Current management of prosthetic joint infections in adults: results of an Emerging Infections Network survey

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ABSTRACT

There is a dearth of guidance on the management of prosthetic joint infections (PJIs), in particular because of the lack of high-quality evidence for optimal antibiotics. Thus, we designed a nine-question survey of current practices and preferences among members of the Emerging Infections Network, a CDC-sponsored network of infectious diseases physicians, which was distributed in May 2012. In total, 556 (47.2%) of 1178 network members responded. As first-line antibiotic choice for MSSA PJI, 59% of responders indicated oxacillin/nafcillin, 33% cefazolin and 7% ceftriaxone; the commonest alternative was cefazolin (46%). For MRSA PJI, 90% preferred vancomycin, 7% daptomycin and 0.8% ceftaroline; the commonest alternative was daptomycin (65%). Antibiotic selection for coagulase-negative staphylococci varied depending on methicillin susceptibility. For staphylococcal PJIs with retained hardware, most providers would add rifampicin. *Propionibacterium* is usually treated with vancomycin (40%), penicillin (23%) or ceftriaxone (17%). Most responders thought 10–19% of all PJIs were culture-negative. Culture-negative PJIs of the lower extremities are usually treated with a vancomycin/fluoroquinolone combination, and culture-negative shoulder PJIs with vancomycin/ceftriaxone. The most cited criteria for selecting antibiotics were ease of administration and the safety profile. A treatment duration of 6–8 weeks is preferred (by 77% of responders) and is mostly guided by clinical response and inflammatory markers. Ninety-nine percent of responders recommend oral antibiotic suppression (for varying durations) in patients with retained hardware. In conclusion, there is considerable variation in treatment of PJIs both with identified pathogens and those with negative cultures. Future studies should aim to identify optimum treatment strategies.

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1. Introduction

Prosthetic joint infections (PJIs) are among the most common indications for long-term intravenous (i.v.) antibiotic treatment and a common reason for outpatient parenteral antibiotic treatment (OPAT) in the USA [1]. Due to an ageing population and more joint arthroplasties being performed, the incidence of PJIs has increased over the past two decades [2]. Unlike many other infections, however, there is no reliable test of cure available for PJIs. The clinical response and functional status during recovery can be used to assess treatment response, but they are limited by subjectivity and inter-rater variability. Providers also commonly use relatively non-specific laboratory tests [e.g. erythrocyte sedimentation rate (ESR), serum C-reactive protein (CRP)] for monitoring purposes or obtain imaging studies, which may not be able to differentiate between ongoing infection and bone restructuring [3]. These limitations may explain the dearth of head-to-head comparisons

of antibiotics or treatment strategies for PJIs [4]. As a result, infectious diseases physicians receive little robust guidance when making clinical decisions for these patients and are largely left to expert opinion [5,6]. For the same pathogen, multiple different antibiotics could be selected [5]. The recommended treatment duration is based on limited evidence [7]. Likewise, the surgical approach lacks standardisation [8].

The Infectious Diseases Society of America (IDSA) is therefore in the process of creating guidelines to standardise the management of PJIs. In the meantime, we wanted to understand better the practice patterns of infectious diseases providers regarding antibiotic treatment and treatment response monitoring. The Emerging Infections Network (EIN), a provider-based sentinel network run by the IDSA (http://ein.idsociety.org/), was utilised. A survey was designed to address the following questions: (i) which antibiotics are most commonly chosen by providers in the EIN network for common PJI pathogens or culture-negative infections, and what criteria influence this choice; (ii) how long are i.v. antibiotics given; (iii) what is the prevalence of oral antibiotic use for PJI treatment; and (iv) what are the most frequently used elements to determine when treatment can be discontinued. In summary, we intended to

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obtain in-depth information on current practices in PJI management, in the absence of robust evidence or national guidelines.

2. Material and methods

The IDSA's EIN is a provider-based, emerging infections sentinel network that was established through a Cooperative Agreement Program Award from the US Centers for Disease Control and Prevention (CDC, Atlanta, GA) [9]. It consists of physicians who practice adult and paediatric infectious diseases medicine, belong to either the IDSA or the Pediatric Infectious Diseases Society, and who have volunteered to participate in the network. EIN member physicians represent ca. 20% of infectious diseases subspecialists in the USA certified by the American Board of Internal Medicine. For the purpose of this study, we focused on EIN members who manage adult patients.

