenny <i>et al.</i> ⁵¹¹ 2013	47	All patients except: 1) fungal infections; 2) repeat failures of previous infection treatments	87%	NS /3 years	Gentamicin loaded bone cement	-
Tibrewal <i>et al.</i> ⁵¹² 2014	50	1) identified organism with available culture and sensitivities; 2) intact soft-tissue cover of the knee	92%	10/ 2 years	ALBC according to specific susceptibility	10 patients required further revision (one infected); three septic episodes managed without revision
Haddad <i>et al.</i> ⁵¹³ 2015	28	1) insignificant bone loss; 2) soft tissue defect allowing for primary closure; 3) non-immunosuppressed (includes diabetes, RA, etc.); 4) isolation of a single low virulence microorganism preoperatively	100%	NS /3 years	ALBC according to specific susceptibility	two-stage revision if any contra-indication with 93% (69/74) success rate (difference was not statistically significant)
Jenny <i>et al.</i> ⁵⁰⁶ 2016	114	1) patient's good general condition; 2) non-acute infection; 3) responsible pathogen sensitive to standard antibiotic treatment; 4) good bone stock without the need for bone grafting *	78%	3/2 years	Gentamicin loaded bone cement in 84 cases	* in one center (54 cases) one-stage was performed routinely and did not follow these criteria; there was no significant difference between both strategies
Zahar <i>et al.</i> ⁵¹⁰ 2016	59	1) PJI with known causative organism	90%	10/9 years	ALBC according to specific susceptibility	11 procedures other than one-stage were performed during the same period

TKA total knee arthroplasty; ALBC antibiotic-loaded bone cement.

When these selection criteria are applied, infection eradication rates after one-stage exchange seem to be comparable to traditional two-stage. However, it is noteworthy that routinely performing one-stage without clear selection criteria, seems to be associated with substandard results⁵⁰⁴⁻⁵⁰⁶.

In addition to comparable infection eradication rates, better functional outcomes after completion of treatment is also often invoked as an advantage of the one-stage approach⁵⁰⁸. Although some studies do find this alleged advantage^{507,513}, a number of other papers dispute this conclusion^{501,505,511}. Radical debridement required in one-stage revision surgery often

leads to extensive soft tissues including ligamentous debridement and subsequent potential instability or flexion and extension gap mismatch in the knee. As such, there is often the need for constrained implants such as rotating hinges in the knee that are associated with higher overall failure rates^{539,540}.

Table XI Summary of selected recent findings regarding two-stage exchange for chronically infected THA.

Study	Number of cases	Success rate after reimplantation	Follow-up Mean/Minimum	Observations
Romano <i>et al.</i> ⁵¹⁴ 2012	183	94% (173/183)	5/2 years	three patients required spacer exchange before 2 nd stage
Neumann <i>et al.</i> ⁵¹⁵ 2012	44	98% (41/42)	6/3 years	two patients died before 2 nd stage (unrelated deaths)
Macheras <i>et al.</i> ⁵¹⁶ 2012	35	94% (33/35)	12/7 years	one patient had reimplantation postponed at 2 nd stage due to persistent infection
Berend <i>et al.</i> ¹² 2013	202	84% (157/186)	4 years/NS	14 patients died before 2 nd stage (no information regarding possibly related causes of death)
Johnson <i>et al.</i> ⁵¹⁷ 2013	66	91% (60/66)	4/2 years	positive intra-operative frozen sections at 2 nd stage precluded reimplantation
Schwarzkopf <i>et al.</i> ⁵¹⁸ 2014	60	94% (45/48)	3 years/6 months	five patients lost to follow-up before 2 nd stage; six resection arthroplasties and one persistent spacer
Gomez <i>et al.</i> ⁵²⁰ 2015	178	82% (89/137)	5/1 years	five permanent resection arthroplasties; 34 retained spacers
Lange <i>et al.</i> ⁵²¹ 2016	130	85% (70/82)	5 years/NS	35 permanent resection arthroplasties; 13 other interventions

In fact, some of the longer-term follow-up studies after one-stage revision knee PJI show significant rates of aseptic loosening and this must also be considered^{510,512}. In addition, as we have already discussed, most one-stage series include selected patients with less extensive bone and soft tissue damage, less previous revision surgeries, etc. that are important predictors of final functional status.

Our personal experience is that a well performed two-stage revision surgery with the use of mobile spacers leads to good functional results. Although we were not able to directly compare the functional outcome of two-stage versus one-stage revision surgery, we did compare infected TKA patients treated with a two-stage protocol with single-stage revision cases for aseptic reasons and a control group of primary complex TKA. We applied a validated patient reported outcome measure, the Knee injury and Osteoarthritis Outcome Score (KOOS) and a satisfaction scale to a total of 11 two-stage revision, five aseptic revision and four primary complex TKA cases all of them with the use of the same semi-constrained implant and a 12 months' minimum follow-up. Infected patients presented at least similar (if not sometimes superior) outcomes in every scale when compared to either control group.

Table XII Summary of selected recent findings regarding two-stage exchange for chronically infected TKA.

Study	Number of cases	Success rate after reimplantation	Follow-up Mean/Minimum	Observations
Mahmud <i>et al.</i> ⁵²² 2012	253	94% (237/253)	4/1 years	7% additional failure rate for aseptic reasons after reimplantation
Kubista <i>et al.</i> ⁵²³ 2012	368	84% (310/368)	8 years/NS	median time to reinfection was 3.6 years
Schwarzkopf <i>et al.</i> ⁵¹⁹ 2013	84	91% (48/53)	2/1 years	six patients died and three patients lost to follow-up before 2 nd stage; three amputations; 19 arthrodesis
Castelli <i>et al.</i> ⁵²⁴ 2014	50	92% (46/50)	7/2 years	-
Sabry <i>et al.</i> ⁵²⁶ 2014	314	72% (209/291)	3 years /2 months	Numerous risk factors for failure are identified
Gooding <i>et al.</i> ⁵²⁷ 2015	115	88% (101/115)	NS /5 years	10 patients required revision surgery for aseptic reasons
Gomez <i>et al.</i> ⁵²⁰ 2015	326	81% (179/280)	5/1 years	six amputations; four arthrodesis; 38 retained spacers
Sakellariou <i>et al.</i> ⁵²⁵ 2015	110	86% (95/110)	NS /2 years	Numerous risk factors for failure are identified

In conclusion, one-stage revision surgery is demonstrably successful and may offer obvious advantages in appropriately selected cases. We do however believe that two-stage revision surgery is perhaps a technique with greater tolerance to error and is therefore easier to adopt in less experienced centers. A massive retrospective Medicare population-based American study focusing on 3069 infected TKA treated with one-stage exchange and 5364 treated with two-stage revision surgery, found that one-stage revision patients had 34% greater adjusted risk of reinfection than two-stage patients⁴⁶¹. Our experience in dealing with prosthetic joint infections requiring revision surgery has been with a two-stage approach. The results of such a protocol have been encouraging.

SPACERS

When a two-stage strategy is preferred, most surgeons agree on the use of antibiotic loaded cement spacers⁸⁵. Spacers accommodate two main goals that are perceived as major advantages. They allow for local antibiotic delivery that is believed to contribute to infection eradication. Garvin and Hanssen in a classic literature review found the success rate for two-stage procedures was lower without the use of antibiotic-loaded spacer, 82% (130/158) compared to 91% (385/423) with them⁵⁴¹. In addition, they help maintain some joint stability and function between stages thus offering some comfort to the patient and preventing soft-tissue contractures. Ultimately, they contribute to an easier and faster second stage reimplantation surgery^{85,542}.

Mobile or Static?

Spacers can be divided into two main groups: non-articulating or static and articulating or mobile. The choice between both types of spacer is not influenced by their influence on the success of infection control but rather on the risk-benefit analysis of added mobility.

A massive literature review performed by spacers' study group of the recent ICM on PJI⁸⁵ found no difference with regards to rates of infection eradication comparing non-articulating or articulating spacers or even different types of articulating spacers. Although it has been previously reported that articulating knee spacers might provide better infection eradication rate than revision with static spacers⁵³², this finding has not been confirmed by others^{543,544}. A similar conclusion was reached for the hip, suggesting static and articulating spacers can be equally considered in the treatment of PJI.

The real difference between them lies in the functional outcome, both between stages and following second-stage reimplantation. Articulating or mobile spacers offer improved patient comfort and better functional outcome after initial removal of the implant and before definitive surgery^{85,514,527,545}. In our experience, pain relief after removal of the infected prosthesis is so notorious that some patients do so well and are so happy with their new level of function that they are willing to adopt the spacer as a definitive solution. While this is uncommon in knees, it is more frequent in low-demand elderly hip patients and even more frequent in shoulders^{520,521,546}. The majority of studies comparing outcomes after second-stage exchange surgery also favor articulating compared to static spacers suggesting there is a relevant yet small trend to better functional and range-of-motion outcomes especially in TKA^{85,543,547}.

Prefabricated or Hand-made?

Regarding its manufacture, spacers may be either prefabricated or surgeon made. Surgeon made spacers have the extra advantage of allowing for easy manipulation of antibiotic(s) that are added to the cement and may be manufactured purely by hand or with the use of molds^{518,545}. There is some scarce evidence suggesting the addition of high dosages increases the amount of antibiotics actually released within the joint as compared to prefabricated spacers⁵⁴⁸. Nevertheless, there are no perceptible differences in the rate of infection eradication or even functional outcomes between them⁸⁵. Still, other issues such as cost and availability, ease of use and specific antibiotic delivery should be considered. Commercially available spacers are naturally more expensive and accessibility may also limit its use in unanticipated settings. Traditionally they have been gentamicin loaded although more recently, spacers containing both vancomycin and gentamicin have become widely available and some manufacturers even produce custom-made spacers with a variety of different antibiotics.

The type and the dose of antibiotic(s) needs to be individualized for each case based on the pathogen antibiotic susceptibility profile as well as the patient's renal function and allergy profile. Choosing the correct drug(s) is of paramount importance. They must possess certain characteristics in order to be effective after cement mixing. Thermal stability is one of them, as the polymerization of PMMA is an exothermic reaction and may otherwise hamper its efficacy¹⁷⁷.

Other important characteristic is water-solubility, to permit elution into surrounding tissues, while allowing a gradual release over time for a sustained bactericidal effect¹⁷⁷. A last but relevant practical issue is that it must be available in powder form since adding a liquid antibiotic to the cement mixture significantly decreases its mechanical strength¹⁷⁷.

Table XIII displays a list of antimicrobials frequently used in bone and joint infections that have been shown effective after being added into bone cement^{85,177}.

Table XIII Antimicrobials frequently used in bone and joint infections that may be added into bone cement.

Amphotericin B	Ceftaroline	Levofloxacin
Amikacin	Ciprofloxacin	Linezolid
Ampicillin	Clindamycin	Meropenem
Aztreonam	Colistin	Piperacillin/Tazobactam
Cefazolin	Daptomycin	Teicoplanin
Cefotaxime	Erythromycin	Tobramycin
Cefuroxime	Fluconazol	Vancomycin
Ceftazidime	Gentamicin	Voriconazole

Another issue is the ideal dosage of antibiotic loading. Although there is insufficient data to make a definitive recommendation, most authors and expert opinions agree it should range somewhere between 10 to 15% of total weight (4-6g per 40g of cement)¹⁷⁷. This much has been shown to be necessary in order to keep antibiotic concentrations in the spacer membrane above minimum inhibitory concentration for several isolates after six weeks⁵⁴⁹. Increasing the dosage not only reduces the mechanical strength of the spacer but also increases the risk of adverse reactions when using common nephrotoxic drugs such as vancomycin and aminoglycosides. Although the overall safety profile of high-dose antibiotic spacers has been well documented, there are some reported cases of spacer induced renal failure^{85,177,550}. The final amount of antibiotic(s) eluted from the spacer is influenced by numerous factors other than dose and type of antibiotics included. The shape and surface area of the spacer as well as the porosity and type of cement used are also relevant⁵⁵⁰. The cement and antibiotic mixing technique is also of great influence. Traditionally, we have been combining both powders (antibiotic and PMMA) first and then add the liquid monomer. We then proceed with hand mixing in a bowl without vacuum to increase porosity of the final cement. Increased porosity, while reducing the mechanical resistance, has been shown to increase antibiotic elution⁵⁵⁰. Recently, it has been suggested that the best way to optimize antibiotic elution may be to gradually add the powder antibiotic after first mixing the PMMA powder with standard amounts of liquid monomer^{551,552}. Another strategy to increase antibiotic elution might be to add some kind inert additives such as sucrose, xylitol or glycine⁸⁵.

Complications and Contra-indications

Presently, there are no clear indications for the use of any specific type of spacer other than technical considerations and feasibility. While mobile spacers seem to be beneficial regarding functional results, their use is not without increased risks. In the aforementioned massive literature review, overall complication rate was found to be 11.6% using articulating and 6.9% using non-articulating spacers⁸⁵.

Some precautions are therefore essential in reducing the risk of complications. Dislocation and fracture are the most frequent mechanical complications when using an articulated hip spacer^{514,520}. While some risk factors such as history of hip dislocation, multiple prior surgeries, abductor muscle insufficiency and patient compliance to the required partial weight bearing protocol are not under direct control by the surgeon, others such as spacer's geometry or resistance, size mismatch between spacer's head and acetabulum, technique of femoral fixation and addressing acetabular and/or femoral bone defects can and should be addressed during spacer choice and implantation. In the past few years, we have been using spacers reinforced with a central metallic core in order to prevent fractures (Fig. 5A)⁵⁵³. We also acknowledge a few technical tips and tricks to prevent dislocation such as: 1) choosing a slightly larger head spacer and if necessary, ream the acetabulum to enlarge it and find adequate head coverage; 2) improve femoral fixation of the spacer stem by avoiding a simple press fit method and using the glove cementing technique; 3) address proximal femur bone defects by using a long-stemmed spacer and; 4) address bone loss in the superior-lateral and posterior-superior part of the socket by creating a temporary cement "tectoplasty" with additional antibiotic-loaded cement⁵⁵³.

When a mobile spacer is chosen for the knee the most frequent complications are tibiofemoral and patellofemoral instability but also wound problems and fractures^{520,550}.

To minimize pain and mechanical complications both the femoral and tibial parts must be cemented in with additional antibiotic-loaded cement^{554,555}. While the spacer must adhere strongly to the bone surface, excessive penetration of the cement mantle must be avoided, because it might further damage residual bone stock at the time of removal.

Despite this theoretical concern, the use of articulated spacers and a crude cementing technique has been shown to reduce the amount of bone loss between stages^{524,547,556}. Tibial components should be implanted with some type of cement keel for improved stability and attention must be paid to the final implant slope^{554,555}. In our experience limited femoral component sizes are an additional source of potential problems when using preformed spacers, especially due to patellofemoral overstuffing. In the past couple of years, we have moved from using articulating knee spacers made using silicone molds to purely hand-made mobile spacers in order to overcome this limitation and reduce costs (Fig. 5B).

Mobile spacers may simply be contra-indicated if a mechanically sound construct cannot be achieved. Major acetabular bone loss may lead to hip spacer dislocation or even pelvic protrusion and in such difficult cases not using spacers at all should be considered as it has

been shown that favorable results are also possible without them^{516,542}. In the knee, major bone loss and/or lack of soft tissue and ligamentous integrity should also advise against the use of articulating spacers⁵⁵⁵. It has been shown that static spacers (Fig. 5C), while not exempt of potential complications, are also able to offer favorable outcomes⁵⁵⁷⁻⁵⁵⁹. A recent study on 133 static knee spacers revealed 14 (10.5%) mechanical complications, most commonly tibia but also femur fractures⁵⁵⁸. Second stage surgery is technically more demanding with their use and a high rate of partial avulsions of the patellar tendon has also been described⁵⁵⁹.

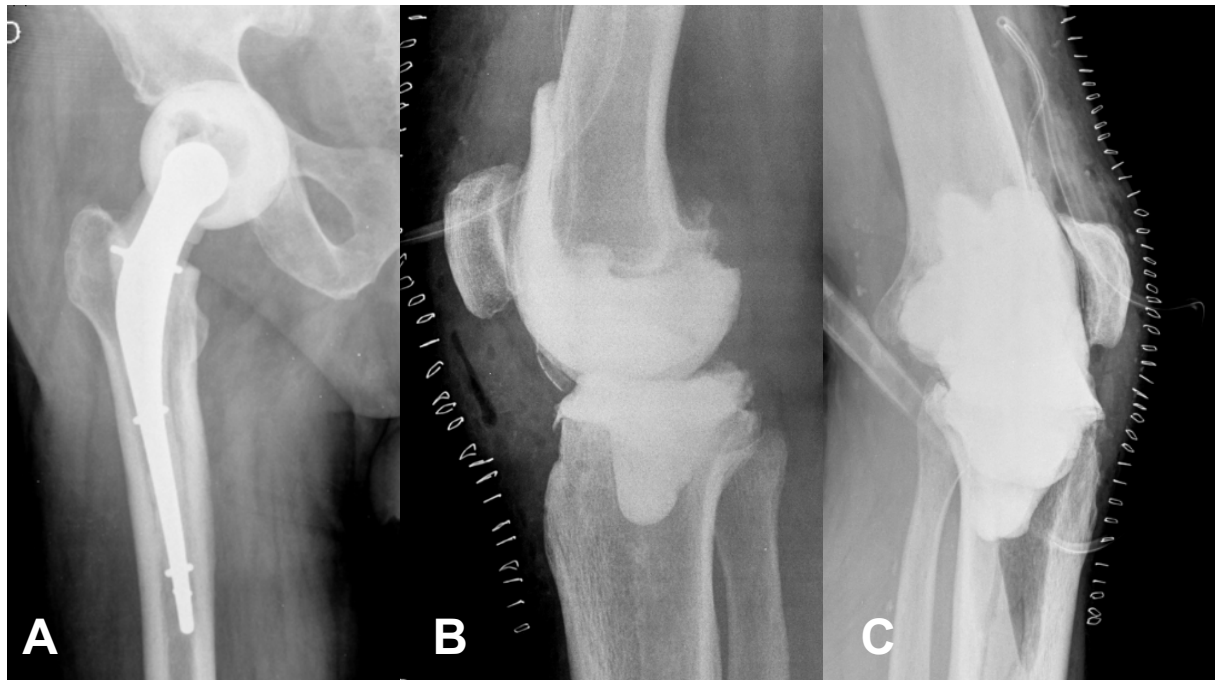


Fig. 5 Different types of antibiotic-loaded cement spacers. A: articulating hip spacer; B: articulating knee spacer; C: nonarticulating knee spacer.

ANTIBIOTIC THERAPY

Antibiotics are usually administered systemically but they can also be delivered locally. Systemic antibiotic therapy is naturally the cornerstone of adjuvant medical treatment. Although a detailed discussion of all the available and appropriate antibiotic(s) is perhaps beyond the scope of this thesis, it is important to once again stress the importance of interdisciplinary cooperation for the appropriate management of PJI. Traditionally, therapy is initially started with IV antibiotics in order to obtain minimum inhibitory concentrations in the shortest time possible and allow for empirical broad-spectrum therapy. When definitive culture results are available the switch to pathogen-specific, highly bioavailable oral therapy can then be safely made^{85,359}. In contrast to the implant retention scenario, there is no evidence to support a chief role for the use of rifampicin in the setting of prosthesis removal⁸⁵.

Ideal duration of systemic antibiotic therapy is also a matter of open debate. Most literature recommends a six weeks' duration after the removal of the infected implant with no clear

evidence to support it against alternative intervals^{12,85,247,359,511-527}. Regarding one-stage revision surgery, 2-6 weeks IV therapy is recommended^{185,359} followed by longer term oral therapy. Most papers report on total duration of antibiotic therapy that extends from six weeks^{507,513} to three months^{503,506,511,512}. In this setting, an analogy can perhaps be made to specific antibiotic therapy after DAIR. Rifampicin associations when dealing with staphylococci and fluoroquinolones when facing Gram negative bacteria are recommended^{247,359}. There is also a lack of solid evidence concerning the usefulness and merits of using serial inflammatory parameters to determine the length of antibiotic therapy^{495,497,498}.

Local antibiotic therapy is a major issue in revision surgery of infected joints as it allows for very high local concentrations that would be impossible to obtain without significant toxicity using systemic antibiotic therapy only. In the two-stage approach, antibiotics are delivered *via* the spacer as previously discussed. The worth of this tactic is further strengthened by the findings of Stockley et al.⁵⁶⁰ that were able to show infection eradication in 100 out of 114 patients (88% success rate) with the use of high-dose antibiotic loaded spacers and no additional oral or intravenous systemic antibiotics. Regarding the one-stage exchange, the possibility of adding effective antibiotics into bone cement seems to be the cornerstone for success of this approach^{507-509,512,513}. Although some have presented favorable results with the use of uncemented implants^{501,503}, it seems that results are not as consistent when antibiotic-loaded according to specific susceptibility bone cement is not routinely used⁵⁰⁴⁻⁵⁰⁶. In trying to overcome this limitation other methods of local antibiotic delivery have been proposed. In 2008, Winkler et al.⁵⁶¹ presented favorable results, on their cohort of infected THA treated with one-stage uncemented revision using allograft bone impregnated with high levels of antibiotics as a carrier. At their last evaluation⁵⁶², 91 hips had been treated using this methodology with a total of eight recurrences (88% success rate). Another method that has been proposed by Whiteside et al.⁴⁸³ is direct intraarticular infusion of antibiotics via Hickman catheter. In their original series of 18 MRSA infected TKA, they had one single recurrent infection (94% success rate). The same authors showed similar favorable results of the same protocol in a different and difficult population of 18 patients with reinfection after revision TKA (89% success rate)⁴⁸⁴. Recently, an independent group showed similar infection eradication infection rates in a study comprising 53 PJI treated with a single stage exchange and direct intra-articular infusion of antibiotics⁵⁶³. Notwithstanding, evidence available regarding alternative antibiotic delivery methods is not enough to acknowledge them as independent factors of improved outcome plus there are potential concerns associated with this practice as we have discussed earlier.

THE SECOND STAGE

Safely reimplanting a new prosthesis after infection eradication is the main goal of the two-stage approach. Failure to perform the second stage may occur for a variety of reasons such as medical comorbidity or mortality, patients lost to follow-up or even patient's satisfaction with their current level of function in the setting of a retained spacer as we have previously discussed^{520,521,546}. Other frequently underreported problems are the complications that arise between stages that are often responsible for not completing the intended treatment. Additional surgeries such as new debridements and spacer exchange with all its inherent risks are not

uncommon^{520,564}. Uncontrolled infection may even ultimately result in definitive treatment with alternative salvage procedures.

Optimal Timing

One of the most difficult decisions when choosing the two-stage approach is to when to go ahead with reimplantation. Preferably, the new prosthesis would be implanted in a sterile and advantageous background. As such, theoretically, there should be enough time complete antibiotic therapy and eradicate infection.

Traditionally, surgeons have been relying on serial measurements of blood inflammatory parameters (most often ESR and CRP) to determine infection status and postponing surgery accordingly. However, there is absolutely no evidence to support this practice that naturally leads to longer intervals between stages and subsequent increased morbidity to the patient. In fact, there is evidence clearly refuting its worth. In 2009, Ghanem et al.⁵⁶⁵ examined a cohort of 109 consecutive infected TKA patients undergoing a two-stage exchange. Infection was eradicated in 86 patients (79%) and 23 patients (21%) were revised for recurrent PJI. They were not able to determine a level for ESR or even CRP that could discriminate between patients in whom infection had successfully been eradicated. A year later, Kusuma et al.⁵⁶⁶ retrospectively reviewed the measurements of 76 infected TKA patients treated with a two-stage exchange protocol and reached the exact same conclusion. Although inflammatory parameters decreased in cases of infection control, they frequently remained elevated not allowing them to identify any patterns indicative of persistent infection⁵⁶⁶. At the same time, Shukla et al.⁵⁶⁷ reported on 87 infected THA undergoing a similar two-stage protocol in which persistent infection was identified in nine hips. Naturally, mean ESR and CRP significantly decreased between stages but it is noteworthy that ESR remained elevated (>30 mm/h) in 50 patients (62.5%) and CRP remained elevated (>10 mg/L) in 22 patients (27.5%) in whom the infection had been eradicated⁵⁶⁷. Bejon et al.⁴⁹⁸ looked at serial CRP measurements of 260 PJI patients, including 1406 separate measurements from 151 patients undergoing two-stage revision (comprising 71 THA, 76 TKA and 4 elbows). They found that the CRP profile was not significantly different in patients experiencing treatment failure. CRP did not predict additional debridement between stages nor did it predict treatment failure at the time of re-implantation⁴⁹⁸. It did however predict delayed re-implantation suggesting definitive surgery was deferred simply due to apprehension caused by elevated CRP⁴⁹⁸. Kubista et al.⁵²³ retrospectively examined data of 368 patients, looking for risk factors for failure after two-stage reimplantation for periprosthetic knee infection. They found no statistically significant differences in mean values for CRP or ESR prior to resection or reimplantation when comparing the treatment failure group (n=58) to the control group⁵²³.

Acknowledging these limitations, some authors further examined the role of joint aspiration before the second stage. Earlier studies focused on cultures results with conflicting results. Mont et al.⁵⁶⁸ compared a control group of 35 patients with a study group of 34 patients in which preoperative fluid cultures were taken four weeks after antibiotic discontinuation. In the control group, there were five infection relapses (86% success rate). In the study group, three patients

(9%) had a positive culture. The protocol was repeated for all three and they subsequently had a successful second revision. There was one case (3%) of infection relapse that occurred in patient with negative cultures. Lonner et al.⁵⁶⁹ looking at 34 TKA found two preoperative false positive cultures and negative cultures in 32 knees. They had 8 cases of persistent infection, none of which were identified on preoperative cultures. In the series by Ghanem et al.⁵⁶⁵, 34 out of 109 infected TKA patients had arthrocentesis before reimplantation as a result of a high clinical suspicion of unrelenting infection. Thirty-three had negative aspirates, but five of them (15%) had positive intraoperative cultures at the time of reimplantation⁵⁶⁵. Just recently, Janz et al.⁵⁷⁰ confirm that the low sensitivity of cultures is also so true in hips. These findings suggest negative synovial fluid culture results are not accurate in ruling out persistent infection. Much as for the first diagnosis of infection, attempts to refine synovial fluid testing have been made in order to overcome the low sensitivity of cultures and offer additional value to preoperative joint aspiration. Kusuma et al.⁵⁶⁶ did show that total leukocyte count was somewhat more accurate than ESR or CRP but still did not have sufficient sensitivity or positive predictive value to reliably diagnose persistent TKA infection. Shukla et al.⁵⁶⁷ performed a similar analysis regarding THA and found that synovial fluid total leukocyte count was the best test for identifying persistent infection, with an optimum cutoff of 3.528 cells/ μ L (sensitivity, 78%; specificity, 96%). In contrast, Newman et al.⁵⁷¹ analyzed data from 98 hips (80 patients) with antibiotic-eluting cement spacers to determine diagnostic accuracy of traditional cutoffs and optimal thresholds total leukocyte count and PMN proportion to diagnose infection in this setting. They found the optimal threshold for synovial total leukocyte count was 1,166 cells/ μ L which corresponded to overall diagnostic accuracy of 78%⁵⁷¹. Hoell et al.⁵⁷² studied 59 infected TKA and 56 infected THA treated with a two-stage protocol, and confirmed that aspiration of synovial fluid with a PMMA spacer in place is not an appropriate method for excluding persistent infection. Results so far are overall discouraging and there is no evidence to support joint aspiration before the second stage⁸⁵. In addition, it seems that most failures after the second stage are probably the consequence of re-infection and not persistent infection. Indeed, the microorganism isolated in failure after the second stage is often different than the one found in the first stage⁵⁷³.

