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Risk factors and treatment outcomes in osteomyelitis

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Outcome indicators of recurrence and amputation were used to evaluate risk factors and treatment choices in 454 patients with osteomyelitis who completed outpatient parenteral antimicrobial therapy (OPAT). Three hundred and fifteen (69.4%) were apparently cured at the time outcomes were measured and 139 (30.6%) had a recurrence. Of the recurrences, 56% occurred within 3 months, 78% within 6 months and 95% within 1 year. Both the initial pathogen and the choice of antibiotic had an effect on the risk of treatment failure. Osteomyelitis caused by *Pseudomonas aeruginosa* was associated with more than a two-fold increase in recurrence (*P* = 0.005) compared with infection caused by *Staphylococcus aureus.* There was a positive correlation between *P. aeruginosa* and amputation. With *S. aureus* infections, the risk of recurrence was more than twice as great with vancomycin therapy as opposed to treatment with β-lactams (*P* = 0.03). Treatment with ceftriaxone was as effective as the penicillinase-resistant penicillins and cefazolin.

Keywords: osteomyelitis, outcomes

Introduction

Osteomyelitis continues to be a frequent indication for the use of intravenous (iv) antibiotic therapy as well as a major healthcare cost item. Osteomyelitis is also a disease in transition, with ongoing changes in predisposing factors, causative organisms and treatment.[1] The relative frequency of haematogenous and relapsing osteomyelitis continues to decline. Conversely, the incidence of bone infections related to joint replacements, complex surgical interventions and wound infections is increasing. The advancing age of the general population has contributed to the increase in the incidence of diabetes and peripheral vascular disease (PVD), which are predisposing and complicating factors of osteomyelitis. There have also been dramatic changes in therapy, which include new antibiotics, new surgical techniques and outpatient parenteral antimicrobial therapy (OPAT).[2–7]

It has been difficult to study outcomes with osteomyelitis because of the heterogeneous nature of the infections, as well as the belief that an unusually long period of follow-up is needed to determine the effect of any treatments. This belief evolved from cases of relapsing *Staphylococcus aureus* osteomyelitis, which are far less frequent today due to improved antibiotic and surgical therapy. Currently, a 12 month follow-up after therapy is considered necessary to evaluate new antibiotics, pursuant to the joint Food and Drug Administration (FDA)/Infectious Diseases Society of America (IDSA) guidelines published in 1992.[8]

Among the first reports of treatment outcomes in osteomyelitis were the classic series of articles by Waldvogel *et al.* in 1970.[9–11] These authors characterized osteomyelitis by pathogenesis and chronicity, with the absence of signs or symptoms of infection 6 months after therapy as the measure of outcome. In their analyses, a 4 week course of high-dose iv antibiotic therapy was more likely to be successful than shorter courses with initial episodes of haematogenous osteomyelitis.[9] These articles set the standard for prolonged iv therapy in adults. More recently, studies have suggested that oral antibiotic therapy may be able to replace at least part of

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the prolonged courses of parenteral therapy in children[12–16] and some adults.[17]

With the current pressures for containing the escalating costs of hospital care and the development of increasing numbers of OPAT programmes, it has become common to provide all or part of the lengthy course of iv antibiotics required to treat osteomyelitis outside the hospital setting to many, if not most, patients with osteomyelitis.[6,18,19] When the OPAT programme at Infections Limited began in 1981, osteomyelitis was the most frequent infection treated.[20] Now it is second to skin and soft tissue infections as the most frequent infection, although the number of treatment days for osteomyelitis is still greater than that for any other infection. Because of the large number of patients with osteomyelitis treated through the Infections Limited clinic, and the likelihood that they would be referred back for recurrences, the opportunity for outcome studies was good.[6,21]

A number of risk factors were considered for analysis but this study focused on the microbiology and antimicrobial aspects of osteomyelitis and their relation to outcomes. Diabetes and vascular disease have been found to be correlated with poor outcomes and hence were considered in the statistical analyses performed.

