Prosthetic joints: shining lights on challenging blind spots

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Keywords:
PJI, Arthroplasty, TKR, THR, Loosening, Implant

Introduction

Fifteen hot topics on joint replacement (JR) and prosthetic joint infection (PJI) with controversies and contentious areas were selected and reviewed by members of the Bone and Joint Working Group of the International Society of Chemotherapy (ISC) with co-opted orthopaedic and infection specialist colleagues. A manuscript was prepared, following an in-depth review of the current literature, with the aim of providing an insight into these complex issues and, when applicable, provide personal views from authors' own experience. There remain many unanswered questions in regards to these and other areas of arthroplasty and more studies are required in some of these fields.

1. Antibiotic prophylaxis in primary arthroplasty (agents, timing and duration).

Peri-operative antibiotics significantly reduce post-operative surgical site infection (SSI) rates in total joint replacement (TJR). A meta-analysis of randomised clinical trials (RCT) showed no differences in SSI rates when choosing one antibiotic over another (mainly glycopeptides, cephalosporins & cloxacillin) in total hip and knee arthroplasty (THA, TKA) [1]. In North America, cephalosporins are used as first-line prophylaxis in primary TJR [2]. In the UK, the most commonly used first-line prophylaxis is flucloxacillin plus gentamicin [3], a choice aimed to reduce the incidence of *Clostridium difficile* associated diarrhoea purportedly driven by cephalosporins. Glycopeptides are considered for patients who are MRSA carriers or have anaphylaxis to penicillin.

In an Australian study, 63% of subsequent infections were caused by bacteria resistant to the original prophylaxis [4]. A Scottish study found 4% to 32% of Staphylococci spp, from PJI, were resistant to the prophylaxis regime [5]. Furthermore, an increasing proportion of Gram negative bacterial (GNB) infections have been reported following TJR [6]. Bosco et al, demonstrated increasing resistant GNB isolates in THA and the addition of gentamicin to cefazolin reduced SSI from 1.19% to 0.55% [7]. Glycopeptide prophylaxis has led to significant relative risk reduction for SSI from MRSA, particularly during increasing prevalence of MRSA [8]. However, combining vancomycin and cefazolin increases the risk of acute kidney injury (AKI), therefore, without clear indications, the routine addition of glycopeptides as prophylaxis for primary TJR should be avoided [9].

There have also been concerns of AKI following the use of flucloxacillin plus gentamicin as prophylaxis in TJR. However, higher-dose flucloxacillin (5-8 g/ day) compared to lower-dose flucloxacillin (3-4 g/ day) could be the reason for subsequent development of AKI [10].

Current recommendations and recent evidence regarding timing and duration of antibiotic prophylaxis (AP) in TJR [11-15] are summarised in (Table 1)

Prophylaxis is an evolving matter, regular reviews are essential based on epidemiological and patient factors. Generally compliance with the following is associated with fewer post-operative infections [16]; 1) a narrow-spectrum antibiotic active against expected pathogens (combination of antibiotics in the case of high incidence of drug-resistant strains), 2) no later than sixty minutes before skin incision, 3) ideally single dose pre-operatively, (maximum 24 hours post-operatively) and 4) re-dosing if operative time exceeds two half-lives of the antibiotic or there is excessive blood loss.

Table 1
Summary of current recommendations and some recent evidence regarding timing and duration of antibiotic prophylaxis in TJR

Recommendations	Recent evidence
The recommendation in the US is for antimicrobial prophylaxis (AP) to be administered within one hour before incision and discontinued within 24 hours [11], while European guidelines recommend a single dose within 30 minutes before incision [12].	A recent review and meta-analysis involving > 4000 patients showed no efficacy of extended post-operative prophylaxis beyond 24 hours for the prevention of SSI in THA/ TKA [13]. No evidence exists that continuing prophylactic antibiotics until all catheters and drains have been removed will lower infection rates [11]. A prospective multicentre study of around 2000 THA, found no difference in SSI between single pre-operative and multiple post-operative antibiotic doses, but a trend to increased SSI when prophylaxis administered during or after skin incision [14]. Wu et al, in a study of > 3000 primary TKA, divided the timing of administration of prophylaxis into 2 categories: within 30 minutes and >30- 60 minutes before surgery. The duration of prophylaxis post-operatively was also divided into 2 categories: within 24 hours and >24 hours. No additional reduction of SSI was found when prophylaxis was given within 30 minutes or > 24 hours [15].

