International Journal of Antimicrobial Agents 49 (2017) 153–161

Contents lists available at ScienceDirect

International Journal of Antimicrobial Agents

journal homepage: www.elsevier.com/locate/ijantimicag

Hot Topic

Prosthetic joints: shining lights on challenging blind spots

Keywords:
Prosthetic joint infection
Arthroplasty
Total knee arthroplasty
Total hip arthroplasty
Loosening
Implant

1. Introduction

Fifteen hot topics on joint replacement 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, to provide personal views from authors' own experience. There remain many unanswered questions with regard to these and other areas of arthroplasty, and more studies are required in some of the fields.

2. 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 (RCTs) showed no differences in SSI rates when choosing one antibiotic over another (mainly glycopeptides, cephalosporins and cloxacillin) in total hip arthroplasty (THA) and total knee arthroplasty (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 carriers of methicillin-resistant *Staphylococcus aureus* (MRSA) or who have an anaphylactic reaction to penicillin.

In an Australian study of patients receiving antibiotic prophylaxis at the time of arthroplasty, 63% of subsequent infections were caused by bacteria resistant to the original prophylaxis [4]. A Scottish study found that 4–32% of staphylococci species from PJI were resistant to the prophylaxis regimen [5]. Furthermore, an increasing proportion of Gram-negative bacteria (GNB) infections have been reported following TJR [6]. Bosco et al demonstrated an increasing prevalence of GNB isolates in THA, and the addition of gentamicin to cefazolin prophylaxis reduced SSI rates from 1.19% to 0.55% [7]. Glycopeptide prophylaxis has led to a significant relative risk reduction for SSI from MRSA, particularly during an increasing prevalence of MRSA [8]. However, combining vancomycin and cefazolin increases the risk of acute kidney injury (AKI); therefore, without clear indications, 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, use of high-dose flucloxacillin (5–8 g/day) compared with lower-dose flucloxacillin (3–4 g/day) could be the reason for subsequent development of AKI [10].

Current recommendations and recent evidence regarding the timing and duration of antibiotic prophylaxis in TJR [11–15] are summarised in Table 1.

Prophylaxis is an evolving matter and regular reviews are essential based on epidemiological and patient factors. Generally, compliance with the following is associated with fewer post-operative infections [16]: (i) a narrow-spectrum antibiotic active against expected pathogens (combination of antibiotics in the case of a high incidence of drug-resistant strains); (ii) no later than 60 min before skin incision; (iii) ideally single dose pre-operatively (maximum 24 h post-operatively); and (iv) re-dosing if operative time exceeds two half-lives of the antibiotic or there is excessive blood loss.

3. Antibiotic prophylaxis for revision arthroplasty for infection: timing and duration

Whilst consensus groups advocate that peri-operative antibiotic prophylaxis should be the same for primary and uninfected revision arthroplasty [17], some consider that 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 which the infection rate decreased from 7.89% to 3.13% ($P = 0.046$) with a significant reduction in PJI due to methicillin-resistant organisms (from 4.2% to 0.9%; $P = 0.049$) [18].

Ideally, antibiotic prophylaxis 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 randomised to receive antibiotics either before skin incision or after obtaining intra-operative cultures [19]; these findings were also supported by other investigators [20].

Whilst there is no consensus nor there is evidence regarding whether to stop or continue antimicrobial prophylaxis until microbiology culture results are available following revision procedures for aseptic loosening, it could be logical to wait for culture results prior to stopping antibiotics in revision arthroplasty due to

http://dx.doi.org/10.1016/j.ijantimicag.2016.10.015

Table 1
Summary of current recommendations and recent evidence regarding the timing and duration of antibiotic prophylaxis in total joint replacement.

Recommendation	Recent evidence
The recommendation in the USA is for antimicrobial prophylaxis to be administered within 1 h before incision and discontinued within 24 h [11], whilst European guidelines recommend a single dose within 30 min before incision [12]	A recent review and meta-analysis involving >4000 patients showed no efficacy of extended post-operative prophylaxis beyond 24 h 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 ca. 2000 THAs found no difference in SSI rates between single pre-operative and multiple post-operative antibiotic doses, but a trend to increased SSI when prophylaxis was administered during or after skin incision [14]. In a study of >3000 primary TKAs, Wu et al divided the timing of administration of prophylaxis into two categories: within 30 min; and >30–60 min before surgery. The duration of prophylaxis post-operatively was also divided into two categories: within 24 h; and >24 h. No additional reduction of SSI was found when prophylaxis was given within 30 min or >24 h [15]

SSI, surgical site infection; THA, total hip arthroplasty; TKA, total knee arthroplasty.

infection. More studies are needed to concur or refute this and to provide better guidance.

4. 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 the prevention or treatment of PJI. Synthetic calcium sulphate 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 rate of PJI; however, clinical studies showing its efficacy are lacking [21]. A meta-analysis involving 35,659 patients receiving arthroplasties showed that use of antibiotic-impregnated cement was associated with a reduction in SSI rates 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, routine use of antibiotics in irrigation solutions compared with saline solution remains controversial [24].

A number of experts recommend the use of antibiotic-loaded bone cement (ALBC) in two-stage exchange arthroplasty with static and dynamic spacers, beads and rods for prophylaxis [25]. Data from the Norwegian registry and others show that routine use of antibiotic-loaded polymethylmethacrylate (PMMA) provides better implant survivorship. ALBC is currently used as routine in Scandinavian countries as well as in many centres in Europe and the USA. Whilst 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 that more studies and trials are required in this field to assist future directions.

5. Operating room (OR) traffic during arthroplasty and rates of infection

OR ventilation, temperature and pressure systems are engineered to maintain a sterile field. Frequent door openings disturb the laminar positive pressure airflow dynamics and correspond to an increased level of microbiological contamination. Bacterial counts in the air of ORs increased 34-fold in an OR with five people compared with 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]. In one study, doors were opened on average 9.5 min per case, and transient loss of positive pressure occurred in 40% of cases potentially jeopardising OR sterility [30].

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

6. Positive urine dip and/or urine culture: are they indications for antibiotic therapy and/or cancellation 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 does 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], the 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 THAs or TKAs, patients were screened for ASB pre-operatively and were treated in an individualised, non-randomised fashion, with PJI 1 year post-operatively as the primary outcome [38]. Although ASB was an independent risk factor for PJI, particularly due to Gram-negative micro-organisms, these did not correlate with isolates from urine cultures. Crucially, pre-operative antibiotic treatment for ASB did not show any significant benefit in preventing PJI. The authors