Given the low accuracy of current laboratory testing to determine infection eradication before second stage surgery, clinical signs of improvement (adequate wound healing, no local inflammatory signs) and blood inflammatory parameters are frequently used together as a surrogate for infection control and effective antibiotic therapy in daily clinical practice. However, this improvement may persist only whilst antibiotic therapy is in place²⁸¹. As such, a holiday period before surgery has been traditionally recommended⁸⁵. Although there is no conclusive evidence to support or refute this practice, the rationale is that continuing observation after discontinuing antibiotics may be informative. Stability or continuing improvement (and not necessarily complete normalization of all parameters) could indicate eradication of the infection while deterioration might indicate recurrence. It is also important to correct the underlying cause for prosthetic joint infection if it is perceivable. Naturally, attention should likewise be paid to the patient's general health status and all efforts should be made to optimize medical comorbidities before revision surgery. Favorable soft tissue status with nice wound healing is equally important to increase chances of success and there should be enough time for adequate soft tissue preparation with muscle flaps if required, especially in cases of previously compromised soft tissues.

Although most authors acknowledge these requirements, the optimal time interval between stages cannot be firmly established⁸⁵. Reports vary from two weeks to several months^{247,514,515,518,523,559,560,574}. Nevertheless, evidence suggests greater time intervals offer no advantage in infection eradication and are associated with worse functional outcomes (besides greatly increasing morbidity between stages)^{85,523,526,564}. Our own experience confirms this assumption. We analyzed every PJI case treated with a two-stage revision surgery in our institution between 2011-2014. We found that among those who did not strictly comply to the suggested protocol, time interval between stages was significantly longer (around 30 vs. 11 weeks) with no added benefit as the reinfection rate was also significantly higher (20% vs. 0%).

Surgical and Medical Management

Persistent infection is an ominous concern that cannot be accurately ruled out before the second stage as we have discussed previously. Delay reimplantation of the new prosthesis and rather perform a second debridement has been advocated if the diagnosis can be made intraoperatively. On the other hand, decision regarding subsequent antibiotic therapy can also be accommodated if a diagnosis is reached postoperatively.

Although preoperative fluid cultures lack adequate sensitivity^{565,569,570}, multiple intraoperative tissue cultures are naturally more accurate and most authors agree that they must be taken during revision surgery. Cabo et al.⁵⁷⁵ reviewed second-stage culture results in 41 cases, showing the surgical site is frequently non-sterile at reimplantation as 18 patients (44%) showed at least one positive culture. They also found 14 (34%) positive antibiotic-loaded spacers cultures⁵⁷⁵. Sorli et al.⁵⁷⁶ reporting on 55 patients (37 knee, 17 hip and one shoulder replacement) showed 11 (20%) cases with subclinical infection in which there was positive culture from sonicated spacer fluid; and two or more tissue specimens positive for the same microorganism. This subgroup of patients exhibited a significantly higher risk of failure 63% (7/11) compared with 25% (11/44) of those without subclinical infection even if most of them (7) received antibiotic treatment according to definitive culture results. A couple of recent papers seems to confirm this increased risk of re-infection among positive sonicate results and a direct correlation seems to exist between higher bacterial load as measured by higher high colony counts and subsequent risk of failure^{26,577}. Nelson et al.²⁶ prospectively followed 36 consecutive patients undergoing two-stage revision for hip or knee PJI. Eighteen cases (50%) had positive sonication results. At a two-year follow up, recurrent infection rate was as high as 30% (11/36) and it correlated significantly with bacterial growth. Reinfection occurred in 78% (7/9) of cases with intermediate or significant bacterial growth (>20 CFU), 22% (2/9) in patients with subtle growth (<20 CFU) and only 11% (2/18) in patients with negative sonication results²⁶. Besides confirming this seeming correlation, Esteban et al.⁵⁷⁷ also found isolating organisms other than those isolated in the first surgery is also clinically relevant. Of course, culture results are not at all useful for intraoperative decision but should be taken nonetheless as it has been shown that second-stage positive cultures are an independent risk factor for treatment failure⁵⁷³.

Intraoperative frozen sections, have been suggested as a means to identify persistent infection intraoperatively and support the decision whether or not to proceed with reimplantation^{564,574}.

However, while this method offers high specificity it has low sensitivity for the diagnosis of infection at the time of reimplantation⁵⁷⁸⁻⁵⁸⁰. Synovial fluid analysis is also a potentially informative test. Traditional leukocyte counts thresholds though, despite their great value in diagnosing infected implants have been shown to be poorly predictive at the time of the second stage^{566,567,571,572}. These limitations have fueled the search for alternative biomarkers also in this scenario. Frangiamore et al.⁵⁸¹ have studied the role of synovial fluid biomarkers such as CRP, IL-6, IL-1 β and alpha-defensin not only in differentiating septic from aseptic failed TKA and THA but also in 35 patients before second-stage surgery. They found that IL-1 β and IL-6 had the greatest decrease between stages. However, cytokines and MSIS criteria lacked adequate sensitivity to rule out infection before reimplantation. Our own ongoing study also shows some synovial fluid biomarkers significantly decrease between stages. Mean values at prosthesis removal were 31.7 mg/L, 126.1 U/L for synovial CRP, and adenosine deaminase respectively (published results). Values at reimplantation surgery are available for 15 cases so far. Mean CRP concentration decreased to 3.6mg/L and ADA decreased to 41.8 U/L (unpublished data). As none of these cases proved to have positive intraoperative cultures or reinfection at follow-up, no assumption regarding their predictive value can be made yet.

In summary, current criteria used to define PJI are able to rule in persistent infection but offer limited screening ability to rule it out at the time of reimplantation^{571,580,581}. As such, we believe the second stage should be regarded as a second chance to deal with the infection with the same vigor as the first stage. Meticulous debridement and thorough diagnostic workup should be performed and adjuvant antibiotic therapy should be instituted if needed. In fact, there a growing body of evidence suggesting prolonged antibiotic therapy after the second stage may improve outcomes. Johnson et al.⁵¹⁷ were among the first to suggest a possible advantage of such a strategy. Decision to give longer-duration oral antibiotics after reimplantation was made by the consulting infectious disease physician and it was not based on a predetermined algorithm nor were there preselected assignment of patients based on any specific factors. They reported no reinfections on a group of 23 THA compared to six (13.6%) relapses in 44 patients not receiving postoperative oral antibiotics although this difference was not statistically significant. Siqueira et al.⁵⁸² also showed chronic suppression with oral antibiotics significantly increased the infection-free survival rate following surgical treatment for PJI. However, their results also included patients treated with DAIR. No significant difference in between the suppression and non-suppression groups was found considering two-stage revision cases only⁵⁸². Just recently, a multicenter study randomized patients to receive 3 months of oral antibiotics or no further antibiotic treatment after intraoperative cultures obtained during the second-stage reimplantation were negative⁵⁸³. So far, at interim analysis, 59 patients were successfully randomized to the antibiotic group and 48 patients to the control group (57 TKA and 50 THA). Results suggest that, at least at short-term follow-up, the addition of 3 months of oral antibiotics appears to be improving outcome as reinfection rate is significantly lower in the antibiotic group: 5% (3/59) vs. 19% (9/48) thus far⁵⁸³. Available evidence is not yet enough to make a definitive recommendation on the optimal medical treatment after the second stage.

Treatment Failure and Salvage Procedures

Treatment failure after septic surgery is a real problem. While it is not the only mode of failure, infection recurrence is probably the most problematic. Recurrent PJI may occur as a result of persistent infection (i.e. caused by the same microorganisms) or reinfection with new microorganism(s) suggesting treatment was effective at controlling the original infection.

Recurrent PJI after DAIR procedures is most often due to identical microorganisms suggesting treatment failed to eradicate infection effectively^{427,429,430,433,434}. A recent paper looked at 153 hip or knee PJI treated with implant retention with 52% (80/153) overall success rate⁴⁴⁰. Focusing exclusively on 43 cases with positive cultures at both initial and recurrent failure, they found 84%(36/43) of them failed with the same organism(s)⁴⁴⁰. Organism persistence was especially prevalent in knee and *Staphylococcus aureus* infections⁴⁴⁰. Reinfection after revision surgery seems different though. Zmistowski et al.⁵⁷³ pooled data of three different institutions regarding 92 patients who failed two-stage exchange and had positive cultures at both initial and recurrent PJI. Only 29 (31.5%) of them had identical microorganisms at treatment failure⁵⁷³. Triantafyllopoulos et al.⁵⁸⁴ made a similar analysis and also found that only 19 cases (40%) were persistent infections and most failures were due to new microorganisms. These findings suggest that treatment failure after two-stage revision surgery is more commonly secondary to a new infection rather than an inability to eradicate the original microorganism. It is also possible that these “new” organisms might have been present from the start but were simply not captured by cultures.

Naturally, failure is likely attributable to a combination of several factors. Some, such as the specific infecting microorganism or treatment with implant retention are more likely to contribute to PJI persistence and others are more likely to originate new infections probably by influencing host susceptibility status^{573,584}.

RISK FACTORS FOR FAILURE

Risk factors for failure of a DAIR procedure have been extensively discussed elsewhere. Much like failure after DAIR, the specific infecting pathogen is one of the main factors influencing outcome after exchange surgery. Indeed, staphylococci, as the original infecting organism seems to be associated with worse outcomes and a higher rate of infection persistence^{12,573}. Notwithstanding, this effect seems to be much more prominent after DAIR than after exchange arthroplasty (either one- or two-stage)⁴⁴⁴. Infections due to methicillin-resistant staphylococci are especially at risk for revision surgery treatment failure^{226,293,585}. Enterococci are also of special concern. A major multicenter European study included data of *Enterococcus* sp. PJI from 18 hospitals of six different countries⁴⁵⁵. Although implant removal was associated with a higher remission rate than DAIR, overall success rate of combined one- or two-stage exchange was only 64% (47/74)⁴⁵⁵. A recent paper focusing on 87 enterococci PJI reached similar conclusions⁴⁵³. Treatment success was 63% (27/43) for a two-stage exchange, 46% (5/11 patients) for a one-stage exchange and only 39% (13/33) for irrigation and debridement⁴⁵³. Gram negative microorganisms on the other hand, constitute a somewhat different problem in revision surgery compared to implant retention. Hsieh et al.⁴⁴⁶ looked at 53

out 346 PJI due to Gram negative bacteria. They found treating Gram negative PJI with DAIR was associated with a significantly lower probability of success than treating Gram positive (27% vs. 47% success rate). However, no difference was found when treatment consisted of a two-stage exchange or resection arthroplasty⁴⁴⁸. On the other hand, Zmistowski et al.⁴⁵⁰ found conflicting results in their study of 31 Gram negative infections in 282 culture-positive PJI. Debridement and implant retention was successful in 70% (7/10) of Gram negative cases⁴⁵⁰. Of those patients undergoing a planned two-stage exchange, successful reimplantation was performed in 52% (12/23) of Gram negative, 51% (52/103) of methicillin-resistant Gram positive, 69% (65/94) of methicillin-sensitive Gram positive and 0% (0/8) of polymicrobial PJI cases⁴⁵⁰. A recent multicenter French study involving 76 patients with Gram negative PJI, found a much better failure rate of only 9% (2/22) after one-stage exchange, and 27% (4/15) after two-stage exchange⁴⁹⁴. Polymicrobial infections, naturally accumulate all sorts of difficulties and are often linked to worse treatment outcomes^{450,458}.

Such findings are not unanimous, Sakellariou et al.⁵²⁵ found the type of isolated pathogen and its virulence were not directly associated with increased incidence of recurrence but placed much more emphasis on patient-related factors such as an history of inflammatory arthritis or being chronic *Staphylococcus aureus* carrier. A number of other patient-related variables have been found to increase the risk of infection recurrence after two-stage treatment. Obesity is a known risk factor for PJI in the first place and it has also been shown to be a major risk for failure after two-stage exchange of both TKA and THA^{586,587}. Diabetes, chronic lymphedema, heart disease or even psychiatric disorders have also already been implied^{523,525,584,588}. It seems logic to expect that all risk factors for first-time infection will also increase the risk of treatment failure.

SALVAGE PROCEDURES

Deciding what the best course of treatment is after recurrence of infection is not straightforward. Although the real impact of previous failed DAIR on the likelihood of success after exchange surgery is not yet fully understood, most surgeons would agree that exchange surgery is the natural choice in this scenario⁵⁸⁹⁻⁵⁹¹.

Failure after revision surgery is much more difficult to address. There is no evidence to support how many septic exchanges are reasonable to attempt⁸⁵. One of the major factors to consider is the causative microorganism and whether it represents persistent infection or a “new” infection. We believe new infections should be managed according to all previously mentioned recommendations although lower success rates are naturally to be expected. Azzam et al.⁵⁹² showed it was possible to manage reinfection after failed two-stage TKA exchange in 10 (44%) out of 18 patients treated with debridement and implant retention. More recently, Kheir et al.⁵⁹³ successfully treated 16 (43%) out of 37 patients with failed prior two-stage exchange in which debridement and implant retention was attempted.

A new exchange procedure (most often two-staged) may also be recommended depending on duration and extent of infection as well as patient willingness and medical fitness to undergo

further surgeries. The risk of recurrent infection must be discussed with the patient. New infections probably reflect an increased host susceptibility rather than previous treatment failure and if such risk factors cannot be mitigated, other alternatives must be seriously considered. Technical aspects such as adequate bone stock for stable fixation of the new prosthesis, viable soft tissues conditions that allow for good wound healing (or possibility of muscle flap coverage) and extensor mechanism status in the knee must also be considered. Reimplantation is feasible if all these conditions are met and infection seems to be adequately controlled after repeat resection. Several authors have reported successful outcomes after repeated two-stage exchanges but unsurprisingly, failure rates are as high as 40-50%^{484,592,594-597}. Patients with persistent infections on the other hand, especially those involving high risk bacteria such as methicillin-resistant staphylococci or enterococci should merit further consideration. We believe that a new attempt is reasonable when treating an otherwise healthy and fit patient, especially if a previous treatment error has been identified. On the other hand, when dealing with a patient at high risk for further treatment failure, salvage procedures are perhaps more sensible^{593,598,599}. Most common salvage procedures are resection arthroplasty (Girdlestone procedure) for the hip and arthrodesis or even amputation for the knee. Chronic suppressive oral antibiotic therapy is also worth considering.

Resection Arthroplasty

Resection arthroplasty was first described by Girdlestone almost a century ago as a salvage procedure for complex hip infections such as tuberculosis. Nowadays, failed periprosthetic hip infections are the most common indication. It is important to acknowledge that simply removing the hip implant is not enough to guarantee infection control. Debridement must be performed meticulously and efforts should be made to extract all residual bone cement, foreign material and infected tissues including bone. If that is not the case, infection may persist despite the absence of an implant⁶⁰⁰ (Fig. 6). When properly performed, it may provide satisfactory pain relief and control of infection^{601,602}. Of course, a significant impact on the functional outcome is to be expected, especially in elderly patients⁶⁰³.

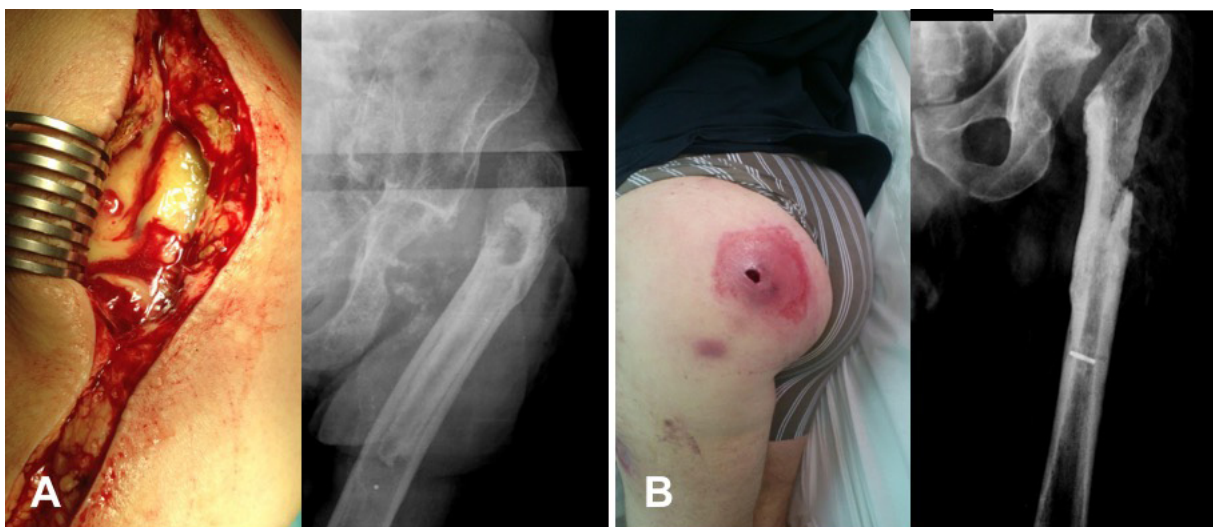


Fig. 6 Examples of failed infection control after hip resection arthroplasty. A: infection resolved after removal of the cement mantle; B: infection resolved after removal of the infected bone segment and broken drill bit.

Resection arthroplasty in total knee replacement is not a common strategy and it has been largely abandoned because of the poor and unpredictable functional outcomes^{604,605}. Our own though limited and retrospective observations, show that resection arthroplasty may be a viable alternative to knee fusion in selected patients²³. A significant impact in the patient quality of life and functional outcome is to be expected in either case. Resection arthroplasty patients have more difficulty walking and often require an external brace but on the other hand are more comfortable sitting and using the toilet²³.

Arthrodesis

Joint fusion is considered to be a main limb salvage procedures for failed periprosthetic joint infection. In contrast to resection arthroplasty, it is rarely considered in the hip but it is of proven value in the knee offering better functional outcomes and patient satisfaction. A recent systematic review⁵⁹⁹, suggests that arthrodesis is the procedure of choice when compared to suppressive antibiotics, amputation or even two-stage reimplantation for management of persistent infection after a failed two-stage TKA exchange.

Several different methods have been proposed to achieve fusion, including external fixation, plating and intramedullary nailing⁶⁰⁶⁻⁶¹⁰. More recently a method of intramedullary stabilization without bone-on-bone fusion has been presented as a means to achieve a stable and painless knee, while preserving the limb length. It has the advantage of overcoming bone defects that often preclude successful fusion and allows for early weight bearing and deambulation⁶¹¹. No method has yet proved to be clearly superior to the others. Each has its own set of limitations and possible complications such as failure of fusion (i.e. nonunion), limb length discrepancy, residual pain, periprosthetic or implant fractures, pin site infections, etc. The most feared and shared complication is recurrence of infection and this seems to be especially prevalent after intramedullary nailing⁶¹². Some authors advocate that performing an arthrodesis in two-stages reduces the risk of persistent infection although there is no real evidence of its advantage over single stage⁸⁵. Final decision on which method and tactic to use depends on individual circumstances, surgeon experience, host factors (both medical and local) and even specific pathogen.

Amputation

Control of the infection is not guaranteed after implant removal. Amouyel et al.⁶¹³ have recently reported on 72 consecutive patients who underwent TKA removal for infection. Prosthesis removal was followed by knee fusion in 29 cases or implantation of a permanent cement spacer in 43 cases. The two-year infection free rate was 69% for patients who underwent knee fusion and 62% for those who had a spacer implanted. After treatment of 32 recurrent infections, 23 cases were labelled as permanent failures (32% overall)⁶¹³.

In desperate cases, above-knee-amputation may be indicated⁸⁵. Especially if infection persists after repeated failed attempts at staged exchange and aggressive debridement, severe bone loss precludes knee fusion, there is inadequate soft tissue coverage or significant peripheral vascular disease or infection recurs after arthrodesis. Many of these patients go through a lot of surgeries and suffering before this option is considered and this might explain why, despite

the obvious suboptimal functional outcomes, patient satisfaction is surprisingly good⁶¹⁴. Khana et al.⁵⁹⁸ specifically assessed patient satisfaction following above-knee-amputation for chronically infected TKA in seven patients. All seven patients reported that they were satisfied with their amputation (six were fitted with a prosthesis limb). Six of seven patients reported that given the choice, they would have chosen amputation sooner⁵⁹⁸. These findings might explain the increasing trend toward amputation when compared to arthrodesis for the treatment of a failed infected TKA in the United States⁶¹⁵.

Chronic Suppressive Antibiotic Therapy

Prolonged suppressive antibiotic therapy is seldom indicated in the management of PJI. In a surgically fit patient, it is considered when all operative treatment options have been exhausted. It may also be considered in an elderly or otherwise poor health status patient where surgical intervention is contra-indicated or in patients unwilling to undergo further surgery. A loose implant is generally considered to be a contra-indication for suppressive antibiotic therapy. A number of other prerequisites such as causative pathogen sensitive to a well-tolerated oral antibiotic that can be safely administered for prolonged suppression and adequate baseline renal and liver function are also important⁶¹⁶. Regular monitoring of the patient is essential to ensure safe treatment with suppressive antibiotics. This includes routine examination and tests to rule out predictable side effects such as renal, liver or gastrointestinal dysfunction. Methicillin-sensitive staphylococci that can be controlled using penicillins, ciprofloxacin-sensitive Gram negative bacteria and streptococci seem to be more manageable pathogens⁶¹⁶.

Chronic suppression with oral antibiotics has been proved to result in superior infection-free survival rates after surgical treatment for periprosthetic joint infection compared with those observed without suppression⁵⁸². It is however an unproven method with high failure rates at the long term⁶¹⁶⁻⁶¹⁸. It should be considered only in selected cases in which prosthesis removal would potentially cause an extremely poor limb or even life threatening situation.

Is Asymptomatic Bacteriuria a Risk Factor for Prosthetic Joint Infection?

Running title: Asymptomatic Bacteriuria & Arthroplasty

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Summary

In this large study of around 2,500 total joint arthroplasty candidates we found a 12.1% prevalence of preoperative asymptomatic bacteriuria. It was associated with higher risk of PJI and appropriate preoperative antibiotics were not effective in reducing the risk.

Keywords

Bacteriuria, Incidence, Prosthesis-Related Infections, Risk Factors

Abstract

Background: Infection is a major complication after total joint arthroplasty. The urinary tract is a possible source of surgical site contamination but the role of asymptomatic bacteriuria before elective surgery and subsequent risk of infection is poorly understood.

Methods: Total hip (THA) or total knee arthroplasty (TKA) candidates were reviewed in a multicenter cohort study. In all cases, a urine sample was cultured and patients with asymptomatic bacteriuria (ASB) were identified. Preoperative antibiotic treatment was decided on an individual basis and it was not mandatory or randomized. The primary outcome was prosthetic joint infection (PJI) in the first postoperative year.

Results: 2,497 patients were enrolled. ASB prevalence was 12.1% (303/2497), 16.3% in women and 5.0% in men (OR=3.67, 95% CI=2.65-5.09, $P < 0.001$). Overall PJI rate was 1.7%. Infection rate was significantly higher in the ASB group (4.3%) than in the non ASB group (1.4%) (OR=3.23, 95% CI=1.67-6.27, $P=0.001$). In ASB group, there was no significant difference on PJI rate in the treated (3.9%) compared to the untreated (4.7%) patients. A significantly higher proportion of PJI due to Gram negative microorganisms was observed in ASB group compared to the non ASB group but these did not correlate to urine isolates.

Conclusions: ASB was an independent risk factor for PJI particularly due to Gram negative microorganisms. Preoperative antibiotic treatment did not show benefit and cannot be recommended.

Introduction

Periprosthetic joint infection (PJI) is one of the most challenging and frequent complications after joint arthroplasty [1, 2]. As the demand for total hip and knee joint arthroplasty is expected to increase substantially over the coming decades, so too will the economic burden of prosthetic infections [3, 4]. Since the incidence of this complication seems to be on the rise worldwide despite antiseptic skin preparation and antibiotic prophylaxis, identifying those potentially modifiable preoperative risk factors is of great interest [5, 6].

The concern with the genitourinary tract as a possible source of hematogeneous seeding has been present as far back as the 1970's when a few case reports [7-10] and a retrospective study [11] found a relation between patients with deep joint infection and perioperative urinary tract infection (UTI).

Although there seems to be enough evidence supporting a relation between postoperative UTI and PJI [11-15], literature studying the correlation between asymptomatic bacteriuria (ASB) and surgical site infection after joint arthroplasty is scarce [15-19]. As such, this finding is not currently considered to be a criterion for delaying total joint replacement surgery [13].

The aims of the present study were: **1)** to describe the prevalence of ASB among elective total hip and knee arthroplasty candidates; **2)** to determine if ASB is associated with an increased risk of PJI and finally **3)** to know whether an appropriate course of preoperative antibiotics is effective in reducing the risk of PJI.

Material and Methods

From January 2010 to December 2011, in three institutions from United Kingdom, Portugal and Spain, a urine culture before surgery was collected from all patients before undergoing a total hip (THA) or knee arthroplasty (TKA). Relevant information about demographics, body mass index (BMI), diabetes mellitus, American Society of Anaesthesiologists (ASA) physical status classification system and duration of surgery were collected retrospectively but unfortunately information regarding duration of surgery and diabetes mellitus was not possible to gather in the British participating institution. Duration of surgery was categorized as under or over the 75th percentile in order to account for different average surgical times between centers [20].