2. Antibiotic prophylaxis for revision arthroplasty for infection – timing and duration

While consensus groups advocate that peri-operative AP should be the same for primary and uninfected revision arthroplasty [17], some consider patients undergoing revision arthroplasties are at higher risk of developing PJI by multidrug-resistant organisms. Liu *et al*, added vancomycin to cefazolin as antimicrobial prophylaxis in 414 patients undergoing revision TKA. Following this their infection rate decreased from 7.89% to 3.13% (p=0.046) with a significant reduction in PJI due to methicillin-resistant organisms (4.2% to 0.9%, p=0.049) [18].

Ideally AP should not be administered until deep intra-articular samples are obtained [17]. However, Tetreault *et al*, found no difference in the concordance rate between pre-operative and intra-operative cultures where patients with known PJIs were randomized to receive antibiotics either before skin incision or after obtaining intra-operative cultures [19], these findings were also supported by other investigators [20].

While there is no consensus nor there evidence about whether to stop or continue antimicrobial prophylaxis until microbiology culture results are back following revision procedures for aseptic loosening, it could be logical to wait until culture results prior to stopping antibiotics in revision arthroplasty due to infection. More studies are needed to concur or refute this and to provide better guidance. .

3. Local antibiotic agents in primary arthroplasty what is their role in prophylaxis?

The capacity of bone cement to release antibiotic molecules (e.g. gentamicin, tobramycin, vancomycin) is claimed to be useful for prevention or treatment of PJI. Synthetic calcium sulfate loaded with antibiotics (e.g. tobramycin, vancomycin) has been reported in an *in vitro* study to have the potential to reduce or eliminate biofilm formation on adjacent periprosthetic tissue and prosthesis material, and thus, to reduce the rates of PJI, however clinical studies showing their efficacy are lacking [21]. A meta-analysis involving 35,659 patients receiving arthroplasties showed that the use of antibiotic-impregnated-cement was associated with a reduction in SSI from 2.3% to 1.2% [22]. On the other hand, the use of gentamicin-containing collagen sponges has not been shown to reduce the incidence of SSI in arthroplasties [23]. Furthermore the routine use of antibiotics in irrigation solutions compared to saline solutions remains controversial [24].

A number of experts recommend the use of antibiotic loaded cement (ALBC) in two-stage exchange arthroplasty with static and dynamic spacers, beads and rods for prophylaxis [25]. There are data from the Norwegian registry and others showing that routine use of antibiotic-loaded polymethylmethacrylate (PMMA) provide better implant survivorship. ALBC is currently used as a routine in Scandinavian countries, in many centres in Europe and the USA. While the practice appears to be safe, its optimal use and the potential for the development of resistance have not been fully assessed. Antimicrobial laden implants containing vancomycin are not in use, but may hold promise for future clinical applications [24]. We believe more studies and trials are required in this field to assist future directions.

4. Operating room traffic during arthroplasty and rates of infection.

Operating room (OR) ventilation, temperature and pressure systems are engineered to maintain a sterile field. Frequent door openings disturb the laminar positive pressure air flow dynamics and correspond to an increased level of microbiological contamination . Bacterial counts in OR's air increased 34-fold in an OR with 5 people compared to an empty room [26]. There is also an exponential relationship between the number of door openings and the number of personnel in the OR [27], with a direct correlation between the activity level of OR personnel and bacterial fallout into the sterile field [28].

High incidences of door openings of 0.64 - 0.66 per minute have been reported for TJR [27, 29]. Doors were opened on average 9.5 minutes per case and transient loss of positive pressure occurred in 40% of cases potentially jeopardizing OR sterility [30].