Materials and methods

Infections Limited is a private clinic that provides consultations in infectious diseases and physician-directed services for a population of ~450 000 people in the greater Tacoma, Washington area. More than 4000 patients have been treated with OPAT by the clinic since the programme's inception in 1981.[20,22] Common practices for OPAT in the clinic are outlined in a handbook for outpatient parenteral therapy for infectious disease.[23] The clinic follows the guidelines for community-based parenteral anti-infective therapy established by the IDSA[24] and is accredited as an ambulatory infusion centre by the Joint Commission for the Accreditation of Health Care Organizations (JCAHO).

Microbiological studies for patients in the clinic are carried out in the Infections Limited laboratory, which is certified by the College of American Pathologists. Therapy is prescribed and managed by seven infectious disease specialists who work in the clinic. Antimicrobial choice and dosing are determined by the individual physicians. The most common dosage regimens used in adults with normal renal function are 2 g of a penicillinase-resistant penicillin (PRP) such as oxacillin, nafcillin or methicillin every 6 h; 2 g of cefazolin every 8 h; 2 g of ceftriaxone every 24 h; and 1 g of vancomycin every 12 or 24 h, with the longer dosage interval being utilized for elderly patients whose renal elimination may be reduced. Rifampicin was not used for combination therapy with *S. aureus*. *Pseudomonas aeruginosa* was routinely treated with ceftazidime or piperacillin plus tobramycin or amikacin.

Medical records were reviewed for patients who were treated for osteomyelitis through the Infections Limited OPAT programme from January 1982 to April 1998. Patients were excluded from the study if (i) an unequivocal pathogen was not identified by initial culture results, (ii) they did not receive at least 14 continuous days of parenteral antimicrobial therapy through the clinic and/or in the hospital, or (iii) more than two different antibiotics were administered. Patients with successful outcomes were followed for at least 6 months.

The diagnostic and bacteriological measures used to determine the presence of osteomyelitis reflect the usual approach to evaluation and management of this infection by infectious disease specialists in the community setting. In general, the initial diagnosis was based on clinical history and physical assessment along with wound or blood cultures and radiographic findings. Standard X-rays were carried out in virtually every case. In addition, bone scans were done in at least 32.8%, computerized tomography (CT) scan in 4.4% and magnetic resonance imaging (MRI) in 2.3%.

Patients included in the analysis were classified as either 'cure' or 'recurrence' based on follow-up information. 'Recurrence' was defined as infection occurring again at the same site from which it had been eliminated previously and which was treated specifically with another course of antibiotics or surgery. If there was no recent information about possible recurrences in the Infections Limited charts, postcards were sent to patients using the last-known address to determine whether each patient had had a recurrence, as evidenced by surgery, or further antibiotic therapy related to the earlier infection. If the postcard brought no response, an attempt was made to contact the patient by telephone.

If a recurrence was documented, an attempt was made to obtain specific information about the microbiology of that recurrence from Infections Limited records or any other available sources. If culture reports were obtained, recurrences were classified as either relapses (original pathogen) or reinfections (different pathogen). A repeat culture showing a pathogen of the same species and with the same pathogen and antimicrobial susceptibility pattern as the original was classified as a relapse without further testing as to whether it was the same exact strain. A new organism was considered a pathogen only if it was specifically treated with an antibiotic by the managing physician. To avoid bias, patients with multiple recurrences were counted only once, at the time of the first recurrence, in the statistical analyses of outcomes.

In order to understand both the role of the initial pathogen and antibiotic choice as potential risk factors for recurrence, patients who were apparently cured were compared with those patients with recurrences. Proportions were compared using Fisher's Exact test,[25] and odds ratios (OR) were calculated to estimate the relative risk (RR) between the two groups.[26] Where applicable, 95% confidence intervals (CI) and *P* values were calculated to better ascertain the statistical

significance of each finding. In some analyses, Cox regression models were also used to study the main effects and fixed covariates of concern on the overall hazard of recurrence.[27] Relative hazards were calculated from these Cox regression models, with 95% CI and *P* values also calculated and displayed.