In all cases a urine sample was obtained (regardless of dipstick test results), placed in a sterile container and cultured using conventional methods in the microbiology laboratory. All isolated microorganisms were identified with standard biochemical procedures. ASB was defined as the isolation of $\geq 10^5$ CFU/mL in the absence of symptoms or signs of urinary tract infection.

Preoperative treatment of asymptomatic bacteriuria was decided by the treating physician and was not mandatory or randomized. For treatment an eight-day course of oral antibiotics (according to *in vitro* susceptibility test) was given the week before hospital admission. Control urine cultures after treatment were not mandatory and only 26 of the 154 treated ASB patients had repeat urine cultures (all of them negative) before surgery. In the untreated ASB candidates no further antibiotics were given pre- or per operatively nor were any other additional prophylaxis measures taken other than normal prophylaxis regimen for each institution (single dose 2g cefazolin in the Portuguese institution, 1.5g cefuroxime in the Spanish institution or 600 mg teicoplanin plus 120mg gentamicin in the UK institution during the induction of anesthesia).

Postoperative UTI occurring in the early postoperative period was diagnosed when urinary symptoms of infection were present and urine culture showed bacterial growth $\geq 10^5$ CFU/mL. After hospital discharge the patients were followed for a minimum of twelve months. The main outcome of the study was the diagnosis of prosthetic joint infection occurring in the first year after surgery according to the CDC definition of implant related surgical site infection [21].

STATISTICAL ANALYSIS

Categorical variables were presented as number of patients and percentages. Continuous variables were compared using the non-parametric Mann-Whitney test as the study population did not meet the normality assumption. Proportions were compared using Chi-square test and Fischer's exact test when necessary with statistical significance defined as a two-tailed P value < 0.05 .

To test the association between study variables and outcome (PJI) logistic regression models were fitted accounting for spatial clustering as data came from three different Centers (center effect).

A multivariable logistic regression model was developed including variables with a P value ≤ 0.20 from the univariable analysis. The role of the variables as potential modifier effect was also studied. The assessment of the model fit was done with the Hosmer-Lemeshow test. Statistical analysis was done by the program SPSS (version 19.0; SPSS, Inc., Chicago, IL, U.S.A.).

Results

A total of 2497 patients were included during the study period with a similar proportion of THA (n=1248) and TKA (n=1247). Distribution among participating institutions is shown in table 1 and no significant differences among them were registered either for ASB or PJI.

Table 1 Differences between the three participating institutions regarding ASB and PJI.

	Overall	UK	Portugal	Spain	P value
	n=2497	n=1495	n=785	n=217	
Preoperative ASB	303 (12.1%)	184 (12.3%)	88 (12.1%)	31 (14.3%)	0.45
Overall PJI	43 (1.7%)	19 (1.3%)	18 (2.3%)	6 (2.8%)	0.10
Gram negative PJI	11 (0.4%)	5 (0.3%)	4 (0.5%)	2 (0.9%)	0.45

ASB Asymptomatic Bacteriuria; PJI Prosthetic Joint Infection.

Approximately two thirds were women (63.0%) and the mean age of the patients was 68.0 years old. Asymptomatic bacteriuria (ASB) was diagnosed in 12.1% of the cohort, 16.3% in women and 5.0% in men (OR=3.67, 95% CI=2.65-5.09, P<0.001). Table 2 shows the microorganisms isolated in these patients.

Table 2 Microorganisms isolated in preoperative urine cultures.

Isolated Species	Frequency
Gram negative	87.6%
Enterobacteriaceae	
<i>Escherichia coli</i>	193 (64.8%)
<i>Klebsiella</i>	21 (7.0%)
<i>Proteus</i>	12 (4.0%)
<i>Citrobacter</i>	8 (2.7%)
<i>Morganella</i>	2 (0.7%)
<i>Pseudomonas aeruginosa</i>	1 (0.3%)
Others	24 (8.1%)
Gram positive	11.7%
Coagulase-negative staphylococci	1 (0.3%)
<i>Staphylococcus aureus</i>	5 (1.7%)
Other	
<i>Enterococcus spp.</i>	22 (7.4%)
<i>Streptococcus spp.</i>	6 (2.0%)
<i>Corynebacterium spp.</i>	1 (0.3%)
Fungi	0.3%
<i>Candida albicans</i>	1 (0.3%)

ASB was significantly more common in obese women over 71 years with an ASA score of ≥ 3 (table 3). There was no significant increase of postoperative UTI prevalence in the ASB group.

Table 3 Main characteristics of the population according to the presence of asymptomatic bacteriuria.

	ASB (n=303)	Non ASB (n=2193)	P value	OR	95% CI
Mean age (range)	70.9 (23-90)	67.7 (21-96)	< 0.001	-	-
Female gender	257 (84.8%)	1315 (59.9%)	< 0.001	3.73	(2.70 – 5.17)
Knee Location	162 (53.5%)	1087 (49.5%)	0.220	1.17	(0.91 – 1.50)
Duration >75th percentile ¹⁾	25 (21.4%)	192 (22.1%)	0.906	0.96	(0.57 – 1.55)
Co-morbidities					
Obesity (BMI $\geq$ 30) ²⁾	127 (47.0%)	735 (36.6%)	0.001	1.54	(1.18 – 2.00)
Diabetes ³⁾	23 (19.5%)	145 (16.6%)	0.433	1.22	(0.75 – 1.99)
ASA ≥ 3 ⁴⁾	61 (25.2%)	320 (18.6%)	0.019	1.47	(1.06 – 2.03)
Postoperative UTI	5 (1.7%)	21 (1.0%)	0.234	1.74	(0.65 – 4.64)

BMI Body Mass Index, **ASA** American Society of Anesthesiologists, **UTI** Urinary Tract Infection. **1)** Data available for 985 patients; **2)** Data available for 2278 patients; **3)** Data available for 993 patients; **4)** Data available for 1960 patients.

The overall PJI rate in the study population was 1.7% (43/2497). Infection rate in the ASB group was 4.3% (13/303) significantly higher than the 1.4% (30/2194) rate in non ASB group (OR=3.23, 95% CI=1.67-6.27, P=0.001). Variables associated with PJI in the univariable analysis were ASA score ≥ 3 , ASB and there was a trend towards significance for postoperative UTI (table 4). Multivariable analysis, performed including variables with a P value ≤ 0.2 , substantiates ASB (OR=3.95, 95% CI=1.52-10.26) and postoperative UTI (OR=6.64, 95% CI=1.24-35.64) as independent predictors of PJI.

Table 4 Risk factors for prosthetic joint infection.

	No PJI	PJI	Univariable analysis			Multivariable analysis		
	n=2454	n=43	P value	OR	95%CI	P value	OR	95%CI
Mean age (range)	68.1 (21-96)	68.6 (51-87)	0.721	-	-	-	-	-
Female gender	1551 (63.2%)	21 (48.8%)	0.005	0.56	(0.37-0.84)	0.102	0.42	(0.15-1.19)
Knee Location	1222 (49.8%)	27 (62.8%)	0.199	1.70	(0.76-3.83)	0.003	1.39	(1.11-1.72)
Duration >75th percentile ¹⁾	209 (21.7%)	8 (33.3%)	0.022	1.80	(1.25-2.59)	²⁾	²⁾	²⁾
Co-morbidities								
Obesity (BMI $\geq$ 30) ³⁾	847 (37.9%)	15 (37.5%)	0.936	0.99	(0.69-1.41)	-	-	-
Diabetes ⁴⁾	163 (16.8%)	5 (20.8%)	0.606	1.30	(0.48-3.54)	-	-	-
ASA ≥ 3 ⁵⁾	368 (19.1%)	13 (38.2%)	<0.001	2.62	(1.66-4.14)	0.083	2.12	(0.91-4.95)
ASB	290 (11.8%)	13 (30.2%)	<0.001	3.23	(2.10-4.97)	0.005	3.95	(1.52-10.26)
Postoperative UTI	24 (1.0%)	2 (4.7%)	0.091	4.94	(0.77-31.56)	0.001	6.64	(1.24-35.64)

PJI prosthetic Joint Infection; **BMI** Body Mass Index; **ASA** American Society of Anesthesiology; **UTI** Urinary Tract Infection; **ASB** Asymptomatic Bacteriuria. **1)** Data available for 985 patients; **2)** Duration >75th percentile was excluded from the multivariable model since data is missing in a significant proportion of the cohort; **3)** Data available for 2278 patients; **4)** Data available for 993 patients; **5)** Data available for 1960 patients.

Postoperative UTI was diagnosed in 26 patients and only five of them had preoperative ASB. All five cases occurred in the untreated ASB group and the same organism was present in the urine before and after surgery. No resistant strains to the prophylaxis regimen were present in these cases. Despite the higher risk of PJI in the early postoperative UTI group, microorganisms isolated in UTI were always different from those in PJI.

A total of 51 microorganisms were isolated in 43 cases of PJI (table 5). The proportion of PJI cases involving GN bacteria was 1.98% (6/303) in the ASB group compared to 0.23% (5/2194) in the non ASB group (OR=8.84, 95% CI=2.68-29.16, P=0.001). In 32 out of 43 cases (74%), the infection was diagnosed within the first 6 weeks after surgery. In the other 11 cases, the diagnosis was made after the first three months. The proportion of GN was identical in the early infection group (8/32) and in the late infection group (3/11).

Table 5 Microorganisms isolated in 43 prosthetic joint infection cases.

Isolated microorganisms	Overall (n=51)	ASB (n=17)	Non ASB (n=34)
Gram positives	72.5%	47.1%	85.3%
CoN Staphylococci	16 (31.4%)	6 (35.3%)	10 (29.4%)
Staphylococcus aureus	15 (29.4%)	2 (11.8%)	13 (38.2%)
Other			
Enterococcus spp.	3 (5.9%)	-	3 (8.8%)
Streptococcus spp.	2 (3.9%)	-	2 (5.9%)
Corynebacterium spp.	1 (2.0%)	-	1 (2.9%)
Gram negative	27.5%	53.0%	14.6%
Enterobacteriaceae			
Escherichia coli	6 (11.8%)	3 (17.6%)	3 (8.8%)
Serratia spp.	2 (3.9%)	2 (11.8%)	-
Proteus spp.	2 (3.9%)	1 (5.9%)	1 (2.9%)
Citrobacter spp.	1 (2.0%)	1 (5.9%)	-
Pseudomonas spp.	2 (3.9%)	2 (11.8%)	-
Others			
Acinetobacter spp.	1 (2.0%)	-	1 (2.9%)
Polymicrobial	6 (11.8%)	2 (11.8%)	4 (11.8%)

ASB asymptomatic bacteriuria; CoN coagulase negative.

Microorganisms isolated in PJI among patients with ASB were not the same as in their preoperative urine cultures in any case (table 6). Although pulsed-field gel electrophoresis was not performed, *E. coli* isolates in the urine and in the joint of patient #4 - an untreated ASB case - presented different antibiotic resistance profiles suggesting they were unrelated. There were no other variables significantly associated with GN infections.

A sub-analysis of ASB population on the effect of preoperative treatment of ASB was performed. As there was no randomization to treatment, biases as to who was selected for

treatment can exist. In order to address possible unrecognized selection biases, a propensity analysis was performed and the results are no different from the ones obtained from the logistic regression analysis. Both groups were similar for the main risk factors except the proportion of females that was significantly higher in treated group (table 7). Infection rates in the untreated ASB group were 4.7% (7/149) and 3.9% (6/154) in the treated ASB group. There was no significant difference between them (OR=0.82, 95% CI=0.27-2.51, $P=0.78$) and they both had a significantly higher rate of PJI than non ASB group (untreated ASB vs. no ASB: OR=3.56, 95% CI=1.54-8.24, $P=0.007$; treated ASB vs. no ASB: OR=2.85, 95% CI=1.20-6.74, $P=0.027$).

Table 6 Microorganisms isolated in PJI among ASB patients.

	ASB microorganism	PJI microorganism
#1	<i>Enterococcus faecalis</i>	<i>Escherichia coli</i>
#2	<i>Klebsiella pneumoniae</i>	<i>Staphylococcus aureus</i>
#3	<i>Escherichia coli</i>	<i>Serratia marcescens</i> , Coagulase-negative staphylococci
#4	<i>Escherichia coli</i>	<i>Escherichia coli</i> , <i>Serratia marcescens</i> , <i>Proteus mirabilis</i> , <i>Pseudomonas aeruginosa</i>
#5	<i>Escherichia coli</i>	Coagulase-negative staphylococci
#6	<i>Staphylococcus aureus</i>	<i>Pseudomonas aeruginosa</i>
#7	<i>Escherichia coli</i>	<i>Staphylococcus aureus</i>
#8	<i>Klebsiella pneumoniae</i>	<i>Citrobacter</i>
#9	<i>Escherichia coli</i>	Coagulase-negative staphylococci
#10	<i>Escherichia coli</i>	Coagulase-negative staphylococci
#11	<i>Escherichia coli</i>	Coagulase-negative staphylococci
#12	<i>Escherichia coli</i>	Coagulase-negative staphylococci
#13	<i>Enterococcus faecalis</i>	<i>Escherichia coli</i>

ASB Preoperative Asymptomatic Bacteriuria; PJI Prosthetic Joint Infection.

Table 7 Microorganisms isolated in PJI among ASB patients.

	Treated ASB (n=154)	Untreated ASB (n=149)	P value
PJI	6 (3.9%)	7 (4.7%)	0.78
Mean age (range)	71.6 (23-90)	70.1 (36-90)	0.059
Female gender	139 (90.3%)	118 (79.2%)	0.010
Knee Location	82 (53.3%)	80 (53.7%)	1.000
Co-morbidities			
Obesity (BMI $\geq$ 30) ¹⁾	61 (45.9%)	66 (48.2%)	0.716
Diabetes ²⁾	4 (18.2%)	19 (19.8%)	1.000
ASA $\geq$ 3 ³⁾	27 (24.3%)	34 (26.0%)	0.882
Postoperative UTI	1 (0.65%)	4 (2.7%)	0.208

ASB Asymptomatic Bacteriuria; PJI Prosthetic Joint Infection; BMI Body Mass Index; ASA American Society of Anesthesiologists; UTI Urinary Tract Infection. 1) Data available for 270 patients; 2) Data available for 118 patients; 3) Data available for 242 patients.

Discussion

Prosthetic joint infection is a dreadful complication of arthroplasty surgery and its prevention is a priority for U.S. Department of Health and Human Services [22]. Under contemporary aseptic conditions and the use of antibiotic prophylaxis the infection rate after joint arthroplasty has significantly decreased [23]. Nevertheless, there seems to be a worldwide trend to an increase in the incidence of this complication and a recent retrospective study performed in California demonstrated a surgical site infection rate of 2.3% and 2% following total hip and total knee arthroplasty respectively [24], which is even higher than the one reported in the present study (1.7%).

Although many orthopedic surgeons worry about an undiagnosed UTI as a possible source of bacterial contamination, the real impact of ASB as a preoperative marker or risk factor for PJI has not been well established and to our knowledge, our study is the largest case series that addresses this matter.

Prevalence of asymptomatic bacteriuria in the present cohort was 12% (16% in women and 5% in men) which is comparable to previous descriptions in total joint replacement candidates ranging from 4-19% [16, 17, 19, 25]. It is also in agreement with previous descriptions of the prevalence of asymptomatic bacteriuria in similar age groups of the general population [26, 27]. In addition, older age, female gender, BMI>30 and a higher ASA score were significantly more prevalent in ASB population which is consistent with previous studies [26-29].

Our data clearly shows that patients with preoperative ASB have a significantly higher risk of PJI when compared to the group of patients with non ASB (4.3% vs. 1.4%). Two classic papers are often cited to illustrate the lack of association between ASB and PJI. Ritter and Fechtman [16] studied 364 total joint replacements and the infection rate in ASB group was 2.8% (1 out of 35) and 0.6% in the non ASB group (2 out of 329). Glynn and Sheehan [17] reported data on 299 patients who underwent total joint replacement, and found the infection rate in patients with bacteriuria was 3.5% (2 out of 57) and 0% (0 out of 242) in non bacteriuria group. The results of this specific paper should be interpreted cautiously as not only patients with ASB but also patients with symptomatic UTI were included. Furthermore there were different antibiotic treatment regimens (before, during and even exclusively after surgery) among patients with bacteriuria. Although both papers found a non significant higher infection rate in the bacteriuria group, neither author assumed a potential relationship because the microorganisms isolated from surgical site infections and urine cultures were not the same.

Nevertheless, our cohort is larger, which made it possible, not only to show an increased risk for PJI but also a significant higher rate of GN infections. It is of great significance that, in accordance with previous studies, microorganisms found in PJI have no direct correspondence with the species found in urine cultures.

Since part of our cohort of patients with ASB was treated with a course of preoperative antibiotics, we analyzed the potential benefit of this strategy. No difference was observed in

the infection rate between both groups (4.7% vs. 3.9%). To the best of our knowledge there is only one study in which patients with ASB have undergone arthroplasty after randomization to antibiotic therapy [19]. The authors identified no case of PJI from urinary origin in patients with asymptomatic bacteriuria whether or not they had been treated with specific antibiotics [19].

Although it is extremely difficult to be sure of the exact pathogenesis of infection (hematogenous or acquired during surgery), the majority of infections in our series occurred within the first six weeks after surgery, suggesting most of them were the consequence of wound contamination during surgery [30]. The lack of correspondence between ASB and PJI microorganisms could be explained by the fact that patients with ASB are at risk for recurrence with a different organism. However, the short interval between preoperative antibiotic treatment and surgery makes recurrent ASB/UTI with a different organism and subsequent hematogenous seeding of the new organism unlikely to justify for most GN infections found.

An alternative potential explanation for the increased risk of infection could be a relationship between ASB and other known risk factors admittedly more common in ASB patients. However, the multivariable model showed ASB to be an independent predictor of PJI after adjusting for the main known risk factors (gender, age, location, duration of surgery, BMI or co-morbidity) suggesting it may actually be a surrogate marker for some kind of other not yet known feature. A plausible explanation could be that skin flora of patients with ASB is different from patients without ASB. The study of Ollivere et al. [31] on a cohort of 558 arthroplasty patients supports the fact that ASB patients are at increased risk for wound contamination. Over 36% of the 39 patients with preoperative positive urine culture showed some form of postoperative delayed wound healing or confirmed superficial infection versus 16% in the other subgroup.

There are limitations of our study. The first is that the definition of asymptomatic bacteriuria relies on a single urine sample. This is not entirely in accordance with the Infectious Diseases Society of America guidelines for the diagnosis of asymptomatic bacteriuria in adults that requires two consecutive urine specimens with isolation of the same bacterial strain in women [32]. The second one regards to the lack of routine control urine cultures to confirm eradication of ASB before surgery. These are of course not ideal conditions to assess the precise value of urine sterilization before arthroplasty. Nonetheless, the prescribed treatment is the usual clinical practice and has been shown to be highly effective in treating urinary tract infection [33]. Data regarding other possible confounding risk factors for ASB and PJI such as urinary incontinence, immobility, residence in a nursing home or long-term care facility or the presence and duration of urinary catheter before and after surgery are not available. Also, preoperative antibiotic prophylaxis regimen was not the same in all three institutions and respective rates of compliance are not available; however, this concern was addressed by performing statistical analysis accounting for spatial clustering. Finally, antibiotic treatment for ASB was not randomized which may lead to selection biases (i.e. physicians may have chosen to treat the patients who they thought were at higher risk). However, a propensity analysis was performed and comparing treated and untreated ASB populations showed no significant differences apart from a higher proportion of females in the treated group. Since female gender was not an independent risk factor for PJI, it seems not to be clinically relevant.

Possible negative consequences of preoperative antibiotic treatment of ASB (e.g. *C. difficile* infection) were not registered. In contrast, the analysis of the influence of treatment helped us to better understand the role of ASB.

In conclusion, ASB is a common finding among total joint arthroplasty candidates and it emerges as an independent risk factor for PJI. Our results support that there is no direct seeding of urine microorganisms on to surgical site but rather, that ASB is a surrogate marker for some kind of condition that increases risk of bacterial colonization/infection especially due to GN microorganisms. Preoperative antibiotic treatment did not show benefit and so, postponing surgery or even treating known asymptomatic bacteriuria patients before surgery cannot be recommended.

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Preoperative *Staphylococcus aureus* Screening/Decolonization Protocol Before Total Joint Arthroplasty - Results of a Small Prospective Randomized Trial

Running title: S. aureus Decolonization and PJI

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Abstract

In order to study the prevalence of *S. aureus* carriage and the impact of preoperatively treating carriers in prosthetic joint infection (PJI), a prospective randomized trial was organized. From January 2010 to December 2012, 1028 out of 1305 total joint arthroplasties performed were screened and selected carriers underwent preoperative decolonization. We observed a 22.2%(228/1028) *S. aureus* colonization rate and only 0.8% MRSA. PJI rate was higher, albeit not significantly, in *S. aureus* carriers than among non carriers - 3.9%(9/228) vs. 2.0%(16/800). Treated and untreated carriers showed no significant differences - 3.4%(3/89) vs. 4.3%(6/139). Most of the 14 *S. aureus* PJI occurred in non carriers suggesting a lack of causal relation between nasal and PJI *S. aureus*. No clear benefit in screening/decolonizing carriers before total joint arthroplasty could be demonstrated.

Keywords

Carrier State; Prospective Studies; Prosthesis-Related Infections; Risk Factors; *Staphylococcus aureus*; Surgical Site Infection

Introduction

Periprosthetic joint infection (PJI) is one of the most challenging and frequent complications after total joint arthroplasty [1;2]. As the demand for total hip and knee joint arthroplasty is expected to increase substantially over the coming decades, so too will the economic burden of infection [3;4]. Despite all the recent focus, the incidence of this complication seems to be on the rise worldwide [5;6]. Prevention is therefore paramount and identifying potentially modifiable preoperative risk factors is of great interest.

Staphylococcus aureus, especially MRSA, is unanimously considered to be a major pathogen implicated in surgical site infection (SSI) and PJI specifically [7;8]. About 20-30% of the general orthopedic population is *S. aureus* carrier and the anterior nasal cavity is the main site of colonization [9;10]. Nasal carriage has long been considered an established risk factor for infection in many situations, such as dialysis, intravascular device bearers and even those undergoing surgery [11]. It has even been reported that *S. aureus* isolated in deep infections match those from the nares in over 80% of cases [12].

This link has driven the interest on treating *S. aureus* nasal carriage status preoperatively to potentially reduce infection rates in many fields of surgery including orthopedics. The goals of the present study are: **1)** to describe the prevalence of both methicillin sensitive and resistant *S. aureus* carriage among elective total hip and knee arthroplasty candidates; **2)** to evaluate the real impact of preoperatively treating carriers by decolonization of the nares and skin bathing in the prevention of PJI.

Material and Methods

Study Design and Patient Population

This is a prospective randomized controlled clinical study that received institutional review board approval. All patients undergoing elective primary total hip (THA) or knee arthroplasty (TKA) at a single institution between January 2010 and December 2012 were eligible for enrollment regardless of preoperative diagnosis. Screening of *Staphylococcus aureus* carriers was made available to surgeons as a part of preoperative patient preparation but it was not mandatory. Our orthopedic department includes 25 surgeons and ten of them perform total joint arthroplasty surgery regularly. Surgeons were informed of the potential benefits of the intervention and asked to cooperate by informing their patients and timely ask for screening before surgery. Patients were enrolled after they gave informed consent.

Three major patient groups were formed: non-carriers, treated carriers and untreated carriers. Information about *S. aureus* nasal carriage status as well as other relevant variables such as demographics, body mass index (BMI), diabetes mellitus, inflammatory arthritis, American Society of Anesthesiologists (ASA) physical status classification system and duration of surgery were collected prospectively.

Study Intervention: Screening/Decolonization Protocol

S. aureus nasal carriage screening was performed in the outpatient setting two to four weeks before surgery. Samples were taken by a dedicated nursing team by swabbing the inside circumference of both nares with the same swab. Each swab was cultured aerobically on the selective and differential mannitol salt agar medium, which was incubated for 48 hours at 37°C. If suspected colonies grew at 18-24 hours, a Pastorex® Staph Plus latex agglutination test (Bio-Rad, Marnes-la-Coquette, France) was performed for the simultaneous detection of protein A, clumping factor and capsular polysaccharides of *S. aureus*. Biochemical identification was performed on Vitek MS® (BioMérieux, Durham, NC, U.S.A.) and detection of methicillin resistance was performed according to the European Committee on Antimicrobial Susceptibility Testing guidelines by use of a cefoxitin screen test.

Patients with nasal cultures positive for *S. aureus* that were allocated for preoperative treatment were reconvened at least one week before surgery, and educated about the rationale for the decolonization protocol, which was performed in the outpatient setting. Patients were instructed to apply a 2% mupirocin nasal ointment (Bactroban®; GlaxoSmithKline, Middlesex, United Kingdom) twice daily to both nares and to bathe with chlorhexidine soap (Cyteal®; Pierre Fabre, Gien, France) daily for five days immediately before the scheduled surgery. No information regarding patient compliancy was gathered.

All patients received prophylactic perioperative antibiotics. The standard regimen was cefazolin 2g administered 30 to 60 minutes before surgery followed by 1g every 8 hours for 24 hours and all patients got it. Identified MRSA carriers in the intervention group or patients with a history of

MRSA infection (regardless of *S. aureus* carrier state) were concomitantly given vancomycin 1g, 60 minutes before surgery followed by 1 g every 12 hours for 24 hours. As such, dual antibiotic coverage occurred in all three groups: non-carriers, treated carriers or untreated carriers.

Follow-up, Outcomes and Definitions

All patients were followed regularly in the outpatient clinic. No patients were lost to follow-up at a minimum of one year after surgery. Duration of surgery was categorized as under or over the 75th percentile in order to account for different average surgical times between THA and TKA[13]. The main outcome of the study was the diagnosis of prosthetic joint infection occurring in the first year after surgery accordingly to the CDC definition of implant related surgical site infection[14].

Definitive diagnosis of prosthetic joint infection (PJI) was made when at least two intraoperative microbiological samples grew the same organism or only one positive sample in the presence of a sinus tract, elevated serum erythrocyte sedimentation rate(ESR)/C-reactive protein(CRP) or elevated synovial leukocyte count or neutrophil percentage in accordance with a recently proposed definition [15]. No cases of culture-negative PJI were found. The primary outcome measure was defined as the overall rate of surgical site infection including all pathogens and a secondary outcome was defined as infections involving *S. aureus* bacteria only.

Randomization Process

Each *S. aureus* carrier was given a consecutive identification number as it was identified in the microbiology laboratory. They were subsequently assigned to the intervention or control group according to an assignment sequence prepared in advance by the first author on an online randomization tool. Allocation ratio between the two groups was 1:1.