The pre-incision period accounted for 30% to 50% of door openings, as patient preparation and room setup are under way. By personnel; circulating nurse and core staff generated 37% to 52% of door openings, surgeons accounted for 9% to 17% and anaesthesia for 10% to 24%. By reason; request for information generated 27% to 54% of foot traffic, delivery or retrieval of equipment in 11% to 22% and staff breaks or staff relief in 20% to 26% [27, 29]. The number and duration of door openings increased in direct proportion to length of surgery, with 1 door opening for 6.9 seconds for each additional 2.5 minute operative time [30]. By complexity; revision surgery had higher 0.84 door openings per minute compared to 0.65 openings per minute for primary procedures [31].

The association between foot traffic and SSI remains mostly observational. The causes of excessive OR traffic must be evaluated locally and should be kept to a minimum. Improvements to theatre storage, door opening deterrents and education of personnel are necessary to reduce foot traffic in the OR.

5. Positive urine dip and/ or urine culture: are they indications for antibiotic therapy and/ or cancelation of a scheduled operation for primary and revision arthroplasty?

Asymptomatic bacteriuria (ASB) has been implicated as a cause of PJI, despite weak supporting evidence. Spanish guidelines advocate treatment of ASB pre-arthroplasty [32], whilst UK

guidance recommends routine urinalysis at pre-assessment, but no specific guidance on subsequent management [33] and the Australian guidance do not recommend this practice [34]. One study concluded that urinalysis/ culture should be offered routinely pre-operatively for all patients, despite reported differences between organisms isolated from pre-operative urine and subsequent post-operative wound cultures [35], recent evidence casts doubt on the benefit and cost effectiveness of this practice.

In a recent RCT [36], authors performed urinalysis in patients, due to undergo hip arthroplasty and randomised those with proven ASB to treatment or no-treatment groups. No significant difference in PJI rate was found between culture-negative and ASB groups, whether treated or not. Interestingly, causative organisms in tissues were distinct from urine isolates in PJI cases with ASB. Similar results were replicated in knee arthroplasty [37]. In a multicentre study of nearly 2500 THA or TKA, patients were screened for ASB pre-operatively and treated in an individualised, non-randomised fashion, with PJI at one-year post-operative as the primary outcome. Although ASB was an independent risk factor for PJI, particularly that due to Gram negatives, these did not correlate to isolates from urine cultures. Crucially, pre-operative antibiotic treatment for ASB did not show any significant benefit in preventing PJI. The authors postulate that ASB may merely represent a surrogate marker for unrecognised risk factors for subsequent PJI [38].

In a prospective observational cohort study with urinalyses pre- and three days post joint replacement; Among 510 patients, 36% had pre-operative ASB and 35% had pyuria. 95% received single dose cefuroxime intravenously as prophylaxis peri-operatively. On the third post-operative day urinalysis identified pyuria in 19% and bacteriuria in 41%. Pathogens on the third post-operative day were different from those in the pre-operative samples in > 50% of patients. Only 5% of patients developed a UTI and two thirds of organisms identified were unrelated to those found during the admission. All symptomatic infections were successfully treated with no perceived effect on the joint replacement [39].

In summary, there are no convincing data to support routine screening and treatment of ASB to prevent subsequent PJI or SSI in patients undergoing arthroplasty. Presence of ASB or a pre-operative abnormal urinalysis in the absence of symptoms should not be reasons to routinely cancel or delay scheduled TJR.

6. Urinary catheter insertion/ removal and prophylactic antibiotics: are they required in patients with prosthetic joints?

While the use of a urinary catheter increases the risk of bacteriuria, as mentioned before, there is weak evidence regarding the risk bacteriuria poses to an implanted prosthesis.

Scarlato *et al*, conducted a prospective observational study that included 99 patients undergoing elective primary hip and knee arthroplasty. Urine specimens were collected at insertion and removal of urinary catheters along with blood cultures upon urinary catheter removal. The incidence of bacteriuria on catheter insertion was 4.4%. The incidence of catheter associated bacteriuria was 1.3%. No bacteraemia cases were detected with urinary catheter removal. Overall 98% of the cohort received antimicrobial prophylaxis, mostly gentamicin, for urinary catheter insertion and removal. However, the timing of antibiotic administration in relation to the collection of urine samples and the exact time between urinary catheter removal and collection of the blood culture specimen were not fully clear in this study [40]. Most elderly patients will have ASB and it has been estimated thatin order to prevent one PJI originating from the urinary tract, 25 000 patients with ASB would need to be treated with antibiotics [36].