Results

Charts of ~1300 patients identified as having osteomyelitis were reviewed. A total of 454 patients was identified who met all inclusion criteria. The great majority (90.8%) of these patients had contiguous osteomyelitis associated with a soft tissue wound or recent surgery. A foreign body was present in 69 (15.2%) and removed in 24 patients during therapy.

Nearly half (45%) of the patients were hospitalized before OPAT. The others were started directly in the outpatient clinic. The mean duration of OPAT for the antibiotics used was not significantly different (PRP, 34 days; ceftriaxone, 30 days; cefazolin, 30 days; vancomycin, 34 days).

Pertinent demographic and clinical characteristics of the 454 patients are shown in Table 1. Locations of infection included foot in 236 (52%), leg in 86 (19%), hand in 45 (10%) and spine in 27 (6%). Comorbid conditions included diabetes in 173 (38%) and vascular disease in 54 (12%). The relative risk of recurrence for diabetes without vascular disease was 4.9 (95% CI 2.5–9.5; $P \leq 0.001$) and for vascular disease without diabetes 1.9 (95% CI 1.2–3; $P = 0.011$). The pathogens initially isolated from these patients are displayed in Table 2. Of the 454 patients, 315 (69.4%) were apparently cured at the time outcomes were measured and 139 (30.6%) had had a recurrence. Of the recurrences, 22 were considered relapses and 23 reinfections. Whether the recurrence was a relapse or reinfection could not be determined in 94 patients for whom repeat culture results could not be obtained. There were 13 deaths (2.9%) and 27 amputations (5.9%) recorded.

Table 1. Demographic and clinical characteristics of 454 osteomyelitis patients receiving OPAT

Age (range 6–92 years; average 51 years)	
≤12	4 (1%)
13–70	379 (83%)
>70	71 (16%)
Sex	
male	295 (65%)
female	159 (35%)
Site of infection	
foot	236 (52%)
leg	86 (19%)
hand	45 (10%)
spine	27 (6%)
other	60 (13%)
Types of osteomyelitis	
haematogenous	27 (6%)
contiguous	409 (90%)
vascular	9 (2%)
other	9 (2%)

Table 2. Microbiology of cultures initially obtained from 454 patients diagnosed with osteomyelitis

Pathogen	No. (% of total)
S. aureus	
methicillin-susceptible	237 (52.2)
methicillin-resistant	9 (2.0)
Non-group D streptococci	62 (13.7)
Coagulase-negative staphylococci	63 (13.9)
P. aeruginosa	20 (4.4)
Other *Pseudomonas* spp.	2 (0.4)
Others	61 (13.4)

The 454 patients were followed for a mean of 27.5 months, with the longest follow-up being 128 months. Figure 1 illustrates the timing of recurrences and the proportion of relapses or reinfections over a period of 4 years. The incidence of recurrence peaked at 3 months at >6%. In fact, about half (56%) of the recurrences occurred by this time. Relapses occurred earlier than reinfections.

Amputations or bone excisions were carried out in 27 cases. Of these procedures, 93% (25/27) were on the legs or feet, 88% (24/27) were carried out in patients who were diabetic and 33% (9/27) in those with peripheral vascular disease (PVD). Amputations that occurred were most common (66.6%) within 3 months of the completion of OPAT, with 81.5% of amputations carried out within 6 months and 100% within 1 year.

The risk of recurrence, as specifically related to the initially recovered pathogen, was also investigated. For the purposes of the analyses presented here, methicillin-susceptible *S. aureus* (MSSA) and methicillin-resistant *S. aureus* (MRSA) were combined, since MRSA cases were few in number and all patients with MRSA infections were appropriately treated with vancomycin.