The study objective was to understand better the practice patterns of infectious diseases specialists who treat PJIs. Survey questions were developed in collaboration between the EIN leadership (SEB and PMP) and the Division of Infectious Diseases at Washington University School of Medicine (JM, MAL and HMB). A subset of EIN Executive Committee members and several Washington University infectious diseases physicians involved in the care of patients with PJIs piloted the survey. In May 2012, the survey was sent out in its final form to 1178 EIN members practicing in North America.

The survey consisted of introductory text and nine questions sent by electronic mail or facsimile; the initial mailing was followed by two subsequent reminders for non-responders, sent 2 weeks and 4 weeks after the original email. Survey questions addressed antibiotic preferences and management practices for PJIs. Antibiotic preferences focused on first, second and third antibiotic choices for the most common causes of PJIs [methicillin-susceptible *Staphylococcus aureus* (MSSA), methicillin-resistant *S. aureus* (MRSA), methicillin-susceptible coagulase-negative staphylococci (MS-CoNS), methicillin-resistant CoNS (MR-CoNS) and *Propionibacterium* spp.]. Also, preferred single-drug or combination regimens for culture-negative infections were elicited for three commonly involved joints (hip, knee and shoulder). One question focused on the addition of rifampicin to the main antibiotic for hardware-associated infections. Participants were asked to rank important criteria for choosing a particular antibiotic (ranking a selection of six criteria in order of relevance, with 1 being the most relevant; the average was inverted with $1/x$ to yield a higher number the more relevant the criterion was). The preferred duration of antibiotic treatment, criteria for defining success, and when antibiotics could be discontinued were also determined. Denominators for some questions varied because not all EIN members responded to all questions. Differences in frequencies were analysed for statistical significance using χ^2 tests, Student's *t*-test and Mann–Whitney *U*-test as appropriate. A *P*-value of <0.05 was considered significant. The statistical package SPSS v.18 (SPSS Inc., Chicago, IL) was used for analyses.

3. Results

3.1. Response rate and demographics of responding physicians

Overall, 556 (47.2%) of 1178 participating physicians responded to the survey. A total of 73 EIN members who have never responded to a survey during their membership were excluded from the denominator, giving a response rate of 50.3% (i.e. 556/1105). Moreover, 85 members responded by email that they do not see patients with PJIs; these individuals were not included in further analyses, which resulted in a cohort of 471 respondents. Not all respondents
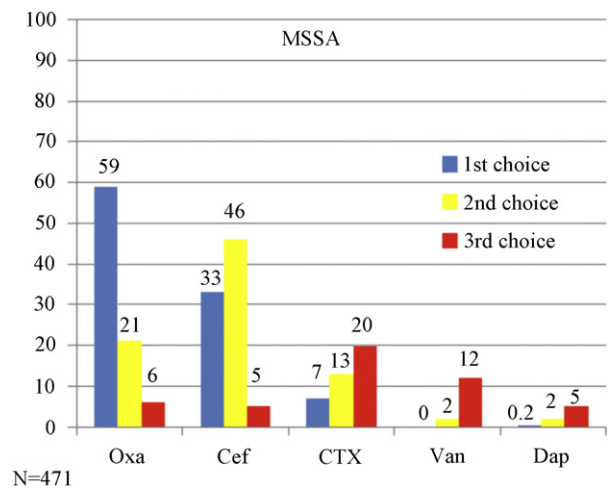
Fig. 1. Antibiotic preferences for methicillin-susceptible *Staphylococcus aureus* (MSSA), as a percentage of all responders. Oxa, oxacillin/nafcillin; Cef, cefazolin; CTX, ceftriaxone; Van, vancomycin; Dap, daptomycin.

answered all questions and therefore denominators for individual questions varied.

The number of respondents per geographic division of the USA, as defined by the US Census Bureau (http://www.census.gov/geo/www/us_regdiv.pdf), was calculated. Providers from all geographic regions were included, with the largest numbers stemming from the South Atlantic (93/556; 17%), Pacific (89/556; 16%), the Mid-Atlantic (84/556; 15%) and the East North Central region (81/556; 15%). Eight providers (1%) responded from Canada. In terms of professional experience, the largest responding group was 160 physicians with ≥25 years of experience (i.e. 59% of 273 in this category). With regard to employment, 188 (34%) were employed by a university hospital or medical school, 177 (32%) were in private practice, 153 (28%) worked in a hospital and 38 (7%) were employed by the Veteran Administration (VA), military or a state-directed institution. The hospitals where patients were seen were university hospitals (181; 33%), non-university teaching hospitals (166; 30%), community hospitals (147; 26%), VA or military hospitals (34; 6%) or others. Data came from small hospitals with <200 beds (10%), midsize hospitals with 200–600 beds (66%) and large hospitals with >600 beds (24%).