Statistical Analysis

Categorical variables are described as number of patients and percentages, and compared using Chi-square test and Fischer's exact test when necessary. Continuous variables are described as mean and range and compared using the non-parametric Mann-Whitney test as the study population did not meet the normality assumption. A significance level of $p < 0.05$ was used for all statistical analyses.

No intent-to-treat analysis was performed. To test the association between study variables and outcome (PJI) a multivariable logistic regression model was developed including variables with a P value ≤ 0.20 from the univariable analysis. The role of the variables as potential modifier effect was also studied. The assessment of the model fit was done with the Hosmer-Lemeshow test. Results are reported as odds ratio (OR) with 95 % confidence intervals (95% CI). Statistical analyses were done using the software SPSS (version 19.0; SPSS, Inc., Chicago, IL, U.S.A.).

Because of the low prevalence of PJI, any study designed to prove a significant decrease in infection rate must necessarily include a massive number of patients. In order to demonstrate

a significant decrease from 4 to 2% (e.g. untreated vs. treated) one would need to include over 1,100 patients in each group. Knowing this study would not be able to reach the figures necessary to be adequately powered, the authors were hoping to determine trends between groups. With the actual number of patients included, the power of this study to detect a difference between treated and untreated groups is around 40% (i.e. clearly underpowered).

Source of Funding

There was no external funding source for this study.

Results

During the study period, 1305 primary total joint (hip and knee) arthroplasties were performed in our institution. Of those, 1028 patients were included in the study after informed consent, yielding a 79% successful screening rate. Figure 1 shows a participant's flow diagram throughout the study.

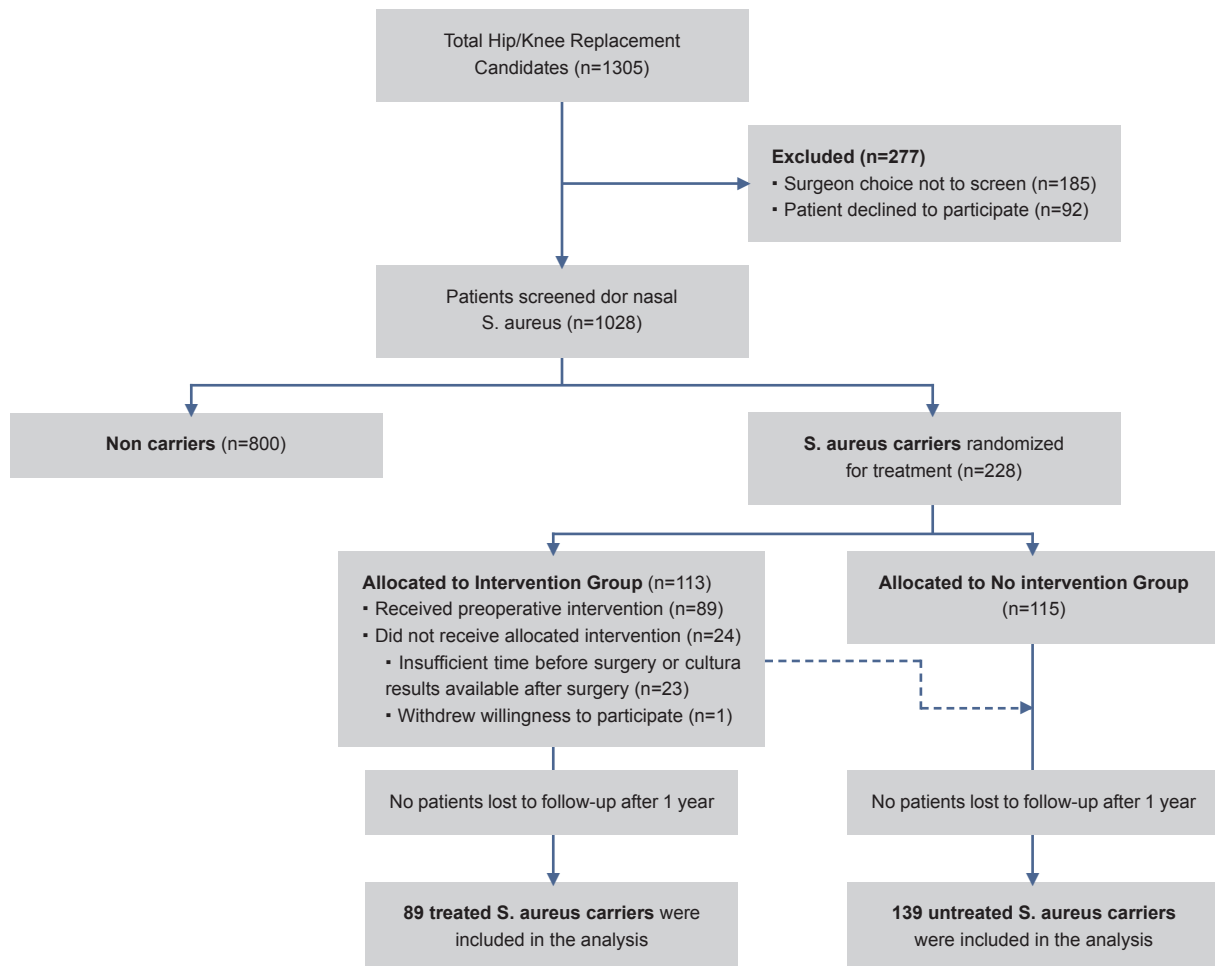


Fig 1a Participants flow chart.

Of the 228 identified carriers, 113 were randomly assigned to the intervention/decolonization group. Unfortunately, 24 patients did not receive the intended treatment. Most cases failed to receive treatment because it was not possible to timely reconvene the patients after culture results became available. This happened in cases where nasal carriage screening was not performed at least two weeks before surgery. One patient withdrew its willingness to cooperate.

All patients were available for outcome analysis as no patients were lost to follow-up in the first year. Outcome analysis was performed considering the 89 patients that received preoperative treatment in one group and the 139 *S. aureus* carriers that were not treated in a second group.

We observed a 22.2% (228/1028) *S. aureus* colonization rate. There were eight patients colonized with MRSA (0.8%). Comparing carrier and non-carriers it is possible to ascertain that

the former are slightly younger and have a significant increased prevalence of inflammatory arthritis and hospital admission within the year before arthroplasty surgery (Table I).

Table I.B Main characteristics of the population according to *S. aureus* colonization status.

	<i>S. aureus</i> carrier	Non-carrier	<i>P</i> value	OR	95% CI
	n=228	n=800			
Mean age (range)	64.5 (23-91)	67.1 (21-92)	0.055	-	-
Female gender	150 (65.8%)	564 (70.5%)	0.173	0.8	(0.58-1.12)
Knee Location	120 (52.6%)	497 (62.1%)	0.01	0.68	(0.50-0.92)
Duration >75th percentile	62 (27.2%)	209 (26.1%)	0.747	1.06	(0.74-1.49)
Co-morbidities					
Obesity (BMI≥30)	76 (33.3%)	287 (35.9%)	0.479	0.89	(0.65-1.23)
Diabetes	50 (21.9%)	164 (20.5%)	0.639	1.09	(0.75-1.57)
Inflammatory Arthritis	15 (6.6%)	20 (2.5%)	0.003	2.75	(1.28-5.74)
ASA ≥ 3	65 (28.5%)	206 (25.8%)	0.404	1.15	(0.81-1.61)
Hospital Stay < 1 year	53 (23.2%)	127 (15.9%)	0.007	1.65	(1.12-2.42)

BMI Body Mass Index, **ASA** American Society of Anesthesiologists.

Table II summarizes the main demographic and clinical characteristics as well as infection rates of the cohort. There are significant differences between THA and TKA candidates. Knee patients are older, predominantly females and more obese. *S. aureus* colonization rate is nevertheless significantly less prevalent among TKA patients.

Twenty-five cases with prosthetic joint infections were identified with an overall infection rate of 2.4%. Table III shows us that there were 14 cases involving *S. aureus* which results in a 1.4% *S. aureus* PJI rate. Although PJI among *S. aureus* carriers considered together is higher than among non carriers - 3.9% (9/228) vs. 2.0% (16/800) - the difference was not statistically significant. If we compare the rate of PJI between untreated carriers only and non carriers - 4.3% (6/139) vs. 2.0% (16/800) - the difference was also not statistically significant. Comparing treated and untreated carriers, PJI rate also did not reveal significant differences either for overall or *S. aureus* infection rate (Table IV) (power of the study to detect a Type-II error is 40%). There was no case of PJI among MRSA carriers.

Table II.B Main demographic and clinical characteristics of the study population.

	Overall	THA	TKA	P value
	n=1028	n=411	n=617	
<i>S. aureus</i> colonization	228 (22.2%)	108 (26.3%)	120 (19.4%)	0.010
Overall PJI rate	25 (2.4%)	8 (1.9%)	17 (2.8%)	0.410
<i>S. aureus</i> PJI	14 (1.4%)	4 (1.0%)	10 (1.6%)	0.380
Mean age (years)	66.5 (21-92)	64.4 (21-91)	67.9 (28-92)	0.001
Female gender	714 (69.5%)	220 (53.5%)	494 (80.0%)	<0.001
Duration of surgery (minutes)	108.8 (43-280)	115.6 (43-280)	104.3 (45-235)	<0.001
Co-morbidities				
Obesity (BMI≥30)	363 (35.3%)	105 (25.5%)	258 (41.8%)	<0.001
Diabetes	214 (20.8%)	74 (18.0%)	140 (22.7%)	0.070
Inflammatory Arthritis	35 (3.4%)	13 (3.2%)	22 (3.6%)	0.727
ASA ≥ 3	271 (26.4%)	109 (26.5%)	162 (26.2%)	0.925

PJI Prosthetic Joint Infection, BMI Body Mass Index, ASA American Society of Anesthesiologists.

Table III.B Microorganisms isolated in 25 PJI cases.

Isolated microorganisms	Overall (n=34)
Gram positives	23 (67.6%)
<i>Staphylococcus aureus</i>	14 (41.2%)
MRSA	6 (17.6%)
MSSA	8 (23.5%)
CoN <i>Staphylococci</i>	6 (17.6%)
MR CoNS	5 (14.7%)
MS CoNS	1 (2.9%)
Other Gram Positive	3 (8.8%)
<i>Enterococcus spp.</i>	1 (2.9%)
<i>Streptococcus spp.</i>	1 (2.9%)
<i>Corynebacterium spp.</i>	1 (2.9%)
Gram negative	11 (32.4%)
<i>Enterobacteriaceae</i>	6 (17.6%)
<i>Enterobacter spp.</i>	2 (5.9%)
<i>Escherichia coli</i>	1 (2.9%)
<i>Serratia spp.</i>	1 (2.9%)
<i>Proteus spp.</i>	1 (2.9%)
<i>Providencia spp.</i>	1 (2.9%)
<i>Pseudomonas spp.</i>	3 (8.8%)
<i>Acinetobacter spp.</i>	2 (5.9%)
Polymicrobial*	5 (20.0%)

MR methicillin-resistant; MS methicillin-sensitive; CoN coagulase negative.

* refers to number of polymicrobial PJI cases: specific microorganisms involved are reflected under their respective categories.

Table IV.B PJI rate comparison between different subgroups.

	Non carriers	Treated <i>S. aureus</i> carriers	Untreated <i>S. aureus</i> carriers	<i>P</i> value
	n=800	n=89	n=139	
Overall PJI rate	16 (2.0%)	3 (3.4%)	6 (4.3%)	0.219
<i>S. aureus</i> PJI	9 (1.1%)	2 (2.2%)	3 (2.2%)	0.470

PJI Prosthetic Joint Infection.

Variables associated with PJI in the univariable analysis were ASA score ≥ 3 , longer duration of surgery and the presence of inflammatory arthritis (Table V). Multivariable analysis, performed including variables with a *P* value ≤ 0.2 , substantiates ASA ≥ 3 (OR=3.42, 95% CI=1.51-7.74) and duration of surgery above the 75th percentile (OR=2.74, 95% CI=1.22-6.16) as independent predictors of PJI. A non significant trend towards higher prevalence of *S. aureus* carriers among infected cases was observed. A similar analysis was performed considering the secondary outcome (infections involving *S. aureus* bacteria) and no relevant differences were found compared to the primary outcome measure.

Out of the 14 cases where *S. aureus* was present in PJI, only five were *S. aureus* carriers pre-operatively. Of those five cases, one untreated MSSA carrier ultimately got an MRSA infection.

Table V.B Risk factors for overall prosthetic joint infection.

	No PJI	Overall PJI	Univariable analysis			Multivariable analysis		
			<i>P</i> value	OR	95% CI	<i>P</i> value	OR	95% CI
Mean age (range)	66.4 (21-92)	70.0 (56-85)	0.22	-	-	-	-	-
Female gender	699 (69.7%)	15 (60.0%)	0.30	0.65	(0.27-1.64)	-	-	-
Knee Location	600 (59.8%)	17 (68.0%)	0.41	1.43	(0.58-3.86)	-	-	-
Duration >75th percentile	259 (25.8%)	12 (48.0%)	0.01	2.65	(1.09-6.38)	0.02	2.71	(1.20-6.10)
Co-morbidities								
Obesity (BMI ≥ 30)	351 (35.0%)	12 (48.0%)	0.18	1.71	(0.71-4.12)	0.48	1.35	(0.59-3.12)
Diabetes	206 (20.5%)	8 (32.0%)	0.16	1.82	(0.67-4.53)	0.39	1.50	(0.60-3.73)
Inflammatory Arthritis	32 (3.2%)	3 (12.0%)	0.02	4.14	(0.75-14.84)	0.08	3.25	(0.87-2.14)
ASA ≥ 3	257 (25.6%)	14 (56.0%)	<0.01	3.69	(1.53-9.10)	0.01	3.04	(1.32-7.05)
Hospital Stay < 1 year	219 (21.8%)	9 (36.0%)	0.092	2.01	(0.77-4.91)	0.14	1.90	(0.81-4.44)

Discussion

Prosthetic joint infection is a serious complication. Fortunately, under contemporary surgery aseptic conditions and the use of antibiotic prophylaxis, infection rates have lowered to residual values. Nevertheless, there seems to be a worldwide trend to an increase in the incidence of this complication. Together with the ever-rising number of arthroplasties performed every year, it contributes to the increasing social and economic burden of infection [5;6].

Staphylococcus aureus is a major pathogen in this setting and it has been extensively shown that patients who carry it in their nasal flora are at increased risk for infection in a multitude of clinical scenarios [11]. In a cardiothoracic surgery study, it has been shown that SSI isolates match those found in the patient's nose in a significant proportion of cases suggesting the presence of an endogenous contamination pathway [12]. The association between nasal *S. aureus* carriage and increased risk of SSI has been extensively shown also in orthopedic surgery [10;16-19].

Our cohort's prevalence of *S. aureus* carriers is comparable to previous descriptions in orthopedic populations that range from 20-30% MSSA and 2-4% MRSA carriers [17;18;20-22]. Interestingly, although we are in a setting where MRSA infections are common [7;23], the prevalence of MRSA carrier status was under 1%. It is possible that using more sensitive methods to detect carriers (e.g. polymerase chain reaction) would add to this prevalence but high level carriers are the ones at increased risk for infection and these patients are detected by standard microbiologic culture methods [18].

This highly prevalent and apparently modifiable risk factor has driven the interest on preoperative *S. aureus* carriers screening and treatment protocols to potentially reduce infection rates. Mupirocin is the most frequently studied drug for the eradication of nasal *S. aureus* carriage and its eradication effectiveness over the short term has been convincingly demonstrated [24]. Notwithstanding, Kalmeijer et al. [25] in a double-blind, randomized, placebo-controlled study focusing on the effect of mupirocin nasal ointment in surgical site infections in orthopedic surgery found that it did not result in a significant difference in overall infection rate. Also in the secondary outcomes (rate of SSI due to *S. aureus* and rate of endogenous *S. aureus* infection) no significant differences were found.

A possible explanation for this, is that extranasal colonization must also be addressed to avoid failure in the prevention of SSI and the addition of whole-body chlorhexidine bathing seems to be important in this regard [26;27]. There seems to be enough scientific evidence that a combined nasal mupirocin/chlorhexidine bathing approach, similar to what was used in our study, leads to a significant reduction in overall SSI. In a paramount study by Bode et al. [28], *S. aureus* deep SSI was significantly lower in the treatment (0.9% - 4/504) than in the placebo group (4.4% - 16/413).

Data on orthopedics and arthroplasty surgery specifically is not so convincing. Further analysis of Bode's paper shows only 172 out of 808 surgical patients were orthopedics (no information

regarding how many of those were total joint replacements is available). In this specific subgroup of patients there was no significant difference regarding *S. aureus* infections between treated and untreated carriers. Focusing exclusively on orthopedic trials using the same approach described in the present study (5 days immediately prior to surgery nasal mupirocin/chlorhexidine bathing) two major papers can be found. In 2010, Kim and co-workers [20] enrolled over 7,000 patients before elective surgery. MSSA carriers were 22.6% of the cohort and 4.4% were MRSA carriers. Non carriers showed the lowest infection rate (0.14%) and MRSA carriers showed a significantly higher infection rate (0.97%). MSSA carriers showed a not significant difference (0.19%) compared to non carriers. Comparing the overall infection rate during the study period to an historic control group of over 5,000 patients, the authors found a significant improvement (0.19% vs. 0.45% respectively) thus favoring preoperative *S. aureus* carrier's treatment. Eligible procedures were arthroplasty but also spine and sports medicine and unfortunately no information regarding specifically total joint replacement patients either on the study population or the historical control group was given.

A year later, Rao et al. [22] reported their results of a prospective cohort study of 3,724 total joint arthroplasty patients. A total of 1,285 out of 1,440 patients operated by three participating surgeons were screened. There were 22% MSSA and 3% MRSA carriers. All positive nasal cultures received preoperative treatment and infection rate was 0.0% (0/321). Enrolled patients were compared to a concurrent control group of 2,284 patients operated by non participating surgeons where 19 infections were present. The authors assumed a similar proportion of 25% *S. aureus* carriage among the later group and calculate 571 patients would be culture positive. They found that if all 19 infections had occurred in the nasal carriers, the infection rate would have been 3.3% (19/571) (RR=1.03, 95%CI [1.02-1.05]) thus advocating the value of preoperative treatment. This methodology is debatable as it assumes non carriers in this concurrent control group would account for no infections. A secondary analysis found the overall infection rate in all patients decreased from 20 (2.7%) in 741 historic control patients to 17 (1.2%) in 1440 patients enrolled in the intervention period (OR=2.32, 95%CI [1.21-4.46]). As such, both previous studies major conclusions are drawn by comparing to their respective historical controls which may lead to false conclusions as many other variables may be in play.

The major limitation of our study is that it should be considered underpowered to show a possible small advantage in preoperatively decolonizing *S. aureus* carriers. The fact that *S. aureus* eradication was not confirmed before surgery may also be considered a relevant limitation. No information regarding patient compliance was objectively gathered and local mupirocin resistance data is not available. However, the proposed treatment has been previously shown to be effective [18;24;29]. Another important issue is that practical flaws led to uneven groups of treated and untreated carriers. The author's choice not to perform an intent-to-treat but rather an actual treated vs. untreated analysis is also debatable from a methodological point of view. Also not having the clonal relationship between nasal and infecting strain is a limitation. This limits our ability to make a detailed analysis on the origin (endogenous or exogenous) of every *S. aureus* PJI.

All things considered, although there seems to be enough evidence that nasal carriage of *S. aureus* at the time of surgery is a risk factor for SSI also in orthopedic surgery, there is no definitive evidence regarding total joint replacement specifically [30;31]. A major multicenter paper focusing mainly on arthroplasties and including almost 4,000 patients found that in most cases of *S. aureus* SSI, either an endogenous origin could not be demonstrated or preoperative nasal colonization retrieved a strain that was different from the infecting pathogen [16]. This lack of causal relation between nasal *S. aureus* and PJI pathogen is similar to our finding that at least 10 out of 14 cases of *S. aureus* PJI may have had an exogenous source. On the other hand a recent multicenter study performed in American hospitals involving over 30,000 hip or knee arthroplasties found a modest, but statistically significant decrease in *S. aureus* infections among hip or knee arthroplasties after an intervention very similar to ours (difference per 10,000 operations, -17 [95% CI, -39 to 0]; RR, 0.48 [95% CI, 0.29 to 0.80])[32]. Nevertheless, patients during the intervention period were younger, had lower Charlson comorbidity index scores, and were less likely to have a history of MRSA carriage (all of which known risk factors for infection) than those during the pre-intervention period. Furthermore, and perhaps the major limitation of this finding is that patients were followed up for no more than 90 days after their operations which is admittedly a short period for PJI.

As such, the authors believe that currently available evidence is not enough to definitively recommend *S. aureus* screening and decolonization as an effective strategy to prevent infection in total joint arthroplasty. A necessarily huge trial addressing the real worth of *S. aureus* screening and decolonization as well as its cost-effectiveness in the particular field of total joint arthroplasty is still missing. Assuming *S. aureus* carriage and PJI rates similar to the present study, over 10,000 patients would have to be screened and followed for up to one year.

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Diagnostic Accuracy of Combined ^{99m}Tc -Sulesomab and ^{99m}Tc -nanocolloids Bone Marrow Imaging in Detecting Prosthetic Joint Infection

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Abstract

Objective(s): Autologous labeled leukocytes combined with sulfur colloid bone marrow scan is the current nuclear medicine gold standard for the diagnosis of prosthetic joint infection. The goal of this study is to assess the diagnostic accuracy of a new nuclear medicine modality for detecting infection in this context.

Methods: Twenty-seven suspicious hip and knee arthroplasties were enrolled prospectively and underwent nuclear medicine testing using ^{99m}Tc -Sulesomab and ^{99m}Tc -nanocolloids sequentially. These results were then crossed with final diagnosis to determine the test(s) diagnostic accuracy.

Results: Isolated ^{99m}Tc -Sulesomab scan shows 100% sensitivity (0.40-1) and negative predictive value (0.31-1) but only 20% specificity (0.05-0.48). Combining it with ^{99m}Tc -nanocolloids bone marrow scan increases specificity (0.75-1) and positive predictive value (0.40-1) to 100%. Furthermore, the combined test has less equivocal readings and higher inter-reader agreement: kappa test value 0.59 vs. 0.44.

Conclusions: The results support the hypothesis that these technically simpler and ready-to-use products may be an alternative to autologous labeled leukocytes/sulfur colloid marrow scan.

Keywords

Prosthetic Joint Infection; Diagnosis; Labeled leucocytes; Bone marrow imaging.

Introduction

Periprosthetic infection is probably the most devastating complication of total joint arthroplasty. Despite recent advances in prophylaxis its prevalence is on the rise [1]. Treatment of an infected implant is quite different from treatment of an aseptic loosening and it is thus crucial to differentiate between them.

The diagnosis of prosthetic joint infection poses numerous challenges particularly when it presents as a low-grade chronic affliction with no signs and symptoms other than unexplained pain or stiffness [2]. There is no diagnostic test that is 100% accurate in this setting. Currently, isolation of organisms and histological analysis from intraoperative samples seem to be the best way to definitively confirm the diagnosis of infection [3]. However, preoperative diagnosis is forced to rely on clinical suspicion as well as careful scrutiny of laboratory and imaging modalities.

Combined indium [^{111}In]-labeled autologous leukocyte and complementary technetium [$^{99\text{m}}\text{Tc}$]-sulfur colloid bone marrow imaging, with an accuracy of 95% or greater, is the current imaging modality of choice for diagnosing prosthetic joint infection[4]. Although this technique is reliable, in vitro leukocyte labeling raises technical difficulties that limit its widespread use[5] and sulfur colloid is increasingly difficult to obtain. Therefore, valid alternatives are needed. The study hypothesis is that autologous leukocyte labeling and sulfur colloid can successfully be replaced for $^{99\text{m}}\text{Tc}$ -Sulesomab (antigranulocyte antibody) and $^{99\text{m}}\text{Tc}$ -colloidal rhenium sulphide (nanocolloids) respectively.

The aim of the present study is to assess the diagnostic accuracy of $^{99\text{m}}\text{Tc}$ -Sulesomab alone and in combination with $^{99\text{m}}\text{Tc}$ -nanocolloids bone marrow imaging in the diagnosis of infection in painful total joint arthroplasties. A secondary goal was to estimate inter-reader concordance of both interpretations.

Patients and Methods

Participants

This study prospectively included patients with total hip or knee arthroplasty suspected of having deep infection. Patients were elected for nuclear medicine testing for having joint pain or unexplained stiffness and abnormal erythrocyte sedimentation rate (ESR) >22.5mm/h or C-reactive protein (CRP) >13.5mg/L[6]. Final decision of whether or not to proceed with revision surgery was based on clinical, laboratory as well as nuclear medicine results. Data collection was planned in advance and started at the time of nuclear medicine testing forward.

In the absence of a true gold standard for the definitive diagnosis of prosthetic joint infection the following criteria were used: at least two intraoperative positive cultures for the same organism(s) or positive intraoperative histological findings (i.e. at least five neutrophils in each of three 400x high-power microscopic fields[3]) even in the absence of culture growth. Negative intraoperative findings or instead favorable clinical and laboratory follow-up of at least one year in non-operated patients was used as criteria for absence of infection.

Imaging Protocol

Nuclear medicine study protocol starts with a 20 mCi ^{99m}Tc-Sulesomab (LeukoScan®, Immunomedics Inc., USA) intravenous injection. Images are acquired at two and four hours timeline. If this scan is negative no further test is performed (figure 1). If this scan shows any periprosthetic activity, the bone marrow scan is performed after intravenous injection of 20 mCi of colloidal rhenium sulphide (Nanocis®, Electra-Box Pharma, Finland), with a minimum 72 hours interval to avoid confounding persistent ^{99m}Tc-Sulesomab activity. These images are acquired for five minutes at 30, 60 and 120 minutes timeline. Both scans are acquired in a double detector gamma-chamber equipped with high resolution collimators in a 256x256 matrix.

Image Interpretation

The rationale behind combined leukocyte/bone marrow scan is the fact that both leukocyte and nanocolloids accumulate in marrow regardless of its location, whereas leukocyte accumulate in infection but nanocolloids does not. The study is positive for infection when there is activity on the sulesomab scan without corresponding activity on the bone marrow scan (i.e. the images are spatially incongruent) as shown in figure 2. Any other pattern is negative for infection (figures 1 and 3).