The Infectious Diseases Society of America (IDSA) determined that there was insufficient evidence to recommend widespread AP after urinary catheterization [41]. There is no evidence to support the continued use of post-operative antibiotics when urinary catheters are in place [17]. The advances in anaesthetic techniques and rapid recovery have facilitated the elimination of prolonged indwelling catheterisation. Unnecessary antibiotics will increase the chances of selection pressure on antimicrobial resistance. There is no evidence that the presence of a urinary catheter or its removal may be associated with an increased risk of peri-prosthetic infection and no AP is needed in these circumstances.

7. Is prosthetic loosening an infection (PJI) until proved otherwise? Tips to decide.

PJI may be present clinically without meeting criteria from Proceedings of the International Consensus Meeting on Periprosthetic Joint Infection [17]. The most common cause of implant failure is aseptic loosening (AL), followed by PJI. In certain cases differentiating loosening due to infection from AL can be challenging and clinical pictures could be misleadingly reassuring. Standard serum biomarkers e.g. white blood cell counts (WBC), C-reactive protein (CRP), erythrocyte sedimentation rate (ESR) may not be conclusive and the use serum procalcitonin (PCT) is not recommended [42]. Combination of these markers with others may be of better diagnostic values [42, 43]. Advanced imaging techniques could have a role in the diagnosis of PJI, but they can be resource and time consuming. Specific serological diagnostics are currently being evaluated for Staphylococci, Streptococci and Propionibacterium acnes [https://clinicaltrials.gov/ct2/show/NCT02222792]. The pre-operative checks of synovial fluid aspirate and evaluation for microbiological and biochemical markers may be of value to assist the diagnosis [42, 44-47].

Surgical or arthroscopic biopsies may be used in certain cases. Experience with histopathology is variable particularly with low grade infections. In a prospective evaluation of 198 patients undergoing revision hip or knee arthroplasty, due to presumed AL, a sonication fluid of prosthesis and tissue samples for microbiology and histopathology at the time of the surgery were investigated. 12 % of patients with pre-and intra-operative diagnosis of AL had post-operative diagnosis of PJI. After a follow up of 31 months, 37.5 % of these patients (PJI group) had implant failure compared to only 1 in the AL group ($p < 0.0001$). The authors concluded that positive histology and positive peri-implant tissue and sonicate fluid cultures are highly predictive of implant failure in patients with PJI. Additionally, patients with greater number of partial revisions for a presumed AL had more risk of PJI [48].

Early loosening is more often caused by hidden PJI than late loosening, especially if it arises in the first four years or in the absence of obvious mechanical causes. Thorough clinical and para-clinical assessments and exhaustive investigations must be carried out to reach a diagnosis and a management strategy.

8. The role of sonication and/ or vortexing or dithiothreitol for microbiological diagnosis of PJI and do these have any impact on long-term patient outcome?

The application of sonication on the explanted prosthesis is aimed to release bacteria from the biofilm into the sonication fluid, which is subsequently cultured. Pre-sonication vortexing enhances the effect of subsequent sonication. In a recent meta-analysis, the pooled sensitivity and specificity of sonicate fluid culture (SFC) were estimated to be 80% and 95% respectively [49], higher than that of conventional periprosthetic-tissue-culture (PTC).

Administration of antimicrobials prior to prosthesis explantation impairs the microbial detection rate of PTC much more than that of SFC; this is likely due to the fact that biofilm bacteria are less susceptible to antimicrobial agents. Portillo et al. demonstrated that, compared to conventional SFC, the inoculation of sonication fluid into blood culture bottles had higher sensitivity, shorter time to culture positivity and not reduced by previous antibiotic treatment [50]. Others have recommended the analyses of sonication fluid with various PCR methods [46, 51] or for laboratories that cannot perform sonication, vortexing a resected device without sonication is probably a reasonable alternative [52].