Using a Cox regression model, the relative hazard of recurrence by bacterial pathogen was analysed after simultaneous adjustment for diabetes, PVD and age >70 years. When *P. aeruginosa* was the initially recovered pathogen, the risk of recurrences was more than twice that of *S. aureus* infections (RR 2.5; 95% CI 1.3–4.7; $P = 0.005$) (Figure 2). Conversely, infections caused initially by non-group D streptococci had a somewhat lower risk of recurrence compared with those initially caused by *S. aureus* (RR 0.6; 95% CI 0.3–1.1; $P = 0.11$) (Figure 2). In a univariate analysis, *P. aeruginosa* infections had an approximately three-fold greater risk of recurrence

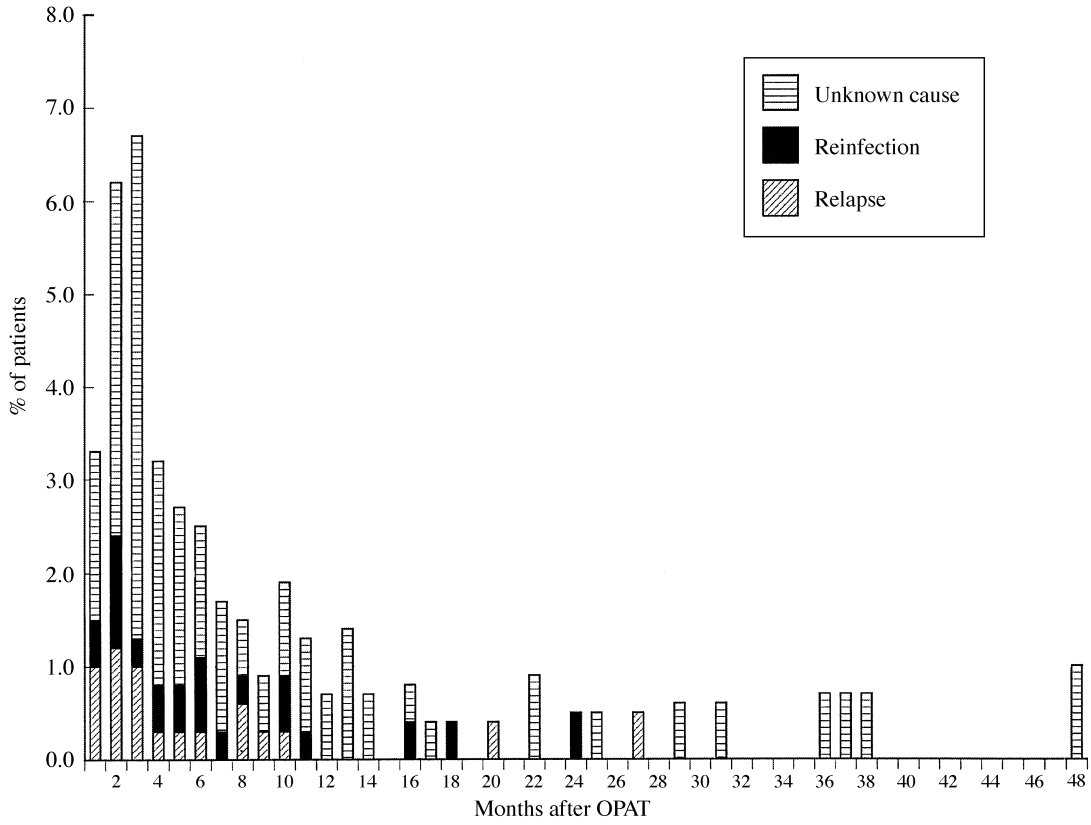

Figure 1. Recurrences were classified as either 'relapses' (original pathogen) or 'reinfections' (new pathogen) or 'unknown' if the pathogen was unknown. The number of recurrences for each month is represented as a percentage of patients for which there was information that month.

(OR 2.9; 95% CI 1.2–7.2; $P = 0.024$) when compared with the other types of infections studied.

There was also a strong correlation between *P. aeruginosa* and amputations. With regard to this risk, three of the 20 (15%) patients from whom *P. aeruginosa* was initially cultured eventually required amputation. When non-group D streptococci were the initial pathogens, four of 62 (6.5%) eventually required amputation. With *S. aureus*, the corresponding figures were 11 of 246 (4.5%) and with coagulase-negative staphylococci, two of 63 (3.2%).