Survey respondents were significantly more likely than non-respondents to have ≥15 years of infectious diseases experience (*P* < 0.0001).

3.2. Antibiotic choices for known pathogens

For PJI due to MSSA, 59% (277/471) of responders indicated oxacillin/nafcillin as their first-line antibiotic choice, 33% (154/471) preferred cefazolin and 7% (34/471) ceftriaxone (Fig. 1). The most frequently selected second choice was cefazolin (46%). Ceftriaxone was cited as second choice for 13% and third choice for 20%. Daptomycin played a minor role, with 0.2% indicating it as first choice and 2% and 5% as second and third choice, respectively.

For MRSA PJIs, 90% (426/471) preferred vancomycin, 7% (31/471) daptomycin and 0.8% (4/471) ceftaroline; the most frequently selected second choice was daptomycin (65%) and the third linezolid (27%) (Fig. 2). Ceftaroline, recently approved by the US Food and Drug Administration (FDA) (for pneumonia and skin/skin-structure infections), was the third choice for 14% of respondents. Telavancin was not included among treatment options for MRSA since it was not commercially available at the time of this survey.

Choices for CoNS varied depending on methicillin susceptibility. The preferences for MR-CoNS followed very closely those for MRSA
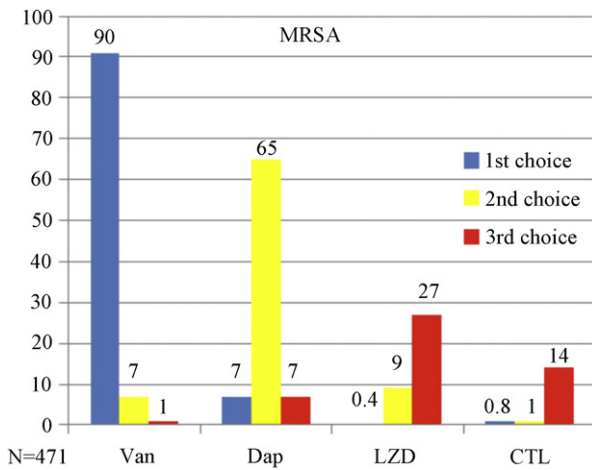
Fig. 2. Antibiotic preferences for methicillin-resistant *Staphylococcus aureus* (MRSA), as a percentage of all responders. Van, vancomycin; Dap, daptomycin; LZD, linezolid; CTL, ceftaroline.
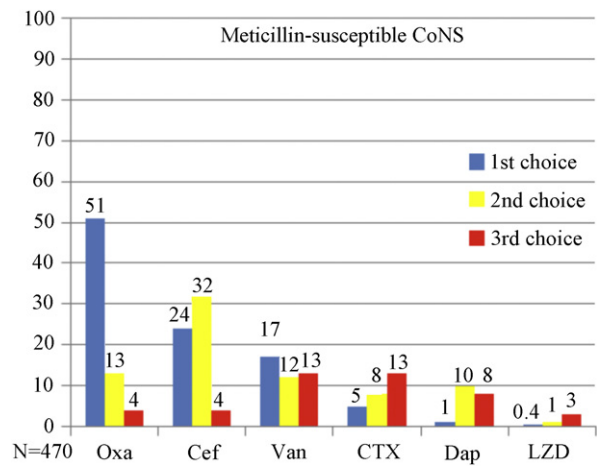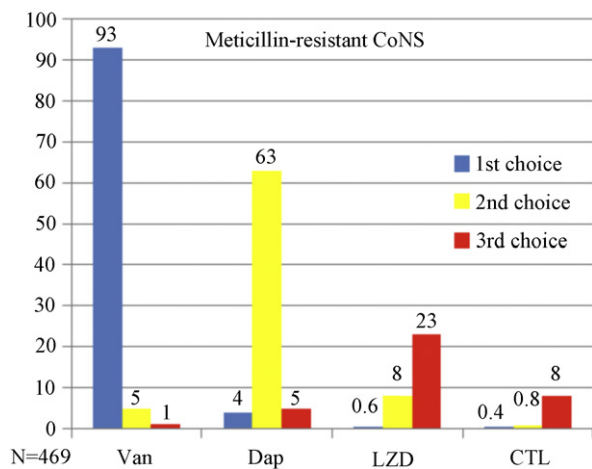

Fig. 4. Antibiotic preferences for methicillin-susceptible coagulase-negative staphylococci (CoNS), as a percentage of all responders. Oxa, oxacillin/nafcillin; Cef, cefazolin; Van, vancomycin; CTX, ceftriaxone; Dap, daptomycin; LZD, linezolid.