Chemical debonding of bacteria is a novel technique which can provide similar results to sonication and can be applied not only to retrieved implants, but also to other bone and joint tissues. Treatment of prostheses with dithiothreitol (DTT) may be a reasonable alternative to sonication to improve detection of biofilm-associated bacteria in PJI with better sensitivity compared to sonication especially when the causative microorganism is *Staphylococcus epidermidis* [53- 55].

Although current data support the use of antibiofilm techniques (sonication or DTT) to improve microbiological yield, these methods have not yet been widely implemented mainly due to lack of trained staff and instrumentation. Many unanswered questions remain regarding the influence of these techniques on antimicrobial management, long-term patient outcome, length-of-stay and costs of care in PJI.

9. Biomarkers and PJI diagnosis: do they help or muddy the picture?

Although many biomarkers have been investigated (46, 47, 56-65), currently, no single biomarker can be considered gold standard for the diagnosis of PJI (Table 2). Further studies are required regarding accuracy and cost-effectiveness of newer markers.

10. The potential role for negative pressure wound therapy with installation (NPWTi) and Reactive Oxygen Surgihoney (SHRO) in the retention of a PJI.

Negative pressure wound therapy with intra-articular instillation (NPWTi) allows cyclical delivery of topical solutions to the wound bed (instillation-phase), followed by a hold time for fluid penetration (hold-phase), and finally negative pressure application to extract the solution (vacuum-phase). A multi-centre observational study involving 32 patients with an infected orthopaedic implant were treated using these techniques with polyhexanide as the instillation solution. 80% with chronic infections retained their implants. Major weaknesses of this study were small numbers and short (4-6 months) follow-up period [66].

Table 2
A number of blood and synovial biomarkers and the diagnosis of PJI

Biomarkers		Reports and comments
Blood	Peripheral blood WBC, CRP and ESR	Common screening tests recommended by guidelines for the evaluation of patients with suspected PJI [56, 57]. Not specific and not sensitive [42]. Serial measurements may be useful to assess treatment response, but CRP alone was a poor predictor of outcome following two-stage revision or debridement and retention surgery [58].
	Serum procalcitonin (PCT)	Although levels >0.3ng/ml can be highly specific (98%), sensitivity is poor (33%) in distinguishing between septic and aseptic joint replacement. Serum PCT cannot be considered a marker to identify patients with PJI [46, 59].
	Blood tumour necrosis factor (TNF)-α	Levels >40ng/ml, has high specificity (94%) but low sensitivity (43%) to diagnose PJI [59]. No a widely available test.
	Interleukin-6 (IL-6)	A meta-analysis found diagnostic accuracy was best for IL-6 followed by CRP, ESR then WBC [60]. In combination, IL-6 >5.12pg/ml and CRP >0.3 mg/dL may be a suitable to discriminate aseptic loosening versus low grade infection [61]. The normal range of serum IL-6 varies, which may reflect a considerable variation in cut-off ranges in different studies [42].
	Lipopolysaccharide binding protein (LBP)	At a cut-off value of >7ng/ml had specificity of 66% and sensitivity of 71%. No more accurate than CRP and therefore cannot be recommended [62].
Synovial	Synovial leukocyte esterase (LE)	Detectable by colorimetric strip test which results in colour change. Sensitivity, specificity, positive predictive value and negative predictive value were 66%, 97%, 89% and 88% respectively in a cohort of 189 patients. Although analysis is subjective and affected by the presence of debris or blood [63].
	Synovial α -defensin protein	A prospective evaluation of 102 patients demonstrated good diagnostic accuracy for first-stage or single-stage arthroplasty with sensitivity of 100% and specificity of 98%. Performs less well for second-stage arthroplasty with reduced sensitivity of 67% although specificity remained at 97% [47].
	Synovial PCT	Limited data suggests it could be more beneficial than serum PCT in the diagnosis of localised SA, particularly in PJIs [46, 64, 65].