Outcomes for osteomyelitis caused by *S. aureus*, which was the most common pathogen isolated initially, were also compared according to the antibiotic used. Oxacillin (46 cases), methicillin (nine cases) and nafcillin (one case) were considered equivalent and together formed the standard for therapy,[28] with a recurrence rate of 28.6%. Ceftriaxone had a recurrence rate of 27.3%. Recurrence appeared to be more likely for subjects treated with cefazolin (34.8%), vancomycin (53%) and 'other' antibiotics (35.3%). Indeed, when compared with infections treated by PRPs (OR 1.0) or ceftriaxone (OR 0.94), vancomycin-treated infections were nearly three times more likely to recur (OR 2.8; 95% CI 0.99–7.2; $P = 0.058$). The difference between cefazolin and PRPs did not reach statistical significance (OR 1.3; 95% CI 0.58–3.1; $P = 0.53$).

In a Cox regression model, also restricted to patients in whom *S. aureus* was the initial pathogen, the primary antibiotic used to treat the infection was again shown to affect the risk of recurrence, even after simultaneous adjustment for diabetes, PVD and age >70 years (Figure 3). In this model, patients initially treated with cefazolin or ceftriaxone were at comparable risk of recurrence when compared with patients treated with a PRP. However, patients treated with vancomycin had a risk of recurrence more than two times higher than patients treated with a PRP (RR 2.5; 95% CI 1.1–5.7; $P = 0.03$).

Discussion

Outcomes studies of 454 patients with osteomyelitis, who were treated with OPAT for all or part of their antibiotic therapy, have demonstrated that both the initial pathogen and the antibiotic used may have a prognostic effect on the course of infection. This study has a number of limitations that should be taken into consideration when interpreting the results. Because it is a retrospective review, randomization was impossible. The diagnosis and management of osteomyelitis relied heavily on the clinical experience and acumen of the seven infectious disease specialists providing direct patient care. Expensive technology and surgery were not

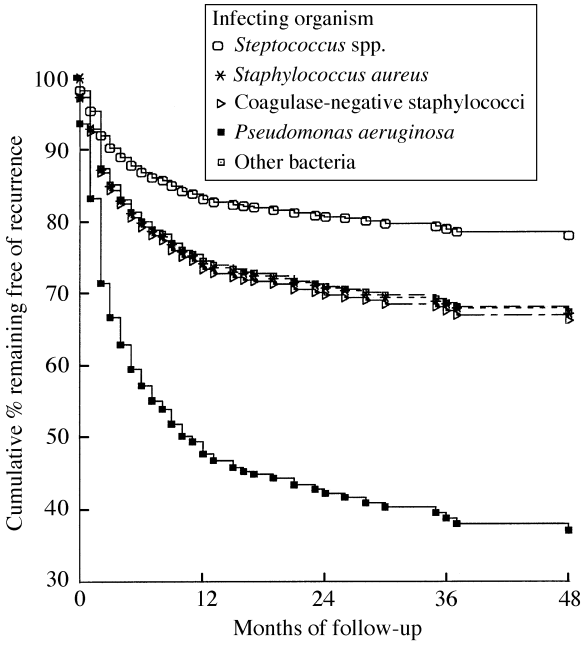

Figure 2. Curves represent survival function for risk of recurrence over time using a Cox regression model for the dominant organism. *Streptococcus* species did not include group D strains. Risk of recurrence (RR) was compared with *S. aureus* (RR 1.0). Analysis reflects results after control for the variables of diabetes, PVD and age >70 years. RR for other bacteria was 0.98 ($P = 0.96$); RR for *Streptococcus* species was 0.6 ($P = 0.11$); RR for coagulase-negative staphylococci was 1.0 ($P = 0.9$); RR for *P. aeruginosa* was 2.5 ($P = 0.005$).