(Fig. 3). For MS-CoNS (Fig. 4), 51% (239/470) and 24% (113/470) selected oxacillin and cefazolin as first option, respectively. However, another 17% (80/470) of providers indicated vancomycin as first choice. Daptomycin was ranked more frequently as a second option for MS-CoNS than for MSSA infections (10% vs. 2%; $P < 0.001$).

If hardware is retained in staphylococcal infections, 55% (256/468) of providers would add rifampicin to the main antibiotic for more than one-half of their patients; 5% (23/468) would never use rifampicin in that setting.

Propionibacterium infections are usually treated with vancomycin (40%; 181/453), penicillin (23%; 106/453) or ceftriaxone (17%; 78/453) (Fig. 5). Providers gave a number of other antimicrobials as options, such as clindamycin, daptomycin and linezolid. The most frequently chosen second-line treatment was vancomycin (18%).

3.3. Antibiotic choices for culture-negative prosthetic joint infections

Most responders (33%) indicated that culture-negative PJIs made up 10–19% of cases; another 23% indicated 20–29% of PJI episodes seen in their practice were culture-negative. A two-drug regimen was chosen by approximately two-thirds of respondents for treatment of culture-negative PJIs [by 68% (313/463) of providers for knee infections, 69% (317/462) for hip infections and 63% (289/458) for shoulder infections]. Combinations of either vancomycin and ceftriaxone or vancomycin and a fluoroquinolone were most popular. The third most common combination was vancomycin with cefepime. Lower extremity culture-negative PJIs are most commonly treated with a combination of vancomycin and a fluoroquinolone [31% (98/313) of knee PJIs and 28% (88/317) of hip PJIs]. Shoulder PJIs are more commonly treated with vancomycin and ceftriaxone (24%; 69/291). If a single-drug regimen was selected for any culture-negative PJI, vancomycin was the most common choice (223/282; 79%). Three-drug regimens were not used frequently (see Fig. 6).

3.4. Criteria for specific antibiotic choices

The most cited criteria for selecting antibiotics were ease of administration (ranking = 0.675, with the maximum mean being 1) and the safety profile (0.638). Patient preference was not indicated as an important determinant of antibiotic choice (0.221), nor were monitoring requirements (0.254) (Fig. 7).

Fig. 3. Antibiotic preferences for methicillin-resistant coagulase-negative staphylococci (CoNS), as a percentage of all responders. Van, vancomycin; Dap, daptomycin; LZD, linezolid; CTL, ceftaroline.
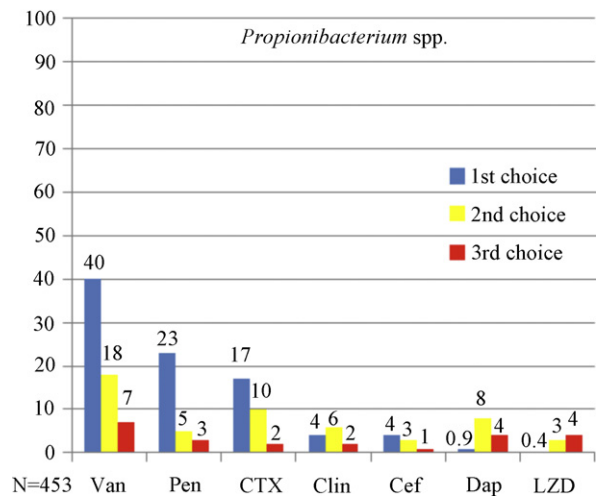
Fig. 5. Antibiotic preferences for *Propionibacterium* spp., as a percentage of all responders. Van, vancomycin; Pen, penicillin; CTX, ceftriaxone; Clin, clindamycin; Cef, cefazolin; Dap, daptomycin; LZD, linezolid.
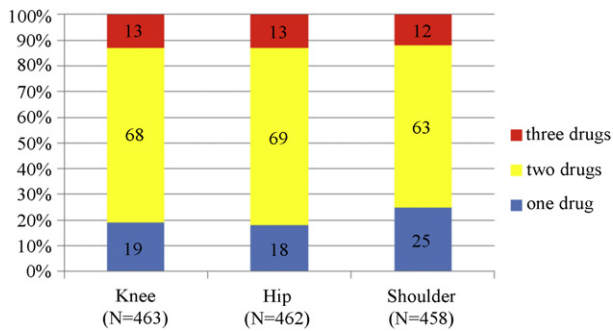
Fig. 6. Preferences for combination regimens for treatment of culture-negative prosthetic joint infections, as a percentage of responders.