Saeed K *et al* reported on the application of NPWTi following surgical debridement in managing a case of *Pseudomonas aeruginosa* chronic PJI with implant retention using gentamicin as the instillation fluid. The system allowed for delivering high concentration of gentamicin locally without systemic toxicity [67]. A recent study examined the outcome of 16 trauma and orthopaedic patients with deep infection involving metalwork using NPWTi in conjunction with standard parenteral antibiotic therapy. The technique included serial debridement, irrigation and negative pressure dressings over a white polyvinyl alcohol foam. The authors report successful resolution of the infection in all cases with no early or unplanned removal of any metalwork [68].

An alternative is local Reactive Oxygen (RO) therapy with debridement & systemic antibiotics. RO therapy is currently delivered via a sterile pharmaceutical grade engineered honey, Surgihoney (SHRO); other delivery mechanisms are being investigated. It is an entirely novel solution to controlling/ eradicating bacteria by slow sustained release of hydrogen peroxide and other oxygen radicals [69]. SHRO is rapidly active in vitro against all Gram-positive and negative bacteria tested [70]. In addition, SHRO is highly antimicrobial and has been found to prevent biofilm formation caused by a range of bacterial species in wounds and reduce the extent of existing biofilms [71]. This makes SHRO highly relevant for local

therapy in arthroplasty with great potential for the control of bioburden and biofilm at these sites, thus providing an alternative to antibiotics, but as it is not a conventional antibiotic, it is less likely to select resistance. SHRO also provides healing and possibly angio-neurogenerative properties). It has been effectively used to treat chronic wounds, to prevent SSI and eradicate colonisation with resistance bacteria [72-74]. SHRO has been used clinically on a limited number of complex revision arthroplasty with safety and efficacy [75].

More *in vivo* studies and clinical trials of these novel technologies and agents are warranted as alternative approaches in managing PJI especially where implant retention is intended or unavoidable

11. Intravenous (IV) to oral to switch post suspected and confirmed PJI- a blanket guide or individualised care plan?

Studies reporting clinical benefit using rifamycins and fluoroquinolones [76] amongst others, in PJI have provided a stimulus for switching to oral antibiotics given the high oral bioavailability of such agents.
A report of early IV to oral antibiotic switch, in 21 PJI cases, demonstrated excellent outcomes with no cases of relapse at 24 - 36 months [77]. These were exclusively Gram positive monobacterial infections and a high proportion (17/21) of two-stage exchange procedures with no debridement and implant retention (DAIR) cases featured. Patients generally received around two weeks of IV therapy before an oral switch. Rifampicin–ciprofloxacin combination therapy was the most commonly used regime. In all cases, but one with negative cultures, individualised, pathogen-specific tailored antibiotic regimes were used.

A Spanish study [78] reported success at follow-up (2-9years) in 38/40 patients with late PJI undergoing two-stage exchange arthroplasty and pathogen-specific solely oral antibiotic therapy. The approach resulted in discharge seven days post-operatively in the majority of cases. Infecting organisms were overwhelmingly Gram positive and predominantly staphylococcal.

For staphylococcal PJI, data support better outcomes with rifampicin containing regimes such as rifampicin-fluoroquinolone [76] or rifampicin-fucidic acid [79] combinations. Other agents with excellent oral bioavailability such as linezolid have also been studied [80, 81]. Moxifloxacin monotherapy also yielded good outcomes in a study of staphylococcal PJI [82]. In Gram negative PJI, improved outcomes are reported with fluoroquinolone therapy [83, 84].

Recommended agents for cases of streptococcal/ enterococcal PJI are beta-lactams or glycopeptides [56]. Lack of oral glycopeptide formulations and relatively poor oral bioavailability of many beta-lactams may hamper an IV to oral switch in such cases. Corvec [85] reported successful outcome with solely oral amoxicillin in combination with moxifloxacin in a small series of Group B streptococcal PJI. Linezolid (in combination with rifampicin) has shown promising in vitro activity against biofilm dwelling *Enterococcus faecalis* strains, however clinical data from linezolid use in enterococcal PJI, although promising [86], is limited.