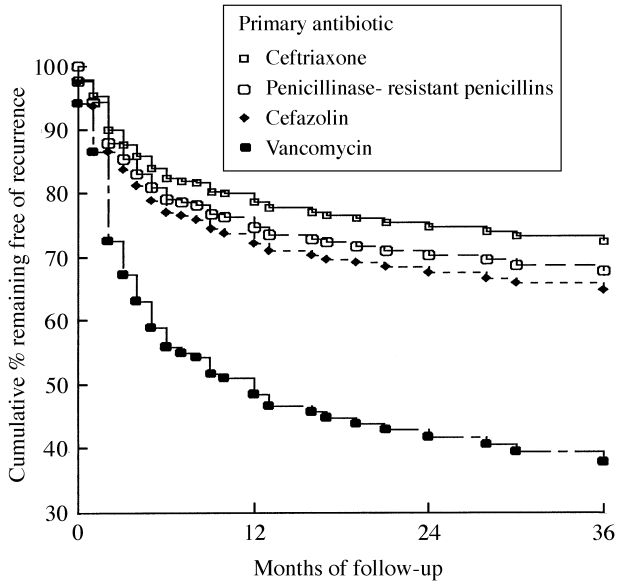

Figure 3. Curves represent survival function for risk of recurrence using a Cox regression model for the primary antibiotics used to treat osteomyelitis. Risk of recurrence (RR) was compared with PRPs (RR 1.0). Analysis reflects results after control for the variables of diabetes, PVD and age >70 years. RR for ceftriaxone was 0.8 ($P = 0.54$); RR for cefazolin was 1.1 ($P = 0.76$); RR for vancomycin was 2.5 ($P = 0.03$).

utilized as frequently as they might have been in an academic centre. Results may have been skewed because the patient population included only individuals treated in an outpatient setting. Finally, not all risk factors could be considered within the confines of this report, which concentrated on those risks associated with specific bacteria and antimicrobial agents. However, in this multivariate analysis, adjustments were made for diabetes and vascular disease, as well as advanced age, all known complicating factors for osteomyelitis. On the other hand, the fact that this series of patients was gathered from an ambulatory care setting eliminated many of the complexities and variables associated with hospitalized patients, which might confound a study of inpatient outcomes. Furthermore, the outcomes were comparable. The lengthy follow-up of study patients clearly shows that the probability of recurrence decreases over time, with a little over 50% of all recurrences occurring within 3 months, 78% within 6 months and 95% within 1 year. Thus, patients can be told that their prognosis for a good outcome increases following the third post-treatment month, with every succeeding disease-free month, and that there is a 95% chance of cure after a disease-free year. Unfortunately, however, many of these patients have other factors that predispose them to some other new infection. The issue of new infections was not addressed in this study.

The decrease in recurrences over time not only has implications on providing advice to patients, but may also play a role in designing future outcomes studies for patients with osteomyelitis. For example, patients may not need to be followed for >12 months to determine whether a new antibiotic is effective. Six months of therapy may be sufficient to determine outcomes if there are enough cases. Confirmation of this type of data will be helpful in stimulating needed trials of new antibiotics by shortening the follow-up time to meet indication criteria for FDA approval.

The fact that recurrences are most likely to happen within a few months following the end of an apparently successful course of iv medication also suggests that more attention should be given to patient care during this time. Whereas these early failures may simply reflect cumulative factors that had been held at bay during the course of intensive antibiotic therapy, it is also possible that upon completion of OPAT other aspects of patient care (e.g. the number of physician visits, wound care, control of diabetes) were not optimally maintained. Perhaps a step-down approach is needed to ensure that gains that have been made in terms of patient care are stabilized to permit infected areas to heal fully. The role of longer courses of iv therapy, prolonged oral antibiotic therapy after OPAT, improved host defences, nutrition supplements, special surgical procedures and enhanced home care should also be investigated.[1,13,17,28,29]

The microbiology of osteomyelitis appears to have specific prognostic implications. *P. aeruginosa*, the third most frequently recovered pathogen in this series, was associated with a much poorer prognosis than any other isolated pathogen. Inadequate antimicrobial therapy may be responsible for these poor results, suggesting that more prolonged courses and/or more intense regimens utilizing combinations of antibiotic agents should be considered. It is also possible that *P. aeruginosa* may simply be a marker for poor prognosis in certain susceptible hosts. It has been reported as a poor prognostic factor in patients with decubitus ulcers.[4,30] In our study, therapeutic failure in pseudomonal infections was independent of diabetes and vascular disease.