3.5. Antibiotic treatment duration and criteria for discontinuing treatment

A treatment duration of 6–8 weeks is preferred by 77% of responders and is mostly guided by clinical response (ranking = 0.795) and inflammatory markers (0.512); imaging has a minor role (0.269). Only two providers (0.4%) opted for a treatment duration of less than 4 weeks. Switching from i.v. to oral antibiotics to complete a treatment course was not a commonly cited practice (73/462; 16%). For patients with PJI and retained prosthetic material who were given oral antibiotic suppression, providers varied in their preferred duration of suppression (23% would treat for months, 35% for years and 41% lifelong); very few providers would not recommend suppression (*n* = 5; 1%).

4. Discussion

With the ageing of the US population, there has been a parallel increase in total joint arthroplasties and subsequent PJIs. Optimum management of these PJIs, however, is compromised for several reasons: (i) the diagnostic work-up does not yield a causative pathogen in at least 7–9.5% of episodes [10]; (ii) very few head-to-head trials of different antibiotics for PJI have been conducted; and (iii) there is no standardised test of cure for PJI. We were interested in better understanding current treatment practices and antibiotic preferences of infectious diseases physicians who provide care to patients with PJIs. Considerable variation in practices was encountered.

Providers chose oxacillin/nafcillin (59%), cefazolin (33%) or ceftriaxone (7%) as first option for MSSA. Oxacillin, nafcillin and other
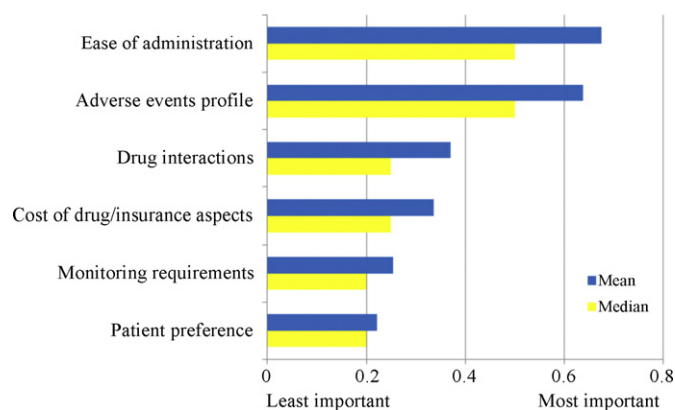

Fig. 7. Most important considerations when selecting antibiotics for prosthetic joint infections (assuming in vitro susceptibility and equivalent efficacy). Six criteria were ranked from 1 (most important) to 6 (least important); mean values were inverted with 1/*x* to yield higher values for more important criteria.

anti-staphylococcal penicillins are considered the standard treatment for MSSA [11], and cefazolin is a reasonable alternative [12]. Cefazolin may have been chosen relatively frequently because its dosing schedule is more compatible with OPAT than that of oxacillin/nafcillin. Another possibility is that providers favour cefazolin in settings of possible penicillin allergy. Although comparative data are lacking for PJIs, studies on the effectiveness of cefazolin for MSSA bacteraemias indicated that it is similar to oxacillin and better than vancomycin [13]. Ceftriaxone, dosed once daily, has recently been favourably compared with oxacillin for bone and joint infections [14] but is not frequently used among EIN members. Treatment for MRSA appears to be much more uniform, with 90% of providers choosing vancomycin as their first-line treatment option. Very little evidence supports the use of daptomycin [15]; it is, however, well tolerated and does not require serum levels to be measured.

With regard to CoNS, it is noteworthy that 17% of EIN members indicated vancomycin as first choice in methicillin-susceptible isolates, although this may be inferior to treatment with β-lactams and is not recommended by experts [5]. Providers were also not uniform in their approach to *Propionibacterium* infections. These skin bacteria are thought to be of low virulence but are considered an emerging pathogen in PJIs [16]. The standard treatment is β-lactams (in particular penicillin and ceftriaxone), to which *Propionibacterium acnes* is almost exclusively susceptible [17]. Here, vancomycin was the predominantly selected first-choice antibiotic; this was unexpected as vancomycin is less convenient than ceftriaxone for administration and may not be clinically equivalent.