In summary, optimal antibiotic choice and route of administration in PJI should be individualised and ideally pathogen tailored, recognising published data for certain pathogen–antibiotic class combinations. The optimal timing of switch to- and choice of oral therapy remains to be determined by future prospective studies, the complexity of which, accounting for variation in host; joint involved; timing of infection; operative approach and infecting pathogen and its susceptibility, may render these difficult to achieve.

12. What is the best strategy and when is the best time for reimplantation following PJI?

The timing and method of reimplantation is broadly dependent upon the timing of infection, causative pathogen, stability of the prostheses and patient comorbidities.

Direct comparisons between one-stage and two-stage strategies are difficult due to a patient selection bias and the lack of RCTs. Conventionally the debate on whether one- or two-stage arthroplasty is the optimum management following PJI has favoured two-stage procedures. However, studies have showed no significant differences in reinfection rates between these strategies [87-89] and one-stage procedure may provide superior outcomes [89]. Hence, a paradigm shift in opinion is emerging. For some, multi-microbial infections, presence of a sinus tract and/or a first PJI revision failure are strict exclusions for a one-stage revision. For others, these parameters are not absolute. Furthermore while some experts believe that the decision for a one or two-stage strategy should be decided intra-operatively. Others believe it is as much pre-operative philosophical approach as an intra-operative assessment.
To apply this new paradigm, at least two levels of reasoning must be considered:
1- How to define exclusive criteria for one-stage procedure?
2- How to optimize this strategy technically and technologically?

A thorough intra-hospital infrastructure could be a major factor for success in one-stage reimplantation which could include, but not limited to:

A. Pre-operative preparation and planning: e.g. assessment for requirement of custom-made implants.
B. Intra-operative arrangements e.g. surgical expertise and knowledge of the antibiogram for the final cement impregnation.
C. Post-operative specific patient care e.g. multidisciplinary therapeutic strategies.

Future research is required regarding the application of computer-assisted surgery that may assist in real-life assessment, potential impact on functional outcome and optimisation of one-stage revision surgery.

If two-stage procedure is chosen, there is no definitive evidence as to the optimal time interval between the two-stages. Successful results have been experienced where reimplantation is conducted within 2-6 weeks of resection while patient receiving systemic antibiotics. Some advocate cessation of antibiotics for 2 to 8 weeks prior to reimplantation. Time intervals greater than 6 months result in suboptimal results in restoring patient function and eradicating infection [90].

The economic impact of PJI is immense; two-stage revision of septic THA costs 1.7 times more than a one-stage revision [91]. Hence, a one-stage strategy is more ideal when considering potential medico-economic aspects. While this point of view still remains controversial, the two-stage option should be reserved in case contraindication (e.g. failure of ≥ two previous one-stage procedures or highly resistant organism) of the one-stage procedure applies!

13. Is it always necessary to use rifampicin in patients treated for prosthetic joint infections with debridement and implant retention (DAIR)?

The use of rifampicin following DAIR is recommended for Gram positive PJI [17, 56]. This has been based on one small RCT [92], which only included 33 patients, of whom 15 had a

PJI. At two years, it reported 100% (12 of 12) cure rate in the rifampicin plus ciprofloxacin group, versus 58% (7 of 12) in the ciprofloxacin monotherapy group (p = 0.02). However, 6 patients didn't complete treatment in the rifampicin group versus 3 in the control group. When reanalysed by intention-to-treat, the difference wasn't statistically significant (p = 0.10).

Theoretical and *in-vitro* evidence supports the use of rifampicin in PJIs following DAIR, since it penetrates biofilms and penetrates/ acts inside mammalian cells. Animal models suggest rifampicin is effective in implant-related infections only when used in combination with a second agent and where there is a low organism burden (e.g. following adequate debridement), but not all studies show a benefit of adding rifampicin to other regimens [93]. Observational studies in humans (the majority of which are retrospective uncontrolled studies) generally report higher cure rates among those who received rifampicin-based therapy compared with those who did not, but are also heterogeneous in their findings and potentially confounded by the systematic differences in patients groups, quality of surgical debridement and clinicians' choices.