Test reading was done by the nuclear medicine doctor (IA) and the orthopedic surgeon (RS) together using the four and two hour images of the sulesomab and nanocolloids scan respectively. The interpretation was done accessing clinical and laboratory information but (naturally) there was no previous knowledge of definitive diagnosis criteria. In order to appreciate inter-observer concordance three different observers (RS, IA and FF) were retrospectively asked to blindly review each scan and classify them as positive, negative or equivocal.

Statistical Analysis

Sensitivity and specificity as well as negative and positive predictive value of both tests were determined using the prospective nuclear medicine and orthopedic surgeon collective interpretations made during the study period. Blinded retrospective interpretations were used to estimate isolated Sulesomab and Sulesomab/Nanocolloids scans inter-reader agreement by applying the kappa test[7].



Fig. 1b Right total hip replacement with obvious osteolysis around the stem and negative sulesomab scan excluding



Fig. 2b Left total knee replacement showing increased uptake in the sulesomab scan in two different anatomic areas with no correspondence in the bone marrow scan in the lateral tibial area (red arrows) indicative of infection.



Fig. 3b Right total knee replacement showing increased uptake in the sulesomab scan with a congruent pattern in the bone marrow scan (green arrows) pointing to aseptic loosening

Results

Twenty-seven patients were recruited between February/2008 and February/2010. There were 25 total knee and two total hip replacements. Three of them were men and 24 women with an average age of 65 years old. Mean time from index surgery was 29.7 months. Laboratory results revealed an average ESR of 29.1 [4-81] and CRP of 18.51 [1.7-48.6]. Nineteen patients (2 hips and 17 knees) were included in the diagnostic accuracy analysis.

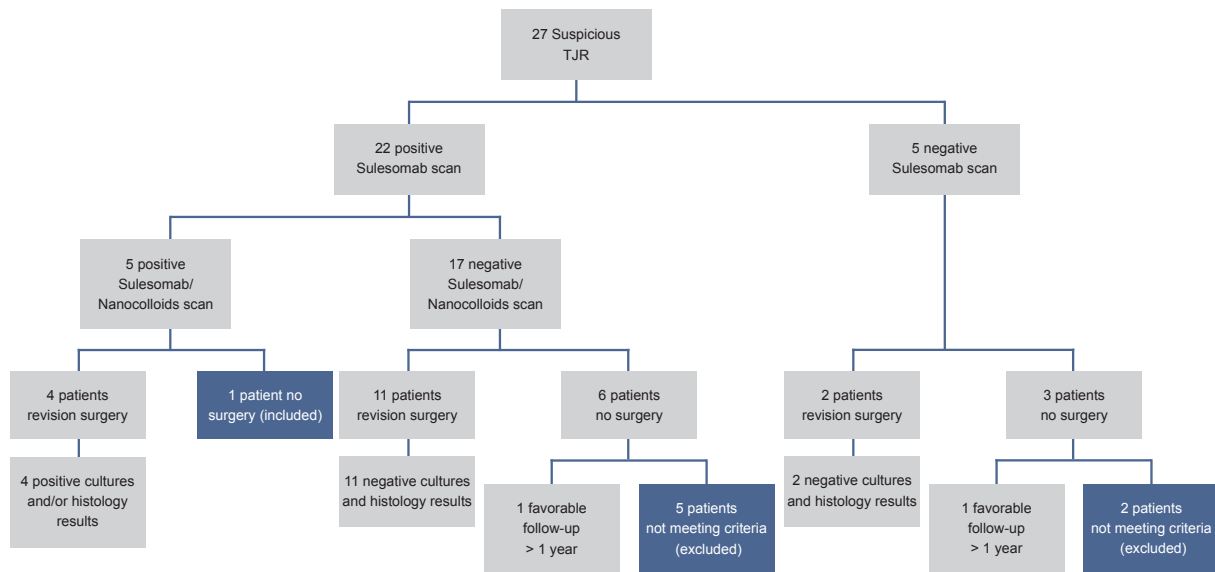


Fig. 4b Flow diagram of every suspicious total joint replacements entered in the study and final outcome or reasons for exclusion.

Methicillin-resistant *S. epidermidis* in two cases, methicillin-resistant and methicillin-sensitive *S. aureus* in one case each were the bacteria isolated in the four positive cases that underwent surgery. The negative cases were classified as aseptic loosening since no microorganism was isolated and histological findings were negative. One positive and seven negative results were excluded for not meeting the criteria for definitive diagnosis (figure 4). The positive case had severe medical conditions that ill-advise revision surgery. Out of the five negative sulesomab scan cases, only two underwent revision surgery. Two of the other three were excluded for not meeting the clinical and laboratory follow-up criteria for negativity. The same was true for five of the six negative combined sulesomab/bone marrow scan that did not undergo surgery. The patients not operated on constitute a heterogeneous group of patients whose symptoms improved or were not serious enough to require revision surgery once infection was ruled out. As such no final diagnosis can be reached.

Table I shows a cross-tabulation of the reference diagnosis criteria with the isolated ^{99m}Tc -Sulesomab scan and combined ^{99m}Tc -Sulesomab/ ^{99m}Tc -nanocolloids bone marrow scan results. Isolated ^{99m}Tc -Sulesomab scan sensitivity was 100% as was the negative predictive value. Combined ^{99m}Tc -Sulesomab/ ^{99m}Tc -nanocolloids bone marrow scan showed 100% specificity and positive predictive value. Table II displays diagnostic accuracy of both tests.

Table I.A Scan results crossed with definitive diagnosis of both tests.

		Infection		
		Present	Absent	Total
Isolated Sulesomab	Positive	4	12	16
	Negative	0	3	3
	Total	4	15	19
		Present	Absent	Total
Sulesomab/Nanocolloids	Positive	4	0	4
	Negative	0	15	15
	Total	4	15	19

Table II.A Diagnostic accuracy results (95% confidence interval) of both tests.

	Sensitivity	Specificity	NPP	PPP
Isolated Sulesomab	100% (0.40-1)	20% (0.05-0.48)	100% (0.31-1)	25% (0.08-0.53)
Sulesomab/Nanocolloids	100% (0.40-1)	100% (0.75-1)	100% (0.75-1)	100% (0.40-1)

NPP negative predictive value; PPP positive predictive value.

The inter-reader agreement as estimated by the kappa test can be seen in table III. In the isolated sulesomab scan it averaged 0.44 for the three pairs of readers and in the combined sulesomab/marrow scan it averaged 0.59.

Table III.A A Kappa test results (95% confidence interval) for the three pairs of readers.

	Pair A-B	Pair A-C	Pair B-C
Isolated Sulesomab	0.50 (0.12-0.88)	0.52 (0.02-1)	0.31 (0-0.77)
Sulesomab/Nanocolloids	0.55 (0.09-1)	0.72 (0.36-1)	0.50 (0-1)

The number of equivocal readings was lower in the combined test as can be seen in table IV.

Table IV.A Blinded interpretation of isolated and combined scans by the three readers.

	Observer A	Observer B	Observer C
Isolated Sulesomab			
Positive	14	11	17
Equivocal	2	6	1
Negative	3	2	1
Sulesomab/Nanocolloids			
Positive	4	2	3
Equivocal	1	1	1
Negative	14	16	15

Discussion

Diagnosing a chronic low grade prosthetic joint infection and differentiating it from aseptic loosening is a crucial and often complex job. Currently there is no preoperative diagnostic modality that offers perfect sensitivity or specificity and therefore the orthopedic surgeon is forced to base his decision on the collective interpretation of different test modalities. Nuclear medicine studies are the imaging modality of choice in this context and combined ^{111}In -labeled leukocyte/ $^{99\text{m}}\text{Tc}$ -sulfur colloid marrow is the gold standard with a diagnostic accuracy of more than 90% for both hip and knee[4, 8-10]. Despite reliable results, autologous leukocyte labeling and imaging is a laborious and technically demanding procedure[11]. Its inherent complexity limits its widespread use as not all centers have the means to employ it. Sulfur colloid is also an increasingly difficult product to obtain in Europe nowadays and therefore there is a need to study valid alternatives.

Sulesomab is an antigranulocyte antibody (Fab fragment of the immunoglobulin G antibody against the glycoprotein cross-reactive antigen-90) and as such accumulates not only in sites of increased concentration of granulocytes in the inflamed tissue surrounding infected prosthesis but also in the bone marrow as a result of phagocytosis by the reticuloendothelial cells[12]. Nanocolloids are small particles that, after intravenous injection, are phagocytosed by macrophages and distributed throughout the body in the reticuloendothelial system thus targeting bone marrow[13]. Both products are available as simple ready-to-use kits. The present study hypothesis is that they can effectively replace autologous labeled leukocytes and sulfur colloid bone marrow scan in the diagnosis of infected total joint replacements.

Antigranulocyte scintigraphy with monoclonal antibodies (especially sulesomab) is increasingly being used in the diagnostic evaluation of suspected infection of prosthetic joint replacements. Sulesomab scan sensitivity and specificity in this context is around 80%[12]. Sensitivity is highly related with the criteria used for image interpretation. Interpreting even slight $^{99\text{m}}\text{Tc}$ -Sulesomab activity as positive raises the test sensitivity simultaneously lowering its specificity[14]. Other authors have shown that it is possible to increase specificity of the isolated sulesomab scan by implementing a dual-time acquisition protocol consisting of early four hour and delayed 20-24 hour imaging[15, 16]. Since this test was used as an initial screening in the present study, the authors chose to interpret any periprosthetic activity in the early four-hour scan as positive. This fact probably explains the high sensitivity and negative predictive value (and conversely very low specificity) found. The explanation for the isolated sulesomab scan lack of specificity lays on the fact that these antibodies also target reticuloendothelial cells present in bone marrow. Hence, its increased uptake around orthopedic implants may be due to the presence of localized expansion of hematopoietically active marrow and not translate real periprosthetic inflammation/infection[12]. Exactly why hematopoietically active marrow develops around joint prostheses is unknown[5]. The goal of adding a bone marrow scan is to compensate for this phenomenon. Although nanocolloids have been used isolated for the diagnosis of orthopedic infections [17], we believe it should be used as an alternative to conventional sulfur colloid scintigraphy since they target the same bone marrow compartment [13]. Nanocolloids will accumulate in the reticuloendothelial cells present in the normal hematopoietically active marrow

but not in periprosthetic osteomyelitis. Infection and subsequent bone metabolism changes destroy bone marrow phagocytes consequently inhibiting nanocolloids uptake [5]. This represents the base of the combined scan interpretation criteria. Any activity in the sulesomab scans without corresponding activity in the marrow scans will constitute a positive test for infection. Our results suggest both sulesomab and nanocolloids are valid surrogates for autologous labeled leucocytes and sulfur colloid respectively. The combined scan reached a very good diagnostic accuracy.

When assessing the accuracy of a diagnostic test it is important to establish its reliability as it respects to agreement between observers. The results demonstrate that combined sulesomab/nanocolloids scan has a lower number of equivocal interpretations than isolated sulesomab (respectively 3 and 9 out of independent 57 readings each). The inter-reader agreement is also higher (average 0.59 vs. 0.44) when interpreting the combined scan. These findings suggest the combined scan is easier to read and more reproducible.

The relatively low number of patients recruited is one of the major limitations of this study as it precludes more statistically powerful findings. The fact that these are the first such cases performed at our institution also hampers a more concordant test reading as they reflect the initial learning curve of the authors. Lastly the criteria we used to define prosthetic joint infection diagnosis (intraoperative microbiological and histological testing) is widely accepted in the orthopedic community but even these tests have been demonstrated to fail in establishing a correct diagnosis[3, 18]. Other tests such as preoperative synovial fluid differential cell count and culture or sonication of the removed implant can be of assistance but their discussion is beyond the scope of this paper[19, 20]. Notwithstanding, this study suggests that combined sulesomab/nanocolloids scan can be a very helpful tool in diagnosing prosthetic joint infection in selected cases and considering clinical and laboratory data together. An isolated negative sulesomab scan is helpful in excluding infection. The studied methodology seems a valid alternative to labelled leucocytes/sulphur colloid bone marrow imaging although it needs validation at a larger scale. The fact that it is technically easier to perform might possibly allow a more widespread use.

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Improving Synovial Fluid Accuracy for the Diagnosis of Prosthetic Joint Infection with Simple and Inexpensive Biomarkers: C-reactive Protein and Adenosine Deaminase

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Abstract

Aims: The aims of this study were to increase the diagnostic accuracy of the analysis of synovial fluid in the differentiation of prosthetic joint infection (PJI) by the addition of inexpensive biomarkers such as the levels of C-reactive protein (CRP), adenosine deaminase (ADA), alpha-2-macroglobulin (α 2M) and procalcitonin.

Patients and Methods: Between January 2013 and December 2015, synovial fluid and removed implants were requested from 143 revision total joint arthroplasties. A total of 55 patients met inclusion criteria of the receipt of sufficient synovial fluid, tissue samples and removed implants for analysis.

The diagnosis of PJI followed the definition from a recent International Consensus Meeting to create two groups of patients; septic and aseptic. Using receiver operating characteristic curves we determined the cutoff values and diagnostic accuracy for each marker.

Results: There were 23 PJIs and 32 patients with aseptic loosening. The levels of total leucocyte count, proportion of polymorphonuclear leucocytes (PMNs), CRP, ADA and α 2M in the synovial fluid were all significantly higher in those with a PJI than in those with aseptic loosening. The levels of procalcitonin were comparable in the two groups.

Cutoff values for the optimal performance in the diagnosis of infection were: total leucocyte count > 1463 cells/ μ L (sensitivity (Sens) = 100%, specificity (Spec) = 71.9%, positive predictive value (PPV) = 71.9%, negative predictive value (NPV) = 100%); proportion of PMNs > 81% (Sens = 78.3%, Spec = 75.0%, PPV = 69.2%, NPV = 82.8%); CRP > 6.7mg/L (Sens = 78.3%, Spec = 93.8%, PPV = 90.0%, NPV = 85.7%); ADA > 61U/L (Sens = 78.3%, Spec = 96.9%, PPV = 94.7%, NPV = 86.1%) and α 2M > 958 mg/L (Sens = 47.8%, Spec = 96.9%, PPV = 91.7%, NPV = 72.1%).

The addition of a raised level of CRP or ADA to the total leukocyte count increased the specificity: total leukocyte count > 1463cells/ μ L and CRP > 6.7mg/L (Sens = 78.3%, Spec = 100%, PPV = 100%, NPV = 86.5%) or with ADA > 61U/L (Sens = 78.3%, Spec = 96.9%, PPV = 94.7%, NPV = 86.1%).

Conclusion: The total leucocyte count in the synovial fluid offers great negative predictive value in the diagnosis of PJI and the addition of more specific markers such as CRP and ADA improves the positive predictive value. Thus the addition of simple and inexpensive markers to the measurement of the leucocyte count in the synovial fluid may reduce the number of equivocal results which demand more expensive investigation.

Introduction

A common and severe complication of total joint arthroplasty is periprosthetic joint infection (PJI).¹ There is however no single, accurate test which may be used to make this diagnosis. A recent International Consensus Meeting agreed on diagnostic criteria, but stated that in patients with less virulent organisms, infection could exist even with negative criteria.² Definitive diagnosis currently relies on a combination of different markers in the serum and synovial fluid and, most of all, adequate intra- operative sampling for microbiological testing.²⁻⁵ The preoperative work-up should include a history and physical examination, then blood tests including erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP), as a preoperative diagnosis of PJI can determine the operative plan for the patient.

If there is a high probability of infection, aspiration of the joint is mandatory.^{2,6} Synovial fluid is then available for tests including microbiological study and leucocyte count. Microbiological examination is lengthy and offers a significant proportion of false-negatives.⁷ The leucocyte count is also an imperfect marker as several different thresholds have been proposed in the literature and the measurement may be influenced by the presence of an inflammatory arthritis or the recent use of antibiotics.⁸⁻¹⁰ These diagnostic limitations have driven the search for the more accurate interpretation of synovial fluid and the development of alternative biomarkers, some of which are prohibitively expensive.¹¹⁻¹³

The hypothesis of this study was that the diagnostic accuracy of pre-operative aspiration of a potentially infected joint could be increased with more simple, readily available and inexpensive synovial fluid biomarkers. We compared the concentrations of CRP, adenosine deaminase (ADA), alpha-2-macroglobulin (α 2M) and procalcitonin in the synovial fluid between infected and aseptic cases, and analysed the performance and optimal cutoff values of these markers. We investigated whether the addition of these tests to the standard synovial fluid leucocyte count may improve the pre-operative diagnostic performance for PJI.

Patients and Methods

The inclusion criteria for this prospective study were potentially all patients undergoing revision total hip (THA) or knee (TKA) arthroplasty (either single-stage for presumed aseptic or first-stage for known infected prosthesis) at our institution between January 2013 and December 2015. All surgeons who undertake arthroplasties were asked to collect intra-operative synovial fluid aspirates and at least four periprosthetic tissue samples from each patient for analysis of biomarkers and microbiological testing. Removed implants were sent for sonication and subsequent microbiological study. If sufficient synovial fluid was available, it was also sent for measurement of the standard leucocyte and differential counts. We excluded those cases with insufficient synovial fluid or tissue samples, or those whose implants were not sent for sonication. We also excluded patients who developed a PJI within four weeks of the initial procedure, and those with a haematogenous infection within four weeks of the development of symptoms, as these were considered to be acute presentations.

We recorded the pre-operative diagnosis (septic or aseptic, hip or knee), gender, age, joint, history of comorbid inflammatory conditions, pre-operative antibiotic treatment (not including the prophylactic peri-operative dose) and the microorganisms which were isolated. When available, the pre-operative ESR and CRP were also documented.

Patients who met the inclusion criteria were prospectively evaluated, and the definitive diagnosis was classified as periprosthetic infection or aseptic loosening on the basis of the recent International Consensus Meeting definition of PJI (Table I).² Post-operatively, tissue cultures were incubated for up to fourteen days and sonication of removed implants followed a standardised, previously validated protocol.³

Table IV.A International Consensus Meeting Definition of Periprosthetic Joint Infection

1) Two positive periprosthetic cultures with phenotypically identical organisms, or
2) A sinus tract communicating with the joint, or
3) Having three of the following minor criteria:
Elevated serum CRP and ESR
Elevated synovial fluid WBC count OR ++ change on leukocyte esterase test strip
Elevated synovial fluid PMN percentage
A single positive culture
Positive histological analysis of periprosthetic tissue

CRP C-reactive protein, **ESR** erythrocyte sedimentation rate, **WBC** white blood cell; **PMN** polymorphonuclear neutrophil.

Synovial fluid samples were collected intra-operatively. A plain tube was used for biochemical studies (CRP, ADA, α 2M and procalcitonin) and a tube with tri-potassium salts of ethylenediaminetetraacetic acid was used for cytological study. When insufficient synovial fluid was available for all tests, the analysis of biochemical biomarkers was favoured.

Cytological examination of the synovial fluid was performed immediately on reception of the fluid in the laboratory. The total cell count was measured with a haemocytometer (Neubauer improved, BRAND GMBH + CO KG, Wertheim, Germany) and the differential count with a Leishman stained smear obtained by cytocentrifugation (Shandon Cytospin 3, Thermo Electron Corp., Waltham, Massachusetts). In order to compensate for possible contamination of the synovial fluid with blood, both total white blood cell and polymorphonuclear neutrophil (PMN) counts were adjusted for by the amount of blood present in the fluid using a previously validated formula:
$$\text{WBC}_{\text{adjusted}} = \text{WBC}_{\text{observed}} - [(\text{WBC}_{\text{blood}} \times \text{RBC}_{\text{fluid}} / \text{RBC}_{\text{blood}})]_{\text{predicted}}$$

In order to decrease the viscosity of the synovial fluid for biochemical analysis, it was diluted in a proportion of 9:1 with a solution of hyaluronidase (0.025 g/L in a phosphate buffer). The final results were obtained following multiplication by the dilution factor.

The level of CRP in the synovial fluid was measured using a high sensitivity immunonephelometric assay (hsCRP, Siemens Healthcare Diagnostics, Marburg, Germany) on a Dimension Vista 500 AutoAnalyzer (Siemens Healthcare Diagnostics) that is able to offer a 0.16 mg/L detection limit. ADA was measured using an enzymatic colorimetric assay (ITC Diagnostics, IZASA, Barcelona, Spain) adapted to the AutoAnalyzer Cobas Integra 800 (Roche Diagnostics, Mannheim, Germany). The level of α 2M in the synovial fluid was measured using an immuno-nephelometric assay (A2MAC, Siemens Healthcare Diagnostics) on a Dimension Vista 500 AutoAnalyzer (Siemens Healthcare Diagnostics). The level of procalcitonin was measured using an electroluminescence immunoassay (Elecsys BRAHMS PCT, Roche Diagnostics) on a Cobas e411 AutoAnalyzer (Roche Diagnostics) that is able to offer a 0.02 ng/mL detection limit.

The study had institutional ethical approval and all patients provided informed consent.

Statistical Analysis

Categorical variables are expressed as counts (percentage) and frequency distributions were compared with the chi-squared test. For small cell counts, Fisher's exact test was used. Continuous variables were expressed as mean values (interquartile range). Differences were tested with the Mann-Whitney U test for non-normally distributed variables.

Optimal cutoff values were determined using receiver operating characteristic (ROC) curve analysis. These curves were generated and the areas under the curve were compared to determine the most appropriate cutoff. More cutoff values were determined using the Youden's index method,¹⁵ which maximises the difference between sensitivity and specificity. Specificity and predictive values of the tests were estimated. Using selected cutoff values, multiple combinations were created, with the aim of improving the ability to confirm or exclude the diagnosis of PJI. The statistical tests were two-tailed and we considered p-values of < 0.05 as statistically significant. Data were analysed using the software Stata (version 14.0; StataCorp, College Station, Texas).

Results

A total of 143 revision THAs or TKAs were performed during the study period. We excluded 88 patients in whom synovial fluid was either not collected or was insufficient, or where microbiological sampling was insufficient with less than four tissue samples being obtained or an implant not being received for sonication. A total of 55 patients met the inclusion criteria; 21 with a pre-operative assumed diagnosis of PJI and 34 with aseptic loosening.

In two patients with a preoperative diagnosis of aseptic failure, the diagnosis was ultimately re-classified as infected, since two or more phenotypically identical organisms were isolated from intra-operative samples (one with two positive tissue cultures and one with one positive tissue culture and positive sonication). Micro-organisms were isolated in a single sample in five other patients but they did not meet other minor criteria for infection. The demographic and clinical information of the patients (including unadjusted leukocyte and differential counts) are shown in Table II.

Table II.C Demographic and clinical information according to the presence of infection.

	Infection cases	Aseptic failures	p value
	n=23	n=32	
Age*	68.0 (61-76)	65.3 (62-71)	0.154
Female gender	14 (61%)	25 (78%)	0.231
Hip:Knee ratio	8:15	7:25	0.201
History of inflammatory conditions	0 (0%)	3 (9.4%)	0.257
Previous antibiotic therapy	3 (13%)	0 (0%)	0.068
ESR* (mm/h)	60.2 (36-82) [†]	27.5 (11-25) [‡]	0.0001
CRP* (mg/L)	65.1 (18-98) [†]	11.8 (2-9) [‡]	<0.0001
Total leukocyte count* (cells/ μ L)	33,790 (14,000-60,000) [§]	384 (41-666) [‡]	<0.0001
Proportion of PMN*	84% (80-96) [§]	30% (11-43) [‡]	<0.0001

ESR Erythrocyte sedimentation rate; CRP C-reactive protein; PMN Polymorphonuclear neutrophils.

* expressed as mean (interquartile range); [†] available in 19 cases; [§] available in 17 cases; [‡] available in 24 cases

Synovial fluid final results (including leukocyte and differential counts adjusted for blood in the fluid) are expressed in Table III. It is noteworthy that in those with a PJI there was a significant increase in the total leukocyte count, the percentage of PMNs and the concentrations of CRP, ADA and α 2M in the synovial fluid compared with aseptic cases. The levels of procalcitonin were comparable in the two groups.

Table III.C Synovial fluid analysis results according to the presence of infection*.

	Infection cases	Aseptic revisions	p value
	n=23	n=32	
Adjusted Total leukocyte count (cells/ μ L)	34,443 (9,532-61,368) [§]	347 (37-544) [¶]	<0.0001
Adjusted proportion of PMN	85% (80-97) [§]	28% (10-42) [¶]	<0.0001
C-reactive protein (mg/L)	31.7 (7.96 -24.72)	1.02 (0.33- 0.82)	<0.0001
Adenosine Deaminase (U/L)	126.1 (67-118)	35.7 (19-42)	<0.0001
α -2-Macroglobulin (mg/L)	895.3 (124-1332)	365.0 (127-505)	0.009
Procalcitonin (ng/mL)	0.050 (0.022 -0.060)	0.034 (0.022 – 0.041)	0.650

*expressed as mean (interquartile range); [¶] Mann-Whitney test; [§] available in 17 cases; [¶] available in 24 cases; **PMN** polymorphonuclear neutrophils.

ROC curves obtained for each parameter are shown in Figure 1. and optimised threshold values in Table IV. In some instances, two different cutoff values were found with different characteristics but a similar combined diagnostic accuracy. Regarding the proportion of PMN, we found the optimal cutoff value to be around 78% to 81%, but it is also noteworthy that the 65% cutoff for the proportion of PMNs, commonly described in the literature,⁹ performs almost as well as the proposed values.

A search for synergic combined interpretation was made (Table V), considering associations where either one or other of the markers were positive, to increase the sensitivity, or alternatively, where both markers were positive, to increase specificity. A total leucocyte count of > 1463 cell/ μ L had a 100% negative predictive value and no other marker was able to increase its sensitivity. A close alternative was the association of a PMN proportion of > 81% with either CRP > 6.7 mg/L or ADA > 61 U/L, which both also exhibited a high negative predictive value. It was possible to increase the positive predictive value of the testing of synovial fluid greatly when combining the differential leucocyte count and other parameters by choosing more specific cutoff values, especially CRP > 6.7 mg/L and ADA > 61 U/L.