Because *S. aureus* is, as it was in this series, the dominant pathogen in osteomyelitis,[28] the increasing frequency of MRSA among staphylococcal isolates becomes an important consideration. Methicillin-resistant strains may be more difficult to treat, although that was not apparent from the small number detected in this series (all our MRSA cases were appropriately treated with vancomycin). However, of great concern regarding the use of vancomycin in staphylococcal osteomyelitis is our finding that it may not be as effective as β-lactam drugs for methicillin-susceptible strains, a finding also observed by other investigators.[18] In fact, in our patients with *S. aureus* osteomyelitis, the likelihood of recurrence following vancomycin therapy was almost three times as high as with β-lactam antibiotics. The reasons for this are unclear; however, it does not appear that treatment courses were any shorter with vancomycin. Factors such as the presence of a complicating foreign body (13% of failures versus 17.5% of successes) did not appear to play a role. The vancomycin findings were also independent of the presence of risk factors such as diabetes, arterial disease or advanced age. It is possible that the failures may be related to inadequate dosing or limited bactericidal activity, which has been reported previously in *S. aureus* endocarditis.[31,32]

The favourable outcome of ceftriaxone in our patients with *S. aureus* osteomyelitis seems to contrast with the expected laboratory findings of higher MICs, compared with those of penicillins and cefazolin. However, the power of numbers of cases in this series provides some assurance that ceftriaxone is at least as potent clinically. Of note, similarly favourable results have recently been reported from another clinical study evaluating the use of ceftriaxone in patients with staphylococcal osteomyelitis.[18] The success rate of ceftriaxone may be due to its long half-life, which allows serum levels of the antibiotic to remain constantly above MICs, a pharmacodynamic pattern that, in animal studies,[33,34] has been shown to be more effective for β-lactam antibiotics than intermittent infusions.

Recurrences after cefazolin therapy were more frequent than after PRPs, but the differences were not statistically significant. However, there have been previous concerns that cefazolin may not be as effective as oxacillin due to greater susceptibility to staphylococcal β-lactamases.[35]

The use of OPAT for the delivery of a wide variety of iv antibiotics to patients with osteomyelitis is a safe, effective and cost-effective treatment modality. The safety of OPAT has been well documented previously.[24,36,37] The findings in this study underscore the efficacy of OPAT in the management of osteomyelitis. The results, at least in staphylococcal osteomyelitis, are similar to those observed in inpatients.[18] As for cost-effectiveness, it has been clearly demonstrated that OPAT saves money compared with the iv administration of antibiotics in the hospital,[38] specifically in patients with osteomyelitis.[39] Savings result primarily from reduced facility and staffing costs. In fact, when OPAT is administered at home, the cost is only one-third that of providing comparable infusion therapy on an inpatient basis.[24,40–43] One important caveat exists, however, with regard to realizing these healthcare savings. Medicare does not cover at-home administration of OPAT, although many Medicare health maintenance organizations do.[44] Thus, home-based administration will actually increase the out-of-pocket medical costs of individuals with traditional Medicare coverage, thereby precluding them from availing themselves of the benefits of at-home programmes.[44] Medicare does, however, cover OPAT delivered in physician's offices or in clinics.

In conclusion, the outcome data derived from this large series of OPAT-treated patients with osteomyelitis provide insight into the prognosis of this infection as well as risk factors associated with treatment failure. For example, these data indicate that recurrences, should they occur, are likely to occur within a few months following the conclusion of apparently successful iv therapy, with only ~5% occurring after 1 year. These data also indicate that the recovery of *P. aeruginosa* is an important marker for a poor prognosis and that *S. aureus* osteomyelitis responds better to a β-lactam antibiotic therapy than to vancomycin, with ceftriaxone therapy at least as effective as cefazolin or PRPs in treating the infection.

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