Very little information is available on culture-negative PJIs, for which antibiotic exposure prior to the diagnostic work-up is a risk factor [18]. It is possible that these infections are caused by atypical pathogens that cannot be identified with traditional microbiological methods [19]. Other so-called culture-negative infections may in fact be inflammatory conditions due to prosthetic material intolerability [20], manifestations of rheumatic disease, gouty arthritis, or represent aseptic loosening. With regard to antibiotic management of these infections, there is very little guidance available in the scientific literature. It is particularly difficult to define treatment failure in affected patients, which complicates the design of future studies on optimal treatment. A multitude of treatment regimens have been used [10]. We found that most EIN providers preferred two-agent regimens (vancomycin and ceftriaxone, or vancomycin and fluoroquinolone). Given that staphylococci are the predominant cause of infection, it is reasonable to make vancomycin the backbone of the regimen; the addition of Gram-negative coverage may or may not be necessary. It is also noteworthy that responders estimated the percentage of culture-negative PJIs to be much higher than reported before [10].

In 1998, Zimmerli et al. demonstrated in a landmark paper that addition of rifampicin (to oral ciprofloxacin) for staphylococcal PJIs with retained hardware resulted in improved outcomes [21]. The underlying rationale for this study was that rifampicin penetrates fairly well into bacterial biofilms and that it has an effect on stationary-phase bacteria, such as those embedded in a hardware-related biofilm. However, rifampicin has the potential for drug interactions and may not be a suitable choice for all patients, e.g. those on anticoagulation. Also, despite further data supporting the addition of rifampicin to oral antibiotics [22,23], there are no clinical data available on rifampicin combined with i.v. antibiotics [24], which is common practice in North America. In this study, we found that providers would give rifampicin to most of their patients with staphylococcal PJIs and retained hardware; this level of acceptance of rifampicin as an adjunctive agent has not been documented before. This isolated finding should be interpreted cautiously as we did not elicit experiences with rifampicin discontinuation due

to interactions or treatment outcomes with rifampicin-containing regimens.

There is no single test of cure for determining the treatment response in PJIs, creating a significant challenge for physicians. Repeat joint aspirations are occasionally done to monitor the treatment response but are more established as a test to rule out ongoing infection prior to re-implant. Therefore, clinicians often rely on surrogate markers such as peripheral white blood count, ESR, serum CRP [25] and, perhaps, imaging studies. By far the most important criterion to EIN members in this survey, however, was how patients responded clinically to the treatment. This endpoint is difficult to capture in a quantitative way and has not been included in current expert recommendations [5,6]. In addition, the optimum duration of medical treatment is not defined [26]. Most EIN members agreed with the standard of ca. 6 weeks of antibiotic treatment following surgery [27].

Another area of much controversy is whether oral antibiotic suppression is required for patients with PJIs managed with debridement and hardware retention and, if so, for how long. This approach is associated with low success rates [28] and should be reserved for patients with a short duration of symptoms, stable implant material, largely intact overlying tissue, and those who are poor candidates for removal surgery. In fact, Koeppe et al. stated in their systematic review of the literature that there is no clear indication for using suppression [29]. The optimum duration is also unclear. Nevertheless, almost all providers (99%) would use oral antibiotics for an extended time. The preferred duration of suppression varied enormously, reflecting the paucity of supporting data.

Limitations of this report include the possibility that the survey responses may not reflect the reality of how providers actually manage PJIs. Also, specific antibiotic choices cannot be linked to outcomes, which is an inherent limitation of surveys. The sample size of ca. 500 infectious diseases physicians was large but may not be representative for the entire infectious diseases physician community. For example, younger providers (possibly with different management preferences) were less likely to respond to this survey. The findings should also not be generalised to other geographic regions with different PJI management strategies. Lastly, we focused on the medical management aspect; surgical strategies have been studied in a previous survey [30].

In conclusion, many preferences and practices in the care of patients with PJIs are based on limited evidence, which may explain the significant variation in management. The upcoming IDSA guidelines are highly anticipated but, given the lack of robust data, are likely to be largely based on expert opinion. Comparative effectiveness studies of different regimens for identified pathogens and for culture-negative PJIs, as well as studies of rifampicin combined with i.v. antibiotics, should be performed in the future.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.ijantimicag.2012.10.023.

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