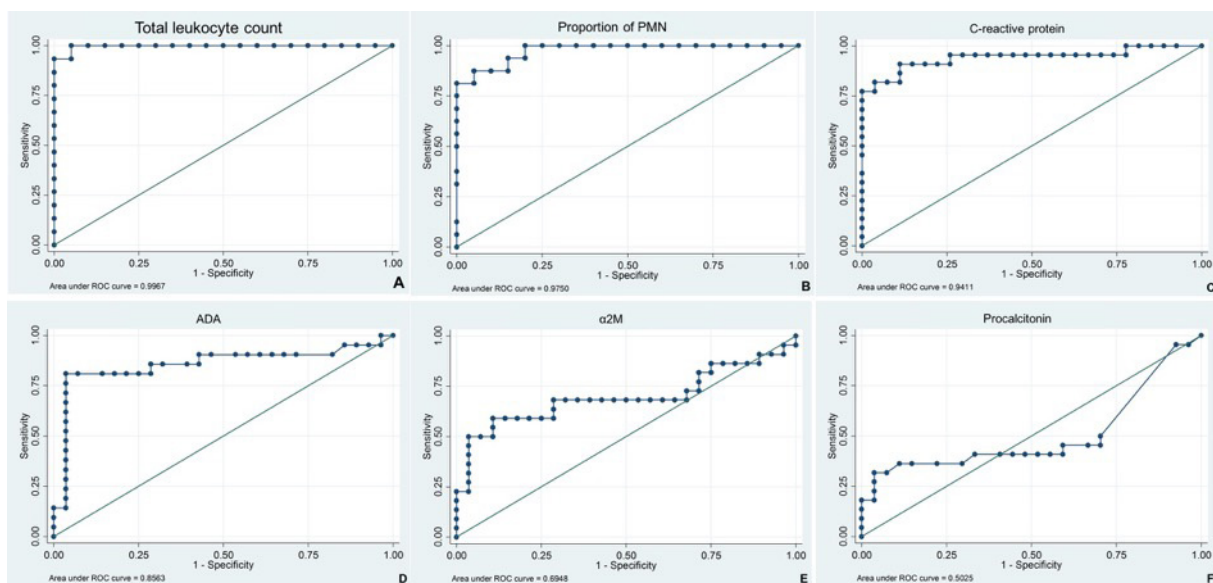


Fig 1C Graphs showing a) receiver operating characteristic (ROC) curve and area under curve (AUC) for total leukocyte count (area under ROC curve = 0.9967); b) ROC curve and AUC for proportion of polymorphonuclear leucocytes (area under ROC curve = 0.9750); c) ROC curve and AUC for C-reactive protein (area under ROC curve = 0.9411); d) ROC curve and AUC for adenosine deaminase (area under ROC curve = 0.8563); e) ROC curve and AUC for alpha-2-macroglobulin (area under ROC curve = 0.6948); f) ROC curve and AUC for procalcitonin (area under ROC curve = 0.5025).

Table IV.C Proposed ROC cutoff values with ideal performance for each test.

	Proposed cutoff(s)	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value
Adjusted Total leukocyte count (cells/μL)	1,463	100%	71.9%	71.9%	100%
	2,064	91.3%	75%	72.4%	85.3%
Adjusted proportion of PMN	78%	87.0%	71.9%	69.0%	88.5%
	81%	78.3%	75.0%	69.2%	82.8%
C-reactive protein (mg/L)	1.6	91.3%	87.5%	84.0%	93.3%
	6.7	78.3%	93.8%	90.0%	85.7%
	8.0	73.9%	96.9%	94.4%	83.8%
Adenosine Deaminase (U/L)	61	78.3%	96.9%	94.7%	86.1%
α-2-Macroglobulin (mg/L)	810	60.9%	90.6%	82.4%	76.3%
	958	47.8%	96.9%	91.7%	72.1%

Table V.C Diagnostic accuracy of selected test(s) values and respective combinations.

	Sensitivity (95%CI)	Specificity (95%CI)	Positive Predictive Value (95%CI)	Negative Predictive Value (95%CI)
One of the test(s) positive				
Leukocyte count > 1,463 or CRP > 6.7 mg/L	100.0% (100.0 to 100.0)	65.6% (53.1 to 78.2)	67.6% (55.3 to 80.0)	100.0% (100.0 to 100.0)
Leukocyte count > 1,463 or ADA > 61	100.0% (100.0 to 100.0)	71.9% (60.0 to 83.8)	71.9% (60.0 to 83.8)	100.0% (100.0 to 100.0)
PMN> 81% or CRP > 6.7 mg/L	95.6% (90.3 to 100.0)	68.8% (56.5 to 81.0)	68.8% (56.5 to 81.0)	95.6% (90.3 to 100.0)
PMN> 81% or ADA > 61 U/L	91.3% (83.9 to 98.8)	75.0% (63.6 to 86.4)	72.4% (60.6 to 84.2)	92.3% (85.3 to 99.4)
Both test(s) positive				
Leukocyte count > 1,463 and PMN> 81%	78.3% (67.4 to 89.2)	75.0% (63.6 to 86.4)	69.2% (57.0 to 81.4)	82.8% (72.8 to 92.7)
Leukocyte count > 1,463 and CRP > 6.7 mg/L	78.3% (67.4 to 89.2)	100.0% (100.0 to 100.0)	100.0% (100.0 to 100.0)	86.5% (77.4 to 95.5)
Leukocyte count > 1,463 and ADA > 61 U/L	78.3% (67.4 to 89.2)	96.9% (92.3 to 100.0)	94.7% (88.8 to 100.0)	86.1% (77.0 to 95.2)
PMN> 81% and CRP > 6.7 mg/L	60.9% (48.0 to 73.8)	100.0% (100.0 to 100.0)	100.0% (100.0 to 100.0)	78.0% (67.1 to 89.0)
PMN> 81% and ADA > 61 U/L	65.2% (52.6 to 77.8)	96.9% (92.3 to 100.0)	93.8% (87.3 to 100.0)	79.5% (68.8 to 90.2)

Discussion

Several different tests can be performed on synovial fluid in the pursuit of a diagnosis of PJI. Microbiological culture is the only test that can identify the pathogen, but it has limited diagnostic accuracy^{16,17} and takes several days to produce a result. Leucocyte esterase reagent strips are readily available and can be informative. A normal result practically excludes infection, whilst a bluntly positive test is suggestive of infection.¹⁸⁻²⁰ The results are equivocal in many patients, either because of blood and debris in the fluid which make the reagent strip unreadable, or because of an intermediate result.²¹

In recent years, the total leucocyte and differential counts have formed the basis of the analysis of synovial fluid, with sensitivity and specificity for PJI around or > 90%. Nevertheless, proposed thresholds vary significantly between different authors, and the counts may be influenced by other factors especially the recent use of antibiotics.⁸⁻¹⁰ In order to overcome these limitations, several different synovial fluid markers have been investigated. They can be divided in two categories: cytokines, and markers with antimicrobial functions, such as synovial CRP and α -defensin.²² Of the cytokines, interleukin (IL)-6 is probably the most studied,^{12,23} but this requires complex and costly laboratory processing which is not widely available. To date, only the α -defensin test has been made commercially available as a quick test specifically designed for the diagnosis of PJI and it has shown promising results, although this test may be prohibitively expensive.²⁴⁻²⁷ A cost-effective approach could be to limit its use to patients with an equivocal leucocyte count, but there is a lack of evidence regarding its accuracy in this specific cohort.

We mainly wished to consider markers which were inexpensive and routinely performed in our own and other laboratories in other clinical circumstances. We chose to focus on CRP, ADA, α 2M and procalcitonin, as well as the leucocyte count. Not surprisingly, the leucocyte count had a good diagnostic performance. Although the literature proposes a range of thresholds from 1100 to 1700^{9,28,29} to > 3000 cells/ μ L^{2,8,10}, it has consistently been shown to be a powerful tool to which every new biomarker must be compared. The serum level of CRP has also long been considered a useful parameter in musculoskeletal and prosthetic joint infections. However, because it is produced by the liver in response to a variety of inflammatory stimuli, it is not specific to PJI and may be normal in low-grade PJI.^{30,31} There is some evidence that measuring the CRP directly from the synovial fluid can improve its accuracy. Zamani et al³² pioneered the evaluation of the ability of the CRP to differentiate between inflammatory and non-inflammatory arthritis. Parvizi et al³³ applied the same enzyme-linked immunosorbent assay methodology to measure the CRP in synovial fluid and differentiate between infected and uninfected revision TKAs. Others have studied the use of less complex standard assay equipment currently available at most hospitals, to measure the CRP in synovial fluid and all found that the level in patients with aseptic loosening was significantly lower than in those with a PJI.³¹⁻³⁴ However, the proposed cutoff values (ranging from 1.8 mg/L to 9.5 mg/L) and respective diagnostic accuracy varied between the studies.³⁵⁻³⁸ Our results suggest that the adoption of a low threshold may be helpful in the exclusion of infection and a high threshold may be indicative of infection. More studies are needed to clarify the optimum diagnostic criteria.

Adenosine is a purine nucleoside with anti-inflammatory and tissue protective properties.³⁸ It has been proposed that the measurement of the levels of ADA in different tissues, especially in serous body fluids, may help to identify activation of the immune system.³⁸ There is much evidence that the levels of ADA in pleural, pericardial, peritoneal and cerebrospinal fluid can distinguish a tuberculous infection from inflammatory conditions accurately. There is also some evidence that the level of ADA in synovial fluid may help in differentiating septic from rheumatoid and crystal- induced joint arthritis as well as monitoring disease activity within the joint.^{32,39,40} However, to the best of our knowledge, there are no studies on the value of the levels of ADA in synovial fluid in the diagnosis of PJI. We found that levels of ADA in the synovial fluid of > 61 U/L offer reasonably good diagnostic accuracy.

The primary function of α 2M is the rapid inhibition of excess proteinases released during tissue injury. Proteinases are liberated by neutrophils at the site of inflammation but they may also be secreted by exogenous sources such as pathogens.⁴¹ Jacovides et al¹¹ showed that the level of α 2M was significantly higher in PJIs than in aseptic failures. They were able to set a cutoff at 0.26 mg/mL (260 mg/L) with 89.5% diagnostic accuracy. The mean synovial fluid concentration of α 2M in our aseptic group was higher than this level (365 mg/L). Although we did confirm that the level of α 2M was significantly increased in infected cases, our optimal cutoff is much higher, and this was the second worst performing marker in our study, with a diagnostic accuracy of < 80%.

The level of procalcitonin in the synovial fluid was the poorest performing indicator which we analysed. The level of procalcitonin in the serum has been extensively studied as a diagnostic and prognostic indicator of systemic sepsis and has been shown to differentiate sepsis from a systemic inflammatory response.⁴² It has also been studied for the diagnosis of bone and joint infection, including PJI,⁴³⁻⁴⁵ without success. The measurement of levels of procalcitonin in synovial fluid have previously been proposed as a method of distinguishing PJI from aseptic loosening. Saeed et al⁴⁶ reported that these levels were significantly higher in septic arthritis than in nonseptic arthritis and suggested that it could be a valuable tool, but their patients were a heterogeneous group with prosthetic and native joints. In our cohort, we were not able to show a significantly higher level of procalcitonin in the synovial fluid in patients with a PJI compared with those with aseptic loosening.

This study has limitations. The levels of ESR and/or CRP in the serum were not available in some patients. It was not possible to obtain enough synovial fluid to perform a differential leucocyte count in some patients. This may have affected the correct final diagnosis. The strict microbiological sampling requirements in the inclusion criteria precluded the results being analysed in many patients. However, it has been shown that the sensitivity of testing for PJI is improved by the use of several periprosthetic tissue samples and sonication of the implants.^{3,47} Positive sonication findings were classified as a minor criterion for PJI if no other tissue culture grew in accordance. If sonication and at least one tissue culture grew the same organism, then it was classified as an infection. In all, two patients with negative tissue cultures had positive results from sonication. In the five patients in whom micro-organisms were isolated in a single sample (either tissue or sonication), there was enough supporting information to

classify them as aseptic. Another possible source of error was the method of diluting synovial fluid for biochemical analysis due to its viscosity.

We believe that the total leucocyte count is very informative and remains the first step in the diagnosis of a PJI. We found that when a lower cutoff is used a very high negative predictive value is to be expected and conversely a higher threshold offers better positive predictive value. We believe a lower cutoff is beneficial as it allows confident exclusion of infection. A positive leucocyte count can be further considered with the combined interpretation of other specific but simple and inexpensive markers, such as CRP and adenosine deaminase.

The diagnosis of PJI by the examination of the synovial fluid of the affected joint relies mostly on the leucocyte count, however simple and inexpensive markers such as the levels of CRP and ADA increase the diagnostic accuracy, namely specificity. Further research is needed to confirm these findings and to establish their role in the presence of confounding variables such as metallosis or inflammatory arthritis.

Take Home Message

- Adding simple and inexpensive markers to synovial fluid traditional leukocyte count examination may reduce the number of equivocal synovial fluid results requiring more expensive investigation.
- Pre-operative diagnostic accuracy for PJI can be greatly enhanced in a relatively simple way, as leukocyte count, CRP and ADA measurement technology is widely available, allowing for straightforward translation.

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Prosthetic Joint Infections Treatment with Debridement and Implant Retention - Results of Prospectively Applying a Predetermined Protocol

Prosthetic Joint Infections Treatment with Debridement and Implant Retention

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Conflict of interest:

The authors declare they have no conflict of interest relating to the content of this paper

Abstract

Study Goal: Treating prosthetic joint infections is complex and the results of debridement with implant retention are often unpredictable. Our hypothesis is that it is possible to offer a good chance for success as long as simple patient selection and treatment guidelines are met. The goal of this paper is to present the results of prospectively applying these principles over the past few years in our institution.

Material and Methods: This is a prospective clinical study including patients with prosthetic joint infection treated since January/2012 and a 12 months' minimum follow-up after treatment discontinuation. Only patients with a stable prosthesis with no signs of loosening, good soft tissues and short duration of symptoms were candidates to debridement with implant retention. Surgery was performed by the same surgeon and it always included mobile parts exchange. Whenever possible, antibiotic therapy included agents effective against bacteria within the biofilm.

Results: Twenty-four patients (15 knees and 9 hips) with a mean age of 65 years were included. One patient was excluded from the analysis of results as a result of unrelated death. There were three cases of treatment failure, resulting in an overall success rate of 87% (20/23) with an average 30 months' follow-up after discontinuing antibiotic therapy.

Conclusion: Following a predetermined treatment protocol allows for good results in the treatment of prosthetic joint infections even when choosing to preserve the implant.

Keywords

Hip Prosthesis; Knee Prosthesis; Prosthesis-Related Infections; Cohort Studies; Prospective Studies; Prosthesis Retention; Therapeutic Irrigation; Anti-Bacterial Agents/therapeutic use; Treatment Outcome

Introduction

Infection is one of the most frequent and feared complications after total joint arthroplasty. The enormous difficulties of its treatment often involve multiple surgeries and hospital stays with a significant impact on the patient's quality of life and even mortality (1).

Despite all the awareness and investing in prophylaxis it has been getting in the past few years, there is actually a worldwide trend to increasing prevalence and associated costs (2, 3). If we also consider the growing number of arthroplasties being performed every year, we can easily reach the conclusion that this is a complication that every orthopedic surgeon must learn how to recognize and deal with.

Surgical debridement and implant retention (DAIR) is an appealing treatment alternative for prosthetic joint infection (PJI). For the surgeon, it is technically less demanding than revision surgery and for the patient it is easier to recover from (4).

However, there is massive controversy in the literature regarding its real efficacy. Success rates vary between 0% and 90%, with an average around 50% both for hips and knees (5, 6). Furthermore, it has been suggested that failure of debridement as first-line treatment may compromise the success of ensuing revision surgery. It is therefore relevant to adequately choose the best therapeutic strategy in each case (7).

Multiple factors influence the outcome of this treatment choice. However, the authors believe that considering simple criteria for adequate patient selection and some basic principles for correct surgical and medical treatment, it is possible to offer a good chance for eradication of infection. Thus, the goal of this paper is to present the protocol adopted by the authors as well as the results of its implementation over the past few years.

Material and Methods

This is a prospective study that started in January/2012 and focuses on patients with a prosthetic joint infection diagnosis treated by the first author. Clinical and demographic variables as well as treatment and clinical and laboratory follow-up information are collected into an institutional database. This database is duly approved by the Institution's Ethic Committee and the National Committee on Data Protection.

The results of all patients treated up to September/2015 with a 12-month's minimum follow-up after antibiotic therapy discontinuation will be presented. The authors believe this is the minimal acceptable requirement as this is the time frame where most failures occur^{430,489}.

Selection Criteria

In order to be considered as candidates for surgical debridement with implant retention, patients should meet the following conditions: 1) stable prosthesis with no signs of loosening; 2) good soft tissues with no sinus tract and; 3) duration of symptoms under four weeks. These criteria were determined after previous analysis of our experience and literature review (10).

Surgical Approach Protocol

Recognizing the specificities inherent to each joint and specific clinical case, debridement obeys a systematic and constant order.

The first step is to excise the previous incision. If the fascia is closed, a superficial debridement is performed gathering samples for microbiology. Once this layer is macroscopically clean a needle is used to perform a joint tap and collect uncontaminated synovial fluid for analysis and only then is the arthrotomy performed. After the arthrotomy, all mobile parts are removed (i.e. liner, femoral head and modular neck, etc.) in order to improve exposure and allow for the cleansing of all prosthetic interfaces. A total synovectomy as well as excision of all devitalized tissues and hematomas or collections are also performed thus improving exposure as well as debridement. At this stage, a minimum of five samples for culture are taken preferably for macroscopically unhealthy tissues and/or those in contact with the prosthesis. After rigorous debridement of all suspicious tissues as well as suture remnants a copious lavage is performed. The first washout is made with 3L of chlorohexidine solution and another one is made with 3L of normal saline. After this, the wound is temporarily closed allowing the entire team to leave prep and change surgical clothes. With a new set of surgical instruments an additional wash using 1L of saline is made before implant new mobile parts to replace the ones that were removed. Usually one single intra-articular drain is used and the wound is closed by layers as tightly as possible using a technique similar to primary surgery (fascial and subcutaneous absorbable sutures and skin staples).

A single debridement is usually performed and only if the clinical scenario requires it (persistent drainage for instances) is a second debridement performed. If failure of the second debridement occurs alternative treatment options including prosthesis removal are strongly considered, especially when facing a patient with major risk factors for failure such as medical comorbidities or difficult to treat pathogens.

Medical Approach Protocol

When facing a suspected prosthetic joint infection, antibiotic therapy is not started before surgery unless in cases of clinical emergency such as imminent sepsis. In the overwhelming majority of cases, antibiotic therapy should start after culture sample gathering, after tourniquet release in knees. Empirical antibiotic therapy starts in the operating room with extended gram-positive and gram-negative coverage. During the entire study period, our protocol was vancomycin with a carbapenem (11). Once definitive microbiology results are available it is adjusted accordingly.

The switch from intravenous to oral therapy does not follow any predetermined time period but rather a conjugation of favorable clinical response (e.g. no wound drainage, diminishing inflammatory blood parameters) and the availability of effective and good oral bioavailability alternatives.

Outpatient oral antibiotic therapy extends for three and six months for hips and knees respectively. Antibiotics are discontinued after the time period defined for each case regardless of inflammatory parameters. Whenever possible, antibiotic regimen includes drug(s) with activity against slow-growing bacteria in the biofilm. Specifically, rifampicin for staphylococci (always in combination) and ciprofloxacin for gram-negative infections.

Important Definitions

PJI cases included in this study were classified according to a previous proposal (10) as: a) Postoperative Acute Infections as those who occur in the first three months after implant surgery and is usually characterized by an acute inflammatory clinical picture with persistent wound drainage that may or may not have macroscopic purulent appearance and; b) Acute Hematogenous Infections that are usually characterized by an acute inflammatory clinical picture appearing in a previously well-functioning and asymptomatic joint in the setting of a document or presumed bacteremia.

Outpatient antibiotic therapy regimen was classified as: a) Optimal Regimen if it included rifampicin for staphylococci infections, ciprofloxacin for gram-negative infections or both in cases of mixed polymicrobial flora and; b) Suboptimal Regimen if these conditions were not met either for unfavorable resistance profile or patient adverse reactions that forced interrupting adequate therapy before the completion of recommended time period.

Success was determined according to the Delphi international consensus (12) as: **a)** failed infection eradication, characterized by a fistula, drainage, pain or infection recurrence caused by the same organism strain; **b)** subsequent surgical intervention for infection after reimplantation surgery; or **c)** PJI-related mortality. Results with a minimum 12 months' follow-up after antibiotic discontinuation success rate as defined by the authors will be presented. Results with a minimum of two years after the last surgery, as recommended in the aforementioned consensus (12), will also be specified.

Statistical Analysis

Given the relatively reduced sample size a descriptive analysis of the results was made not searching for statistical correlations that would be clearly not significant.

Results

Twenty-four patients with infection of a total hip (THA) or total knee (TKA) arthroplasty, in which debridement with implant retention was chosen as initial treatment, were included in this study. Table I summarizes main clinical and demographics information. Table II shows corresponding microbiologic findings.

Table I.D Clinical and demographic information of the study population.

	Total
	n=24
Age *	65.2 (24-83)
Female gender	17 (71%)
Joint	
Hip	9 (38%)
Knee	15 (62%)
ASA score ≥ 3	10 (42%)
Relevant Comorbidities	
Obesity (BMI>30)	12 (50%)
Diabetes	7 (29%)
Immunosuppression	2 (8%)
Liver failure	2 (8%)
Type of infection	
Acute postoperative	18 (75%)
Acute Hematogenous	6 (25%)
Duration of symptoms until surgery (days) *	17.2 (6-28)
C reactive protein (mg/L) *	100.7 (1-364)
Erythrocyte sedimentation rate (mm/h) *	71.4 (20-104)

* average (minimum-maximum); **ASA** American Society of Anesthesiologists; **BMI** Body Mass Index.

These are consecutive unselected cases, from the first author clinical practice and most of them are primary prosthesis (12 TKA and six THA). Notwithstanding, infections after aseptic revision surgery were also included (one TKA and two THA) and even after two-stage revision surgery for previous infection (one knee and one hip). An infection of a knee mega-prosthesis after high grade osteoblastic osteosarcoma resection of the distal femur was also included. It is noteworthy that, according to the previously described protocol only acute postoperative and hematogenous infections with short duration of symptoms were included.

Table II.D Microbiology findings among the study population.

	Total
Number of infections	n=24
Polymicrobial infections	8 (33.3%)
Culture Negatives	0 (0.0%)
Isolated microorganisms	n=35
Gram positive	25 (71.4%)
<i>Staphylococcus aureus</i>	9 (25.7%)
MRSA	2 (5.7%)
MSSA	7 (20.0%)
Coagulase-negative staphylococci	10 (28.6%)
MR CoNS	7 (20.0%)
MS CoNS	3 (8.6%)
Other Gram positives	6 (17.1%)
<i>Enterococcus spp.</i>	3 (8.6%)
<i>Streptococcus spp.</i>	2 (5.7%)
<i>Corynebacterium spp.</i>	1 (2.9%)
Gram negative	10 (28.6%)
Enterobacteriaceae	9 (25.7%)
<i>Enterobacter spp.</i>	3 (8.6%)
<i>Escherichia coli</i>	3 (8.6%)
<i>Proteus spp.</i>	2 (5.7%)
<i>Klebsiella spp.</i>	1 (2.9%)
<i>Pseudomonas spp.</i>	1 (2.9%)

MR methicillin-resistant; MS methicillin-sensitive; SA *Staphylococcus aureus*; CoNS Coagulase-negative staphylococci.

Table III shows information regarding the different treatment variables considered. Only four cases (17%) needed a second debridement. Antibiotic therapy regimen was considered suboptimal in four cases: one polymicrobial infection including a ciprofloxacin-resistant Gram negative bacilli, one MRSA case that was also rifampicin-resistant, one case of methicillin-resistant *S. epidermidis* in which a rifampicin induced decompensation of a known liver insufficiency occurred after seven days forcing its discontinuation and one other MRSA case with significant patient intolerance to the therapy with incoercible vomiting that led to irregular antibiotic(s) intake. Interestingly, there were no failures among these four cases. On the day of antibiotic therapy discontinuation, erythrocyte sedimentation rate was above 30 mm/h in 11 cases and C reactive protein above 10mg/L in four cases. There were no significant differences of the registered variables between success and failure cases.

Table III.D Summary of treatment related variables.

	Total
	n=24
Average number of debridements	1.2
Need for a repeated debridement	4 (17%)
Duration of hospital stay (days) *	23.8 (13.5-29.8)
Duration of IV antibiotic therapy (days) *	15.6 (11.0-18.8)
Duration of total antibiotic therapy (weeks) *	
Hip	15.7 (12.9-14.6)
Knee	25.9 (22.7-26.7)
Antibiotic therapy regimen	
Optimal regimen	20 (83%)
Suboptimal regimen	4 (17%)
CRP at the end of antibiotic therapy* (mg/L)	6.6 (2.4-7.0)
ESR at the end of antibiotic therapy* (mm/h)	32.5 (14.0-50.0)
Follow-up time (months)	
Since surgery	35.2 (20.2-48.2)
Since the end of antibiotic therapy	30.0 (15.5-44.9)

* mean (interquartile range); IV intravenous; CRP C reactive protein; ESR erythrocyte sedimentation rate.

One patient died about one year after surgery and only six months after antibiotic discontinuation thus not reaching the minimum follow-up required. It was therefore excluded from final results analysis. However, it was not considered a treatment failure as she died of unrelated causes (i.e. acute myocardial ischemia) while she was completely asymptomatic of the operated joint and TKA was being considered for the other knee. One other patient died during the study period also for unrelated causes. However, because he died after more than four years after antibiotic discontinuation and had no signs of infection, it was included and considered a treatment success. As such, with a mean follow-up period of 30 months (minimum 12 months) after antibiotic therapy discontinuation, there were three treatment failures, with an overall success rate of 87% (20/23). If we consider the two years' minimum follow-up after surgery, success rate was 85% (17/20). Table IV shows clinical information regarding the three failures. All of them were ultimately successfully treated with two-stage exchange surgery.

Table IV.D Summary information concerning the three failures.

Relevant history	Type and Joint age	Infection clinical features	Microbiology	Antibiotic Therapy Regimen	Mode of Failure
69 years old women, Oral anticoagulation for AF	14 months old primary TKA	Acute inflammatory/infectious arthritis after trauma and significant hematoma and cutaneous abrasion; 15 days' duration of symptoms (operated the same day she entered the ER)	Methicillin-sensitive <i>S. aureus</i>	Empirical vancomycin + imipenem after surgery	Early failure with extensive skin necrosis the first few days after debridement (fig.1)
73 years old man, Morbidly obese (BMI=42), COPD	3 weeks old primary TKA	Persistent wound drainage	Methicillin-sensitive <i>S. aureus</i>	3 months' rifampicin 600mg qd + levofloxacin 500 mg qd	De novo pain and femoral lytic lesions 15 months after antibiotic discontinuation (fig.2) Prosthesis removal/spacer implantation 19 months after debridement
76 years old women, Myelodysplastic syndrome with pancytopenia	3 weeks old primary TKA	Persistent wound drainage	Methicillin-resistant <i>S. epidermidis</i>	6 months' rifampicin 600mg id + linezolid 600 mg bid (4 weeks) followed by clindamycin 600 mg tid	Pain worsening immediately after antibiotic discontinuation Prosthesis removal/spacer implantation 9 months after debridement

AF atrial fibrillation; **ER** emergency room; **TKA** total knee arthroplasty; **THA** total hip arthroplasty; **BMI** body mass index; **COPD** chronic obstructive pulmonary disease.