There is very limited evidence to support the use of rifampicin in the setting of one- or two-stage revision arthroplasty, or in GNB infections. Adverse drug reactions, drug interactions, and the emergence of rifampicin resistance may limit the use of rifampicin-based treatment. Overall, in Gram positive PJIs (particularly Staphylococcal) following DAIR, there is theoretical and observational evidence to support the use of rifampicin, but considerable doubt remains about the applicability of this evidence in real-world settings. Larger RCTs assessing the effect of rifampicin combination therapy on cure rates, taking into account, dosage, adverse events, cost and the degree of debridement are necessary before this question can be definitively settled.

14. How long is a piece of string? Duration of antibiotic therapy following debridement, antibiotics, and implant retention (DAIR) for prosthetic joint infection.

Following DAIR, patients are treated for a variable period with IV antibiotics, followed in most cases by a course of oral antibiotics (ranging from none at all to over 12 months, depending on the institution/ situation).
This uncertainty is reflected in international guidelines, with 2-6 weeks IV therapy with 3 to 6 months of oral antibiotic therapy, commencing during or following the IV course [17, 56].

At least one observational study suggests that the "magic numbers" of 3 and 6 months for total antibiotic duration are probably too long [94]. In a systematic review including data from 710 patients treated with DAIR for PJI, the "success" (infection eradication) rate varied widely between studies, from 15.8% to 75% [95]. There was insufficient information included in the studies to judge the influence of antibiotic duration on success rates, but appropriate patient selection and the degree of surgical debridement both emerged as important predictors of success. A single open-label non-inferiority RCT addressing this question has recently been published [96]. This study compared a total antibiotic duration of 8 weeks with 3 months (hips) or 6 months (knees) in 63 patients with Staphylococcal acute PJI following DAIR. IV antibiotics were given for up to 7 days, and then switched to oral rifampicin plus levofloxacin. The cure rate at 12 months was non-inferior in the short course group (73%) compared with the long course group (58%). However, in the subgroup with knee infections short course treatment did not meet the criteria for non-inferiority. . This study suggests early oral step down and shorter course treatment is probably as good as longer courses, but this needs to be confirmed with larger RCTs.

In summary, there is insufficient evidence to guide the duration of antibiotic treatment following DAIR. Large RCTs are needed to compare shorter with longer durations of IV and/or oral antibiotics following DAIR.

15. Role of OPAT for treatment of PJIs

The use of Outpatient Parenteral Antibiotic Therapy (OPAT) has rapidly grown worldwide. It consists in the administration of parenteral antimicrobial therapy in various settings (including patients' homes and physicians' offices) thereby minimising or even avoiding hospital admission or stay. OPAT has several benefits: saving in healthcare costs, lower risk of hospital-acquired infections and improvement in patient's comfort. Bone and joint Infections (BJIs), including PJI, represent one of the main indications for OPAT, as they often involve prolonged parenteral antimicrobial therapy [97]. However, the accurate selection of patients eligible to OPAT is critical; many factors must be taken into account such as the severity of the infection, comorbidities and the patient's social context. It is recommended to establish an interdisciplinary and coordinated OPAT team (involving a family member/ caregivers, a physician, an infection specialist, an infusion nurse and a pharmacist) in order to ensure a complete monitoring of patient's clinical condition and laboratory values. Antimicrobials with long half-lives are generally preferred because their lower frequency of administration improves compliance and reduces complications associated with frequent catheter manipulations. However, the first dose of a newly prescribed intravenous drug should always be administrated in supervised settings [98]. Although OPAT has been successfully adopted for PJI treatment worldwide, substantial differences in OPAT management (concerning antibiotic choice, duration of therapy, delivery route and infusion devices) have been reported among different countries. Data from International OPAT Registry may represent the basis for future efforts to standardize the OPAT programs of different countries in order to determine the most suitable and safe management of PJIs in outpatient settings [99].

Conclusion:

This review has covered some challenging topics in the delivery of arthroplasty and the management of PJI. While the conclusions may largely represent consensus views of this working group, there are nevertheless recommendations from research and highlighting further requirements for research in these contentious areas.

Funding
No funding was obtained for this work, all done in own time and as part of routine work.

Declaration
Nothing to declare and no conflict of interest related to this work

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