Fig. 1d Clinical aspect of the surgical wound at: **A)** third postoperative day; **B)** tenth postoperative day; **C)** fifteenth postoperative day

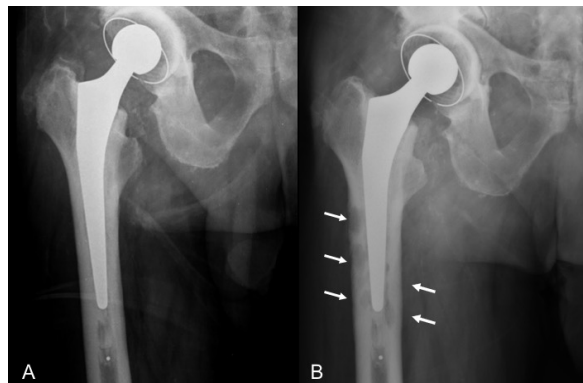


Fig. 2d Radiographic appearance at 13 months after debridement (ESR and CRP were normal at this visit); **B)** radiographic appearance 5 months later with obvious lytic lesions in the femur (with the arrows) and de novo peri acetabular radiolucent line

Discussion

As the number of total joint arthroplasties continues to grow every year, and despite all the efforts around prophylaxis, prosthetic joint infections are becoming a more common problem. Debridement with implant retention (DAIR) is an appealing treatment alternative but its success rate is very inconsistent with results in the literature varying from 0% to 90% (5, 6). Many variables may influence the final outcome. Some of them like patient comorbidities or responsible pathogen(s) virulence elude the control of the surgeon (8,13,14). Others such as correct patient selection, rigorous surgical debridement and selected antibiotic regimen are directly under the control of the medical team (9, 15-19).

Naturally, the first indispensable condition to go ahead with DAIR is that we face a stable prosthesis with no signs of loosening. In other words, a prosthesis worth saving. Inability to adequately close the wound and soft tissues or the presence of a sinus tract are also often considered absolute contra-indications as they exponentially increase the risk of treatment failure (17).

Short duration of symptoms seems to be a major criterion in choosing this treatment alternative with an ideal time threshold located somewhere between 3-4 weeks (8, 14, 17, 20-22). It is very important to distinguish between duration of symptoms and “joint age” or time elapsed since its implantation. Regardless of the time elapsed since the original surgery, acute infections may occur by hematogenous spread into previously asymptomatic joints. In these cases, DAIR is proven as effective as in postoperative infections (13, 15). In acute postoperative infections, our policy when facing a suspicious case is not to start antibiotics on its own. We believe it will mask the manifestations of infection that can be very subtle. We advocate tight clinical and laboratory surveillance with serial measurement of inflammatory parameters. If these parameters show an increasing trend or wound drainage persists after the tenth postoperative day we go ahead with a formal debridement.

A thorough surgical debridement is perhaps one of the most important and probably the most difficult variable to objectively assess. The main goal of surgery is to lower as much as possible the bacterial load within the joint in order to facilitate the role of antibiotics and patient immune system. In this regard, mobile parts exchange seems very relevant. Not only does it increase exposure as it allows for cleansing of the prosthesis interfaces thus helping to fulfill the goal of surgery. It has been widely shown that mobile parts exchange increases the probability of success (23, 24).

A main determinant of success after DAIR is the type and specific characteristics of the bacteria causing the infection. Staphylococci infections, specifically *S. aureus*, have been frequently associated with worse outcomes (8, 13, 20). Naturally this variable cannot be influenced by the surgeon and is often not known when deciding to operate. However, antibiotic regimen can and should be optimized. When choosing to perform a DAIR one must acknowledge the presence of bacterial biofilm remnants and whenever feasible drug(s) active against slow growing bacteria in the biofilm should be chosen (19). Although a detailed

discussion of the more appropriate antibiotic(s) is beyond the scope of this paper, it is important to highlight the crucial role of rifampicin in staphylococci infections (9, 15) and ciprofloxacin in gram negative infections (16, 25). In our series, all three failures occurred in the 18 PJI cases where a *staphylococcus* sp. was found despite adequate antibiotic therapy.

The ideal duration of antibiotic therapy is a matter of open debate, although it is still recommended to extend treatment for at least three months in hips and six months in knees (26). Byren et al (8) showed not only that the risk infection relapse increases after antibiotic discontinuation but also that treatment longer than 180 days did not increase the likelihood of cure. These findings suggest that infections are either cured or not in this initial stage and that prolonging therapy only postpones the treatment failure. An issue often encountered in clinical practice is to use the monitoring of inflammatory parameters to decide when to discontinue therapy. It has been shown that this practice lacks real predictive value (27, 28).

It has been repeatedly shown that adopting a clear treatment concept based on scientific evidence leads to significant improvement in the results when compared to an ad hoc approach (29, 30). It is important to stress that such an improvement does not depend on significant technical breakthroughs but rather on the compliance to simple principles of patient selection and the strict adherence to predetermined treatment rules. The fact that failures in the treatment of prosthetic joint infections often occur on the medium/long term cause a false sense of immediate success among surgeons thus contributing to the perpetuation of the same mistakes and preconceived notions of the past.

Conclusion

The results of employing our protocol over the last few years have been encouraging. The current success rate of around 85% is located in the favorable end of the spectrum and compares very favorably with the 30% success rate of our previous 2008 study (10). We could thus prove that it is possible to improve and reproduce the best results in the literature also in clinical daily practice as long as one adopts an evidence-based approach.

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Treatment of Prosthetic Joint Infections with Two-stage Exchange Surgery - Results of a Prospective Study with a Management Protocol

Treatment of Prosthetic Joint Infections with Two-stage Exchange Surgery

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The authors declare they have no conflict of interest relating to the content of this paper

Abstract

Study Goal: Revision surgery with implant removal, because it offers predictable results, is considered to be the gold standard in the treatment of prosthetic joint infections. Our belief is that a protocolized approach may offer better infection control as well as reduce patient morbidity. The goal of this paper is to present the results of our management protocol and the results obtained with its implementation.

Material and Methods: This is a prospective clinical study including patients with prosthetic joint infection treated between January/2012 and December/2015 thus allowing a twelve months' minimum follow-up. Prosthetic joint infection definition followed internationally established criteria and medical and surgical treatment was performed in a standardized way. Every patient underwent prosthesis removal and high-dose antibiotic spacer implantation.

Results: Twenty-nine patients (19 knees and 10 hips) with a mean age of 67 years were included. There were two related deaths. Infection eradication was achieved in all cases, although it was not possible to complete the second stage in two cases. Among the 25 patients who completed the second stage, the mean time interval between stages was 11 weeks. There were no cases of infection relapse at a mean 30 months' follow-up. Overall success rate is 86% (25/29).

Conclusion: Following a protocolized approach resulted in good results with significant reduction of morbidity between the two stages without compromising safety.

Keywords

Revision hip arthroplasty; Revision knee arthroplasty; Prosthesis-Related Infections; Cohort Studies; Prospective Studies; 2-stage exchange; Anti-Bacterial Agents/therapeutic use; Treatment Outcome

Introduction

Infection is one of the most dreadful complications after total joint arthroplasty. It is often the first or second cause for revision total knee arthroplasty (1, 2) and the third most common reason for revision total hip after aseptic loosening and instability (2, 3).

Despite all the awareness around it over the past few years, there is actually a worldwide trend to its increasing incidence along with associated economic burden (4).

Treating this complication is hard and arduous and it is therefore advisable that it is undertaken by an experienced multidisciplinary team (5). Nevertheless, it often leads to significant patient morbidity and mortality even when it is possible to eradicate infection (6). The presence of bacterial biofilm in prosthetic joint infections (PJI) is responsible for most of the difficulties. Bacteria become about 1,000 times more resistant to antibiotics and the host's immune system is unable to eradicate it (7). Most of the tissue destruction is caused by this "frustrated phagocytosis" and persistent inflammation around the implant (7). Currently once a mature biofilm is formed, there is no way to eradicate in vivo. As such the only alternative is to remove it by removing the prosthesis.

In this regard, two-stage revision surgery is the most frequent treatment option worldwide although one-stage surgery may be indicated in specific circumstances (8, 9). Two-stage revision surgery consists in surgical debridement and removing the infected implant, with or without using a temporary cement spacer with high dose antibiotics, before implanting a new prosthesis in a second surgery.

The purpose of this paper is to present the author's two-stage management protocol for the treatment of PJI as well as the results of its implementation over the past few years.

Material and Methods

This is an ongoing prospective study that started in January/2012 and focuses on patients with prosthetic joint infections treated according to predetermined protocol. Several different clinical and demographic as well as treatment and laboratory follow-up variables are collected into an institutional database. This database is duly approved by the Institution's Ethic Committee and the National Committee on Data Protection.

Results concerning patients treated up to December/2015 will be presented so a minimum 12 months' follow-up after the second surgery is possible. Results with at least two years follow-up will also be presented as is suggested in an international multidisciplinary consensus (10).

Success of the procedure was defined accordingly to the previously mentioned consensus as: a) failed infection eradication, characterized by a fistula, drainage, pain or infection recurrence caused by the same organism strain; b) subsequent surgical intervention for infection after reimplantation surgery; or c) PJI-related mortality (10).

Selection Criteria and Definitions

Every patient with chronic PJI or those with acute infections who do not meet predetermined criteria for debridement and implant retention surgery, specifically stable prosthesis with no signs of loosening and adequate soft tissues (e.g. sinus tract or inability to close the wound) are considered candidates to two-stage revision surgery. These criteria were defined after analyzing our previous experience and literature review (11).

Chronic infection diagnosis follows the definition and criteria proposed in a recent international consensus meeting on PJI (5) and are exposed in table I.

Table I.E International Consensus Meeting Definition of Periprosthetic Joint Infection.

1) Two positive periprosthetic cultures with phenotypically identical organisms, or
2) A sinus tract communicating with the joint, or
3) Having three of the following minor criteria
Elevated serum CRP and ESR
Elevated synovial fluid WBC count OR ++ change on leukocyte esterase test strip
Elevated synovial fluid PMN percentage
A single positive culture
Positive histological analysis of periprosthetic tissue

CRP C-reactive protein, **ESR** erythrocyte sedimentation rate, **WBC** white blood cell; **PMN** polymorphonuclear neutrophil.

Erythrocyte sedimentation rate (ESR) is considered positive above 30mm/H and C-reactive protein above 10mg/L. Total leukocyte count in the synovial fluid above 3,000 cells/ μ L and polymorphonuclear neutrophil (PMN) proportion over 80% are also considered positives.

Sonication of the removed implant is routinely performed and subsequent microbiology findings are interpreted as a single sample to be interpreted with the rest of the data. In our institution, histological analysis of periprosthetic tissue is not routinely performed.

Surgical Treatment Protocol

Recognizing the specificities inherent to each joint and specific clinical case, two-stage surgery obeys a systematic and constant order.

During the first surgery, all the implant is removed but also all and any inert material including bone cement, screws, etc. Furthermore, every ill looking soft tissue is meticulously debrided. If there is a sinus tract it must be completely excised. If it is not possible to include it in the approach of the joint, it must be removed separately. Although one should seek to preserve structures that are vital to the postoperative functional status (e.g. knee extensor mechanism), the priority is to cure the infection and as such, debridement must be as radical as possible. Alongside complete synovectomy and removal of all devitalized soft tissues (e.g. muscle necrosis, collections, etc.) also all infected bone must be debrided. In the hip, it is in this stage that the socket size is evaluated and reamers are used to create an appropriate cavity for the chosen spacer head. During debridement, at least five representative tissue samples are gathered for culture, favoring macroscopically purulent tissues and/or those in intimate contact with the prosthesis specifically the pseudo-membrane that usually forms between the bone and the implant. A copious lavage is then performed. The first washout is made with 3L of chlorohexidine solution and another one is made with 3L of normal saline. After this, the wound is temporarily closed allowing the entire team to leave prep and change surgical clothes. With a new set of surgical instruments an additional wash using 1L of saline is made before spacer implantation. Usually one single intra-articular drain is used and the wound is closed by layers as tightly as possible using a technique similar to primary surgery (fascial and subcutaneous absorbable sutures and skin staples).

Whenever possible, we prefer to use spacers instead of simple resection arthroplasty. Our first-choice is to use spacers that allow mixing the type and dosages of the selected antibiotic(s). Mixing antibiotics in the cement is performed on a separate table and starts by adding powder antibiotic(s) to the cement powder. Finally, the liquid is added and the mixture is performed without vacuum so as to increase the porosity and increase antibiotic elution. When the infecting organism is unknown we add 3-4g vancomycin and 1-2g meropenem to each 40g of bone cement with gentamicin (0.5g). In specific cases of resistant microorganisms or an history of adverse reactions, added antibiotics may be adjusted. Out of the ten cases of hip infection articulating spacers with metallic core reinforcement made using silicone molds and the fore mentioned mixture were used in eight (Fig. 1A). In one case of documented vancomycin allergy and methicillin-resistant *staphylococcus* infection, daptomycin was used as an alternative. The other case presented proximal femur bone loss and required a long-stemmed spacer so a commercially manufactured spacer containing gentamicin was used. In order to minimize pain and mechanical complications, the spacer is fixed to the bone using a coarse cementing technique (same antibiotics mixture) as not to hamper its removal

in the second surgery. Among knee infections, articulating knee spacers made using silicone molds were used in the first nine cases (Fig. 1B). In the nine most recent cases (since January/2014) were hand-made (Fig. 1C). In one case of previous revision for infection a static spacer was used for there was not enough bone stock. In the distal femur tumor mega-prosthesis, a custom-made articulated spacer with vancomycin and tobramycin was specifically manufactured.

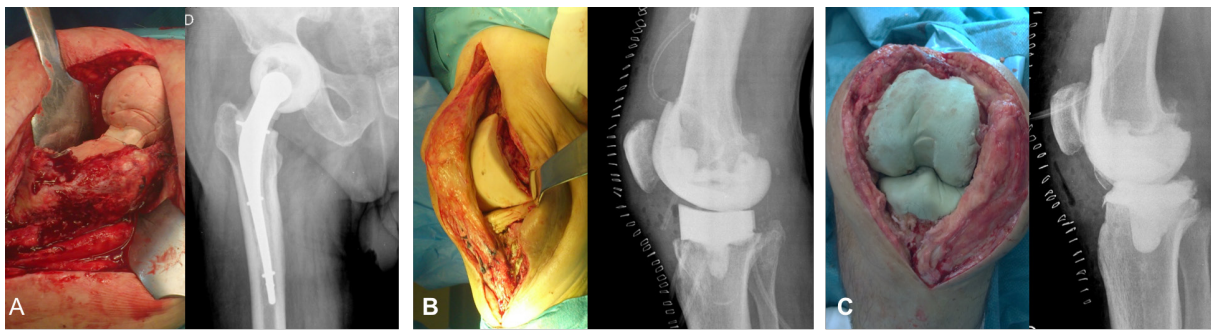


Fig. 1e Clinical and radiographic appearance of the different spacers used: **A)** articulating hip spacer with metallic core made using silicone molds; **B)** articulating knee spacer made using silicone molds; **C)** handmade articulating knee spacer by directly molding bone cement into osseous surfaces

Specificities of the second surgery largely depend on the bone and ligamentous defects that result from the first stage. It is important to stress that, more than just removing the spacer this surgery should include a new debridement and several samples for culture should be taken again.

Medical Treatment Protocol

When facing a suspected prosthetic joint infection, antibiotic therapy should not start before surgery except in cases of manifest clinical emergence. In the overwhelming majority of cases antibiotics should start only after sample gathering for culture has ended, in the knee after the tourniquet is released. Empirical antibiotic therapy start still in the operating room and comprises wide spectrum antibiotics active against Gram positive and Gram negative microorganisms. During this study period, our protocol is to use vancomycin combined with a carbapenem (12). Once definitive microbiology results are available therapy is adjusted accordingly.

The switch from intravenous (IV) to oral therapy does not obey any predetermined timeline but rather a conjugation of favorable clinical response (e.g. no wound drainage, diminishing inflammatory blood parameters) and the availability of effective and good oral bioavailability alternatives. Exceptionally it may be necessary to do the full period of IV therapy. Usually it lasts around six weeks but it may be necessary to prolong it in rare cases who require waiting for complete wound healing (e.g. muscle flaps) or associated other site infections require it.

Deciding when to perform the second stage does not depend exclusively on the inflammatory parameters and even less so of their complete normalization. Usually the decision is made after a two weeks' window period after antibiotics discontinuation. We decide to go ahead with

the second stage when the following conditions are met: a) inflammatory parameters steady or descending trend regardless of their absolute values; b) favorable soft tissues with nice wound healing and no local inflammatory signs; c) correction of the cause for infection if it is obvious (e.g. leg ulcer, urinary tract infection, etc.); d) general health status and comorbidities optimization (e.g. diabetes control, malnutrition, immunosuppression, etc).

In the second surgery, prophylactic antibiotics are not withheld and start before skin incision and follows the same wide spectrum protocol described earlier. When definitive culture results are available, antibiotics are discontinued or adjusted to oral therapy if bacterial growth demands it.

Statistical Analysis

Given the relatively reduced sample size a descriptive analysis of the results was made not searching for statistical correlations that would be clearly not significant.

Results

Twenty-nine patients with infected total hip (THA) or total knee (TJKA) arthroplasty, treated with two-stage revision surgery were included in this study. Table II shows the main clinical and demographic characteristics of the cohort. It is noteworthy that revision surgery was undertaken in three acute infections (two TKA and one THA) after failure of debridement and implant retention to control infection; one case of acute THA infection after revision surgery for recurrent instability and with two new dislocation episodes after surgery and; one acute postoperative TKA infection in which the prosthesis was found to be loose intraoperatively.

These are unselected, consecutive cases the majority concerning primary arthroplasties (15 TKA and seven THA). Nevertheless, infections after aseptic loosening were also included (two TKA and three THA) and even one TKA case after previous revision for infection several years back. An infected tumor mega-prosthesis after resection of distal femur fibrosarcoma was also included. It is important to emphasize that 12 of the 29 cases had previously undergone treatment attempts with debridement and implant retention.

Table II.E Clinical and demographic information of the study population.

	Total
	n=29
Age*	67.1 (30-84)
Female gender	14 (48%)
Joint	
Hip	10 (34%)
Knee	19 (66%)
ASA score ≥ 3	13 (45%)
Relevant comorbidities	
Diabetes	19 (66%)
Obesity (BMI>30)	14 (48%)
Inflammatory arthritis	2 (7%)
Chronic renal failure	2 (7%)
Type of infection	
Chronic	24 (83%)
Acute/Hematogenous	5 (17%)
Joint age at the first stage (months)*	34.2 (1-192)

* mean (minimum-maximum); **ASA** American Society of Anesthesiologists; **BMI** Body Mass Index.

Table III displays information about microbiology findings. It is noteworthy that there was no growth in any sample taken during the first surgery in three cases. All those patients were under antibiotics (two in the setting of failed surgical debridement and one that had been prescribed even before any surgery for persistent wound drainage).

Table III.E Microbiologic findings among the study population.

Number of infections	n=29
Polymicrobial infections	9 (31.0%)
Culture Negative	3 (10.3%)
Isolated microorganisms	n=38
Gram positive	31 (81.6%)
<i>Staphylococcus aureus</i>	7 (18.4%)
MRSA	1 (2.6%)
MSSA	6 (15.8%)
Coagulase-negative staphylococci	17 (44.7%)
MR CoNS	7 (18.4%)
MS CoNS	10 (26.3%)
Other Gram positive	7 (18.4%)
<i>Streptococcus spp.</i>	6 (15.8%)
<i>Enterococcus spp.</i>	1 (2.6%)
Gram negative	6 (15.8%)
<i>Enterobacteriaceae</i>	5 (13.2%)
<i>Escherichia coli</i>	2 (5.3%)
<i>Enterobacter spp.</i>	1 (2.6%)
<i>Providencia spp.</i>	1 (2.6%)
<i>Serratia spp.</i>	1 (2.6%)
<i>Pseudomonas spp.</i>	1 (2.6%)
Fungi	1 (2.6%)

MR methicillin-resistant; MS methicillin-sensitive; SA *Staphylococcus aureus*; CoNS Coagulase-negative staphylococci.

Table IV shows information about treatment related variables. As would be expected, inflammatory parameters were high in the vast majority of cases. However, five out of 24 patients in which it was measured, presented normal ESR below 30mm/H and in three patients CRP was below 10mg/L. In two cases, both markers were below diagnostic thresholds (one THA with chronic years long sinus tract and one TKA under antibiotic therapy for persistent wound drainage). In the first stage, a total of 146 culture samples were gathered, averaging about five samples in each case. There was growth in 96 (66%) of them. There was an overall improvement regarding inflammatory markers between both stages. Nevertheless, in six out of the 22 in which it was available, ESR was above 30mm/H and in eight patients CRP was above 10mg/L. In five cases, both were still high. During the second stage a total of 103 culture samples (≈ 4 samples/patient) were taken and only three displayed bacterial growth. One isolated sample grew *Propionibacterium acnes* in a patient with previous methicillin-resistant *S. epidermidis* infection and was therefore dismissed as contamination. In the second stage of the patient with the infected tumor megaprosthesis two samples had positive growth (a methicillin-sensitive *S. aureus* and a methicillin-resistant *S. epidermidis*). Since the first stage had shown methicillin-resistant *S. epidermidis* these findings were considered. The second stage consisted of a total femur arthroplasty after removing the proximal femur and the patient was prescribed a four-month period of rifampicin and levofloxacin. Up to now, with 13 months'

follow-up after antibiotics discontinuation the patient remains pain free and with no other signs of infection relapse.

Table IV.E Summary of treatment related variables.

	Total
Presentation at the first stage	n=29
C-reactive protein (mg/L) *	78.3 (25.1-122.7)
Erythrocyte sedimentation rate (mm/H) *	56.4† (35.0-81.0)
Microbiology samples: total number/ positive	146 / 96
Treatment	n=27
Duration of hospital stay (days) *	22.4 (13.0-26.0)
Duration of IV antibiotic therapy (days) *	15.2 (9.8-15.3)
Total duration of antibiotic therapy (weeks) *	6.4 (5.9-6.7)
Presentation at the second stage	n=25
Time interval between stages (weeks) *	11.2 (9.1-11.9)
C-reactive protein (mg/L) *	8.1 (1.9-12.0)
Erythrocyte sedimentation rate (mm/H) *	32.1‡ (23.0-44.0)
Microbiology samples: total number/ positive	103 / 3

* mean (interquartile range); IV intravenous; † available in 24 cases; ‡ available in 22 cases.

In four cases the protocol was not completed. In two cases, there was PJI-related deaths and two other lacked desire for further surgery. A 76-years old man with THA infection underwent the first stage while in septic shock and died during the first 24 hours with intravascular disseminated coagulation. A second death occurred in an 83-years old woman with severe heart failure, stage IV chronic renal failure and TKA infection that required a flap for wound closure after the first stage. She died of multi-organ failure while still in the hospital about one month after surgery. An 84-years old woman with infection after a THA performed for a femoral neck fracture, expressed the will of not undergoing further surgery after the first stage even though infection was seemingly eradicated. The spacer was ultimately removed for mechanical reasons, after more than two years at a time that she was bedridden. All samples taken for culture were negative at that point. The remaining case in which a second stage was not completed concerns a 73-years old woman with multiple previous surgery for recurrent hip instability. Despite a temporary cement tectoplasty (Fig. 2), a dislocation of the spacer occurred and after discussing the risks and limitations of all the options, the patient chose resection arthroplasty.

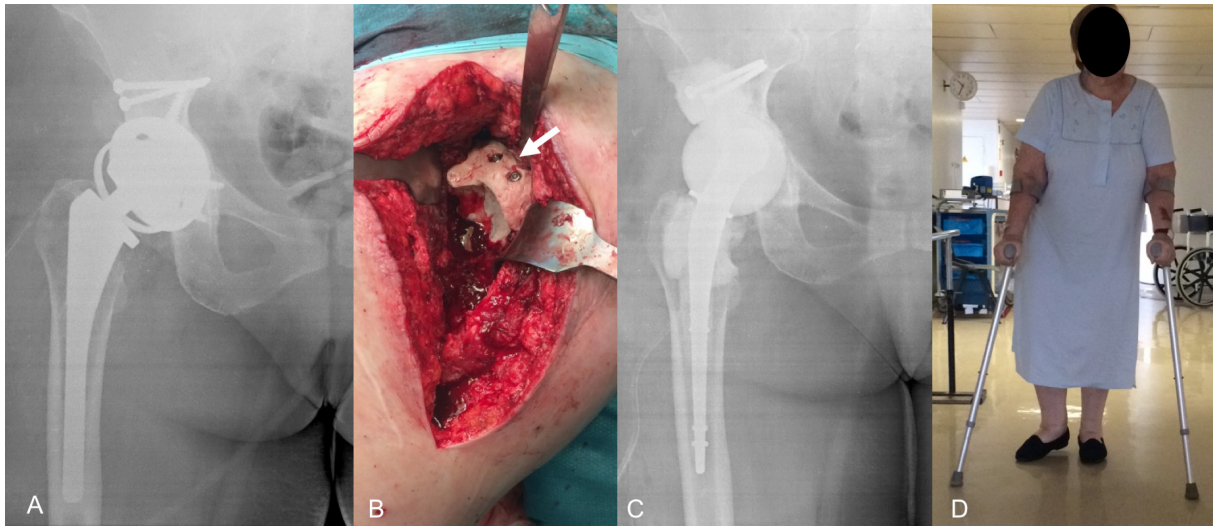


Fig. 2e **A)** radiographic appearance of THA after revision with structural allograft and restrictive sock for recurrent instability; **B)** intraoperative photograph depicting acetabular temporary reconstruction with cement tectoplasty (white arrow) without the spacer; **C)** radiographic appearance of the reconstruction after spacer implantation; **D)** clinical appearance of the postoperative rehabilitation showing (limited) functional ability of this solution.

Again, in this surgery all culture samples were negative. There was another death during the study period but, because it was of unrelated causes, it occurred over 15 months after the second stage and the patient was asymptomatic of his hip, this case was included in the results and deemed a success.

As such, with a mean follow-up of 30 months (minimum 12 months) after the second stage the overall success rate is 86% (25/29). To the best of our knowledge, it was possible to eradicate infection in every case and there is still no infection relapse after the second stage. However, the truth is that treatment was not completed in four cases. If we consider a minimum two years' follow-up after surgery, success rate is 83% (19/23).

Discussion

Given the increasing prevalence of patients living with some type of arthroplasty and since infections may occur at any point in the life of a prosthesis, this is a growing problem for which the orthopedic community must be prepared (4, 13). It has been repeatedly shown that infection must be a part of the differential diagnosis of any painful arthroplasty as it may be present without obvious signs or symptoms and if actively looked for, it may be present in a significant proportion of cases thought to be aseptic, especially in the first years after surgery (14, 15).

Revision surgery with removal of the infected implant is considered to be the most reliable treatment alternative with the best success rates published between 80-90% (5, 16). Although revision surgery in a single stage is increasingly being advocated especially in selected cases (9, 17, 18), two-stage surgery is still the most common option worldwide (8). We believe this a technique with greater tolerance for error and it is maybe easier to adopt in less experienced centers. Still, the quality of surgery is crucial. Debridement must be rigorous and all infected foreign bodies as well as devitalized bone must be removed. Keeping infected bone as to not create additional difficulties in the eventual second stage reconstruction may seriously hamper the main goal of eradicating infection and thus prevent completing the desired final outcome.

Using an antibiotic loaded spacer, though it is not indispensable and may even be contraindicated in some cases (e.g. major acetabular bone defect), seems to be an important adjunct to infection eradication. It allows very high local drug(s) concentrations that would be impossible to obtain using systemic antibiotic therapy only (19). Using spacers that allow adding the most appropriate drug(s) in the desired dosages seem to increase the amount of antibiotics actually released within the joint (20). Nevertheless, there is no real clinical evidence of increased efficacy in eradicating infection between these spacers and commercially available ones (5). The use of an articulating spacer should be preferred over a static as it not only maintains some joint function between stages as it tends to offer better functional results after revision surgery (5). Using articulated spacers is not without risks though and some precautions must be taken to minimize them (21, 22).

One of the most difficult decisions along this procedure is when to advance for the second stage. Traditionally, most surgeons prefer to wait for the normalization of inflammatory parameter such as ESR and CRP. In our institution's previous experience this lead to a time interval between stages of almost 11 months (11). Adopting the criteria previously described allowed reducing that interval to around two months without a negative impact in infection eradication, even with persistently elevated inflammatory parameters in a significant proportion of cases. In fact, it has been repeatedly shown that ESR and CRP are unreliable and not predictive of the real probability of cure. Therefore, this practice should be abandoned (23, 24). Even in preoperative diagnostic investigation, the negativity of these parameters is no guarantee of absent infection as is demonstrated in this and other studies (25).

Prior administration of antibiotics is one of the main culprits for this and other difficulties in the diagnosis of prosthetic infection. In addition to masking laboratory findings, it will also influence the reliability of intraoperative cultures during revision surgery, which may not only compromise the diagnosis but also the result of treatment (26). In our series, all cases of negative cultures occurred in patients under antibiotic therapy emphasizing the importance of withholding antibiotics prior to surgery and the gathering of appropriate samples whenever possible. Sampling should always include four or five representative tissue samples (5).

It has been consistently demonstrated that adopting a clear concept of treatment based on scientific evidence leads to a significant improvement in results when compared to an ad hoc approach (27, 28). It is important to emphasize that this improvement does not depend on significant technical innovations, but rather on applying simple principles and strict compliance with the predetermined treatment rules. The adoption in our institution of a protocolized approach for the treatment of prosthetic infections in the last few years has led to very encouraging results allowing cure of infection in all patients. It is important to point out that they were obtained in an unselected cohort of cases that included circumstances with increased risk of failure such as persistent infection after surgical debridement (including a tumor prosthesis) or after previous revision for infection (29, 30). Nevertheless, it is important to emphasize that in four out of 29 cases (14%) the treatment was not completed and the second stage was not possible. This is a number often overlooked in the literature when discussing the success of the two-stage approach and is probably its greatest weakness. Still, current results compare very favorably with the 56% of patients who ended up with arthrodesis or resection arthroplasty in our previous analysis even after excluding mortality as a cause of failure (11).

Conclusion

The overall success rate, at around 85%, is at the favorable end of the spectrum in the literature. This improvement was achieved while at the same time significantly reducing morbidity between both stages and not compromising safety as proven by the absence of recurrent infection after the second stage. These findings confirm that it is possible to reproduce the best results of the literature also in our daily clinical practice and also highlight the advantages of a protocol approach based on scientific evidence.

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CONCLUSION AND FUTURE DEVELOPMENTS

Naturally, a lot of issues and controversies remain unanswered in this vast field of prosthetic joint infections. Improving clinical multidisciplinary collaborative efforts but also cooperation between clinicians and basic research scientists and even industry and regulatory agencies is key in providing better PJI management in the future.

Prophylaxis

Due to the presence of an implant, a very small number of bacteria reaching the wound is enough to cause relevant infection making prevention of PJI extremely demanding. Most traditional prophylactic strategies (e.g. skin decontamination, OR asepsis, etc.) aim to reduce the number of bacteria reaching the wound via the surrounding environment, the so called exogenous contamination. Notwithstanding its remarkable importance, a second route for bacterial seeding into the joint is has been recently recognized. The host itself harbors a huge number of bacteria that, in the right circumstances, may become pathogenic. This so called endogenous contamination and its real weight are yet to be fully understood.

In trying to understand the potential role of asymptomatic urinary tract colonization we performed research in the subject that raised a lot of interest warranting an editorial commentary by Duncan⁶¹⁹ and correspondence with Uçkay et al.^{620,621} To the best of our knowledge, it remains up to now the largest prospective survey of its kind. Adjusting for known risk factors in a multivariate model, ASB independently raised the risk of PJI >3-fold. However, preoperative treatment of ASB did not influence it and among patients who had both ASB and PJI, the causative organisms did not match at all. Our findings advise against this common practice with associated costs, possible side effects of unnecessary antibiotic therapy (i.e. adverse drug reactions, altering native flora, contributing to antimicrobial resistance) and most of all, no apparent efficacy. Several questions remain unanswered though. If ASB is an independent risk factor for PJI but no causal relation seems to exist, does ASB itself constitute a real threat or is it just a surrogate marker of vulnerability? If so, are the same mechanisms that facilitate urinary tract colonization involved in facilitating joint infection? Remarkably, a significantly higher proportion of Gram negative bacteria PJI was found in ASB patients suggesting there is maybe some kind of specific susceptibility. Would it be possible to mitigate this inherent risk by the use of different perioperative antibiotic prophylaxis? Prospective randomized trials are needed to answer these questions. Until such trials can be completed, preoperative screening for ASB should be avoided, apart from careful research protocols.

Staphylococcus aureus carriers are another pool of patients with well-known increased risk of infection. There is enough evidence that an endogenous route of joint contamination does occur as there is a significant proportion of patients who develop PJI with bacterial clones similar to those in previously isolated in the nares¹⁰³. As such, it is currently recommended to treat known nasal carriers. However, implementing a screening and targeted decolonization strategy in daily practice is complicated. A too long period between outpatient screening and surgery increases the risk of misclassification but on the other hand, results need to be communicated in time, patients need to be reconvened and instructed towards appropriate therapy. This is both labor and time consuming. Another problem regards the sensitivity of nasal swab to detect carriers. Molecular PCR-based screening techniques may be more fast and allow more flexibility than traditional widely available cultures but not only are they more expensive but have also been shown to have limited sensitivity⁶²². It has also been shown that screening multiple body site is much more accurate and using nasal swabs as a surrogate may at best identify only two thirds of true MRSA carriers⁶²³. Whether the same is true for MSSA remains unknown. In addition, though the endogenous route is clearly supported by the evidence, the exogenous *S. aureus* contamination pathway may still be preponderant in some settings such as our own where at least 10 out of 14 cases of *S. aureus* PJI may have had an exogenous source¹⁰⁹. As such, we remain skeptic about the real worth and cost-effectiveness of implementing a screening and targeted decolonization strategy. An universal decolonization protocol would have the advantage of easy and less resource-consuming implementation, no carrier would be left untreated due to screening sensitivity issues or timely identification and treatment problems and it would probably be less expensive as costs with screening outweigh treatment. The chief concern with universal decolonization is that unnecessary treatment may promote mupirocin resistance spread. Although it has been suggested that universal decolonization seems to be associated with an equally low risk of mupirocin resistance in *S. aureus*, a better option would be to find adequate alternatives for mupirocin nasal ointment⁶²⁴. Povidone-iodine-based skin and nasal antiseptic has already been shown to be just as effective as mupirocin with the added advantage of fast acting. Significant reductions in the number of *S. aureus* colony forming units were found after just one hour of treatment and extending up to 12 hours⁶²⁵. There is some evidence that universal treatment with such products may lead to similar infection rates as screening and selective mupirocin treatment of carriers with significant cost savings and ease of implementation⁶²⁶. Larger studies investigating this alternative strategy are needed.

Alongside minimizing wound contamination, prophylaxis emphasis is also on optimizing the host's ability to fight bacteria that manage to get to the joint. Perioperative antibiotics are a chief component of such strategy and further research is needed on the optimal institutional-specific regimen (according to resident flora) or even patient-specific regimens according to known risk factors such as *S. aureus* carrier or ASB status.

One other major component of this equation is the prosthesis itself. Once it is implanted the so-called "race for the surface" begins between the bacteria and the host tissues⁶²⁷. According to this model, when the host cells colonize the implant surface first, the probability of attachment of bacterial cells is very low and vice versa. The speed at which the biofilm develops on the prosthesis depends on the number and kind of bacteria reaching it, the immune state of the

patient but also the characteristics of the implant surface. Surface characteristics of a biomaterial such as roughness, hydrophobicity, and electrostatic charge are in play⁶²⁸ but also a number of potential receptors for bacterial adhesive ligands offered by the protein film that covers an implant immediately after its placement into the host body⁶²⁹. As a result, there is a strong need for intrinsic implant surface antibacterial functionality to overcome the implant-induced defects in local immune response and prevent bacteria from quickly adhering to the implant and produce a protective biofilm barrier. The research on new biomaterials or alternative implant coatings is currently a major research topic. This goal can be achieved in several different ways.

Romano et al.⁶³⁰ proposed a classification of antibacterial coatings according to their strategy of action. *Passive surface finishing/modification* of an existing biomaterial that results in a substantial change of its susceptibility to bacterial colonization would constitute a first group. Several different anti-adhesive surface modifications have been proposed, but only a few will probably be suitable for clinical use. Most of them seem to offer limited antibacterial and anti-biofilm activity and their use in prosthetic joints specifically is further limited by a potential interference with osteointegration.

Active surface finishing/modification is a separate group. Coatings included in this class, feature pharmacologically active pre-incorporated antibacterial agents, like antibiotics, antiseptics, metal ions, or other organic and inorganic molecules. A well-known example that is already being extensively used especially in tumor megaprosthesis is silver ion coating⁶³¹. Silver is however, cytotoxic to bone cells preventing the coating of the intra-medullary part of the prosthesis and costly, thus limiting its use to a small number of cases. Other metallic ions such as zinc for instances, also have potent antibacterial effects on a wide spectrum of bacterial species^{632,633}. However, potential toxic side effects of these metals remain a strong concern. Non-metal elements such as iodine, chlorhexidine or selenium have also shown great promise. Of these, povidone-iodine is probably the most interesting and there is already data of its efficacy in the clinical setting⁶³¹. Another path is to use organic compounds with antibacterial properties of which using antibiotics is by far the most studied alternative. A large number of studies have investigated the efficacy of surfaces coated with covalently linked antibiotics⁶³⁰. In fact, despite the theoretical advantages of non-eluting systems, this concept is limited by the fragility of the coatings and killing activity potential of bacteria which might not be directly adjacent to the implant. To overcome these issues, combinations of antibiotics with other compounds such as porous hydroxyapatite or biodegradable polymers⁶³⁴ that control antibiotic elution have been proposed. To avoid the risk of drug resistance, some antiseptic agents such as chlorhexidine or even antimicrobial peptides or cytokines are being explored. Antimicrobial peptides (ex. chitosan) are a new class of antibiotics with very interesting features. They are highly active against a broad spectrum of microorganisms, highly selective towards microorganisms and not mammalian cells, present fast killing even at low concentrations and most importantly, they have a much lower tendency to induce resistance⁶³⁵. Long-term impact of permanently coated implants with antibiotics and other organic compounds, does raise concerns regarding possible induction of bacterial resistance, local or systemic toxicity and possible detrimental effects on implant osteointegration. In addition, regulatory issues apart, its large-scale application seems very challenging in the foreseeable future.

Perioperative antibacterial local carriers or coatings would be a better way to overcome such challenges. Instead of pre-manufactured surface modifications, that require the use of specific implants, a different approach would be to provide a traditional implant with an antibacterial carrier or coating at the time of surgery. Such a universal coating would allow the use of different, already existing, implants and biomaterials making it a versatile solution. Traditional antibiotic-loaded PMMA, bone grafts or even bone substitutes⁶³⁶ are examples of such a way to deliver implant protection but are associated with several already discussed limitations. Biocompatible antibiotic delivering hydrogels represent a possible alternative solution with demonstrable *in vitro* efficacy^{634,637}. Resistance to press fit insertion of uncemented prosthesis, favorable elution kinetics and lack of adverse osteointegration effect are key to assuring *in vivo* efficacy as it has already been hinted^{638,639}. A hypothetically better alternative that would reduce the risk of drug resistance would be to apply the same principle in delivering alternative antibacterial agents such as antiseptics or antimicrobial peptides.

In addition to innovative device technologies, another possible future approach to prevent PJI would be through vaccination and immunization against common pathogens or biofilm antigens⁶⁴⁰.

Diagnosis

PJI diagnosis is often a difficult and laborious task. The matrix-enclosed sessile biofilm bacteria elicit a much lower and more localized inflammatory response than an equivalent number of planktonic bacteria would. This limited inflammatory response often eludes traditional clinical and laboratory diagnostic criteria. In addition, biofilm-mode bacteria are often in a slow-growing phase thus diminishing the sensitivity of traditional bacterial isolation and culturing methods.

The fact remains that presently, there is no bullet proof, gold standard definition of infection. In current clinical practice, PJI diagnosis must rely on the combined interpretation of different diagnostic modalities that must be thoroughly and systematically considered along with sound clinical judgment. Synovial fluid investigation seems to be the best available preoperative tool. A number of different tests should be performed once a sample is collected.

However, in correctly understanding how to interpret existing literature, one must be aware of a major predicament. Often, especially in acute infections, prosthetic joint infection presentation is quite clear cut (i.e. major elevation of inflammatory parameters, obvious local wound signs, purulence around the prosthesis, etc.). The real struggle is differentiating between certain chronic low-grade infections depicting pain alone from other types of aseptic failure. In fact, most studies about diagnostic performance of a particular test compare aseptic failures to all infected cases regardless of type of infection. This small detail may be contributing to overestimation of the real diagnostic worth of each test in the real clinical practice dilemma of aseptic vs. chronic low grade infection distinction.

We focused on optimizing the interpretation of synovial fluid examination in this specific setting. That is why we focused exclusively on chronic painful total joint replacements requiring revision surgery and excluded acute infections. The goal was to investigate simple, inexpensive and widely available tests that could easily make the transition into every day management such as leukocyte differential counts, high sensitivity C-reactive protein or adenosine deaminase. We were able to prove the added practical value of such strategy but a number of different issues demand us to continue with further research. Should synovial CRP and ADA threshold values be different in each specific joint? What is the accuracy of these markers in patients with inflammatory arthritis? Will the levels of these markers be useful in determining optimal timing for the second stage? It is also conceivable that these biomarkers prove its usefulness in other settings such as differentiating septic from non-septic acute native joint arthritis.

Notwithstanding, intraoperative culture samples are still a critical step in reaching a definitive diagnosis. Correct multiple tissue sample gathering and processing have greatly enhanced our ability to detect pathogens over the last few years and should be regarded as the first line intervention in those seeking to improve. More expensive and labor intensive strategies such as sonication and other biofilm disruption techniques that are already available seem to be especially important in cases where bacterial load is lower, previous cultures are negative and/or previous antibiotic treatment has been initiated. New molecular-based techniques of bacterial identification should be viewed mainly as investigational tools at least in the near

future. Not only because of cost and availability but also because of struggles in accurately interpreting some findings. These highly sensitive techniques have raised interesting questions and defy the limits of pathogen mediated vs. real aseptic prosthesis failure. Palmer et al.⁶⁴¹ using molecular diagnostics were able to show a significant proportion of patients with knee osteoarthritis and no signs of infection, undergoing primary arthroplasty, have confirmed bacterial biofilms present where traditional cultures have been negative. Are all joints really sterile and therefore should all encountered bacteria be viewed as potentially pathogenic or are modern diagnostic techniques too sensitive and lack specificity? Ultimately currently accepted definitions of PJI may be in need of revision. Staats et al.⁶⁴² performed a retrospective matched-pair analysis in 98 patients who had undergone revision surgery after total joint arthroplasty. They found that in the group of 49 patients with less than three minor criteria (insufficient to consider them infected), long-term implant survival was significantly inferior than the group of 49 patients with absolutely no positive criteria.

While many of the characteristics of biofilm implant-related infections have now been well characterized, challenges remain for translating this paradigm shift into clinically meaningful diagnostic benefits. A promising research path based on serological detection of elevated levels of antibody to microbial antigens, specifically “anti-biofilm” antigens is underway^{640,643}. Recently, it has been demonstrated that noninvasive detection of serum antibodies is able to diagnose PJI in the clinical setting^{644,645}. Artini et al.⁶⁴⁴ demonstrated that an enzyme-linked immunosorbent assay (ELISA) designed to detect IgM serum antibodies to staphylococcal slime polysaccharide antigens showed promising results (95% specificity; 90% sensitivity) in detecting delayed orthopedic joint prosthesis infections due to staphylococci. Marmor et al.⁶⁴⁵ went a step further and tried to use a multiplex immunoassay that measured serum IgG with antigens from three *Staphylococcus* species, *Streptococcus agalactiae* and *Propionibacterium acnes*. However, compared to traditional cultures of intraoperative samples it has shown limited sensitivity and specificity with authors acknowledging limitations regarding bacterial species not included in the assay, cross reactivity between antigens from species in the same genus and naturally inherent limitations of the fact that sole detection of IgG’s may not provide accurate information soon after the onset of infection. There are even others trying to come up with lateral flow immunoassays that would rapidly and inexpensively diagnose biofilm infections by detecting host antibodies against these biofilm-upregulated antigens in different biologic samples such as serum or synovial fluid⁶⁴⁰. Antibodies against biofilm surface proteins, have also been shown to accumulate rapidly in the site of infection and it is conceivable that this fact could be used to accurately diagnose infection if such antibodies can be conjugated with some kind of marker (e.g. radionuclide)⁶⁴⁰.

Treatment

Selecting the best treatment alternative for each specific situation is possibly the most challenging decision in PJI management. Accurately classifying each case taking into account major variables that influence outcome such as type and duration of infection, specific pathogen but also host characteristics would be ideal. Although numerous classification systems exist for PJI, a flawless classification system is still lacking. An ideal classification system would be comprehensive, and at the same time simple enough to use in clinical practice. It would help guide correct treatment choice and hold intrinsic prognostic value.

It is critical to acknowledge the biofilm paradigm as it conveys extreme implications in the treatment of PJI. For a number of known and probably several not yet fully understood mechanisms, bacteria within the biofilm are resistant to antibiotic levels up to 1,000 times higher than their planktonic counterparts⁶²⁷. In addition, biofilms are resistant to the host immune system as it has been shown that antibodies fail to penetrate them and even activated phagocytes cannot kill bacteria in biofilms⁶²⁷. Costerton et al.⁴² suggested that much of the tissue damage in chronic biofilm infections is caused by this “frustrated phagocytosis” and persistent inflammation around the implant. It is critical to acknowledge that, up to nowadays, once a mature biofilm is formed there are no effective ways to eliminate it *in vivo*.

It is therefore logical that the success of debridement and implant retention depends largely on the short duration of infection before treatment. Nevertheless, biofilm forms and matures in the first hours and days after bacteria reaching the implant and therefore the use of antimicrobials effective in disrupting biofilm and/or killing bacteria within it is decisive. Further research is needed regarding potential adjuvants for intraoperative biofilm disruption. Chlorhexidine and acetic acid are examples of such strategies that are already being used but they offer limited efficacy. Adequate postoperative anti-biofilm antibiotic therapy is also a cornerstone for successful implant retention. Presently, rifampicin and ciprofloxacin to some degree are the only effective therapy and alternative drug(s) are desperately needed. Antimicrobial peptides are also a possible therapeutic tool if an effective delivery methodology can be devised. If *in vivo* biofilm disruption therapy becomes real, the need for revision surgery would greatly diminish. For the time being it is crucial to adequately select cases in which DAIR is likely to succeed since patients who have undergone DAIR and failed, often undergo multiple subsequent surgical procedures adding morbidity and cost to the process. Gardner et al.⁵⁹⁰ reported a failure rate of 42% in 19 patients treated with revision TKA after failed DAIR. A multicenter retrospective study, focusing on 83 patients undergoing two-stage revision knee surgery after failed previous DAIR procedures, found a 34% failure rate⁵⁹¹. Comparing such results with traditionally higher success rates of the two-stage revision approach, the authors suggested failed DAIR procedures could lead to prohibitively high failure rates of two-stage reimplantation thus recommending caution in its use⁵⁹¹. However, more recent findings seem to call into question this concern, Brimmo⁵⁸⁹ et al. retrospectively looked at 750 patients who had undergone 2-stage revision, 57 (7.6%) of them after undergoing DAIR within 2 years before revision and 693 as initial PJI treatment. Even after adjusting for multiple variables a lower risk of failure (albeit not statistically significant) was found in the group with failed previous DAIR suggesting it may not be as detrimental as previously supposed.

Notwithstanding, in an effort to accurately predict the probability of success thus helping decide on the best course of treatment, some authors have tried to come out with prognostic preoperative scores^{429,434}. Data on prospectively applying these tools or even including pathogen specific indications and analyzing its implications are however still missing. In the future, such tools may prove to be of major importance.

There is still open debate around a number of other issues. What is the best management for persistent postoperative wound leakage? It is our personal belief that every suspicious wound should be viewed as infected until proven otherwise. As such, we advocate a formal DAIR procedure following all of the previously described steps especially deep debridement and culture samples gathering that will dictate the correct of treatment in each case (i.e. prolonged antibiotic therapy or not). Whether a single or multiple debridements should be performed is also doubtful. Our current practice is to try a second debridement only when it is necessary. If it fails, especially in a patient with risk factors such as medical comorbidities, polymicrobial or “high risk” pathogen infections, strong consideration is given to another treatment alternative such as revision surgery or excision arthroplasty depending on the patient’s general health status.

Once a mature biofilm is formed in a chronic infection, the only currently viable alternative is to surgically eradicate it by removing the implant as well as all foreign material and dead tissues that can potentially host it. Whether this exchange revision surgery should be performed in a single or two-stage procedure has been the topic of discussion for many years now. There is a recent trend towards favoring one-stage exchange. If successful, it offers obvious benefits to the patient. In fact, at least in selected cases, it seems to offer favorable infection eradication rates. It is nevertheless important to stress that: 1) infection eradication rates after two-stage have consistently shown to be good despite including those difficult to treat cases that are often excluded from the one stage approach and, 2) routine unselected one-stage approach has yet to prove similar worth. On the other hand, in addition to patient morbidity throughout treatment, a major handicap of the two-stage approach concerns patients not completing the second stage. The proportion of patients who do not actually complete the second stage is a very important and often over-looked problem. In our experience, it accounted for all treatment failures (four out of 29 patients) and recent studies suggest the proportion of patients who fail to undergo subsequent reimplantation may be as high as one-third⁵¹⁹⁻⁵²¹. The scant available information regarding this specific cohort of patients may have been contributing to overestimation of the success of the two-step exchange as others have also noticed⁵²⁰.

As such, debate seems to have moved on definitively from whether one- or two-stage revision surgery is better, to which are the specific circumstances that dictate the best course of action. One of the most widely adopted algorithms for selecting circumstances-adapted treatment including the choice between one- and two-stage exchange is the one proposed by Zimmerli et al.²⁴⁷ in 2004. There is reiterated evidence that strictly following these patient selection algorithms seems to offer favorable results^{501,646,647}. The best way to prove the actual significance of such selection criteria or even finding new ones would be to conduct unselecting randomized controlled trials and this work has already started⁶⁴⁸. Still, it is also

our belief that the two-stage approach is perhaps more forgiving and tolerant to error. We also believe that before embarking in one-stage exchange surgery one should gain experience in prosthetic joint infection surgery and management, understand the biofilm and its implications in optimal surgical but also medical/antibiotic therapy as well as assemble a multidisciplinary dedicated team.

A number of other unanswered questions demand continuing research. What is the optimal antibiotic regimen and is there a role for of resorbable local antibiotic delivery biomaterials in both DAIR and exchange surgery? When a two-stage approach is preferred, what is the optimal timing for reimplantation and what the proper serum or synovial tests to determine it should be? Is there a role and what are the indications for antibiotic therapy after reimplantation surgery?

Interpreting existing literature is also hampered by a widespread heterogeneity on reported clinical outcomes, the most important fact being different definitions of success. In an attempt to overcome this issue and uniform outcome reports, an international consensus was developed with the goal to create a consensus multidimensional definition for success after PJI treatment⁶⁴⁹. The consensus definition of a successfully treated PJI is: **(1)** infection eradication, characterized by a healed wound without fistula, drainage, or pain, and no infection recurrence caused by the same organism strain; **(2)** no subsequent surgical intervention for infection after reimplantation surgery; and **(3)** no occurrence of PJI-related mortality⁶⁴⁹. Future research should comply as much as possible with this common ground in order to facilitate discussion and outcome comparison.

Still, we believe definition of successful PJI treatment must progress past looking solely at infection eradication or associated mortality. As knowledge evolves and the number of patients where successful infection eradication becomes greater, other variables such as functional outcomes after completion of treatment, re-revision rates for causes other than infection (i.e. instability, aseptic loosening, etc.) and health-related quality of life must be considered. Optimizing treatment costs are also an important matter especially in this era of worldwide financial concerns. In the future, one of the major challenges is to define the role of DAIR, one-stage or two-stage revision surgery in view of this perspective.

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