Cost-minimization analysis and audit of antibiotic management of bone and joint infections with ambulatory teicoplanin, in-patient care or outpatient oral linezolid therapy

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Bone and joint infections are significant causes of morbidity, mortality and healthcare costs. The cost of treatment for such infections is driven primarily by the length of hospital stay. Many of these infections will require treatment with prolonged periods of parenteral antibiotic therapy. Clinicians and healthcare managers are being attracted increasingly by administering treatment in the ambulatory setting as this offers clinical, economic and quality of life advantages from both the hospital’s and patient’s perspective. Our retrospective audit of managing 55 treatment episodes of bone and joint infections with teicoplanin delivered in the outpatient or home setting revealed that the mean cost of care per episode of infection was less with treatment in the ambulatory setting (£1749.15) compared with the in-patient setting (£11400) or compared with the hypothetical situation of treatment with oral linezolid in the home setting (£2546). Teicoplanin therapeutic drug monitoring appears to be valuable in establishing optimal serum levels, which appear to correlate with good clinical outcomes. The potential for alternative day or thrice weekly dosing with teicoplanin may offer further cost advantages whilst maintaining equivalent clinical effectiveness.

Keywords: teicoplanin, linezolid, bone and joint infection, therapeutic drug monitoring, cost minimization

Introduction

Osteomyelitis, primary septic arthritis and prosthetic joint infection (PJI) are significant causes of morbidity, mortality and fiscal costs.1,2 The cost of PJI in the USA, for example, is in excess of $50 000 per managed case.3 A combination of surgical and antimicrobial therapy is the mainstay of current management. The specific aim of antibiotic therapy is to penetrate bone and surrounding tissues and kill bacteria. For acute osteomyelitis and primary septic arthritis, with or without adjunctive surgery, treatment is often curative. In contrast, for chronic osteomyelitis and PJI, antibiotics are administered to either ‘sterilize’ the surgical site prior to operation or suppress infective exacerbations in conservatively managed patients.

The current standard of care, i.e. 4 weeks of high-dose intravenous therapy, is based on Waldvogel et al.’s excellent series of articles.4–6 Although studies of children and diabetic adults have suggested a role for oral treatment,7,8 for many experts, parenteral therapy remains the standard of care. A recent systematic review of antibiotic therapy for bone and joint infections failed to recommend a preferred antimicrobial regimen based on the available evidence.9 In clinical practice, therefore, β-lactams, flucloxacinil or clindamycin are generally used for methicillin-sensitive staphylococcal and streptococcal infections, whilst the glycopeptides are the antimicrobials of choice for methicillin-resistant staphylococci, a particular problem in PJI.10,11 To maximize tissue penetration and prevent the development of antimicrobial resistance, many clinicians use adjunctive oral rifampicin or fusidic acid therapy.12,13

Until relatively recently, bone and joint infections were common reasons for prolonged hospitalization to receive intravenous antibiotic therapy.14 The healthcare costs and

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patient inconvenience associated with this, however, have decreased for hospitals investing in the development of an outpatient and home parenteral antimicrobial therapy (OHPAT) programme, thus permitting the cost-effective management of large numbers of patients in the ambulatory environment. As many of these infections are either empirically managed or due to resistant species, glycopeptides are usually preferred. Although not available in the USA, teicoplanin is particularly attractive for the OHPAT setting, offering once-daily intravenous administration by bolus injection, minimal toxicity, infrequent therapeutic drug monitoring (TDM) and proven clinical efficacy. The intramuscular route provides an effective and alternative option but is not widely used. Furthermore, a number of centres have recently reported success with reduced frequency (alternate day or thrice weekly) teicoplanin regimens, which are likely to offer clinicians improved cost-effectiveness.

The last 24 months has seen the advent of linezolid, the first oxazolidinone antibiotic, which has broad-spectrum activity against Gram-positive bacteria, including methicillin-sensitive and -resistant staphylococci. Its potential for use in bone and joint infections is theoretically high by virtue of the convenient twice-daily oral regimen, high (100%) bioavailability and excellent penetration into diseased tissues. In addition, there are early reports of clinical success in documented infections unresponsive to glycopeptides. The results of ongoing studies to assess the clinical effectiveness and long-term safety of linezolid in bone and joint infection, particularly with reference to myelo-suppression, are awaited with interest.

As oral therapy taken at home may potentially offer patients, hospital managers and clinicians cost advantages, we performed a cost-minimization analysis of patients treated with teicoplanin by an established OHPAT service, compared with ‘traditional’ in-patient care and hypothetical outpatient oral linezolid therapy. In addition, as a secondary remit we audited our antibiotic management of these complex groups of patients with particular emphasis on the need for TDM of teicoplanin levels and with a view to producing a subsequent antibiotic management protocol that would be subject to further audit. We did not aim to evaluate the clinical impact of specific interventions in the management of these infections. Therefore, we are unable to provide information about the frequency of procedures such as surgical drainage or prosthesis and implant removal. We accept the importance of these interventions in relation to outcome but this is well beyond the remit of our study.

Results

Since April 1998, data have been recorded for all patients managed by our OHPAT service as part of an ongoing clinical research and quality assurance programme. Using a standardized data collection sheet to record patient-specific information from the above registry and the hospital’s laboratories results database, basic demographic, clinical, microbiological and pharmacological data were ascertained for each recorded bone or joint infection episode. We also collected length of in-patient hospital stay and time on OHPAT. The mean duration of treatment data presented here is only that spent in the home or outpatient setting. Indeed, a small number of patients were never hospitalized. In the cost-minimization analysis we have compared with this the hypothetical time that may have been spent as an in-patient or at home with oral linezolid. The clinical microbiology and management data are presented in Table 1; 71% of culture positive patients had an MRSA/MRSE infection sensitive to glycopeptides.

We identified 55 treatment episodes in 50 patients treated with either teicoplanin monotherapy or teicoplanin in combination with oral rifampicin. Four of these episodes were septic arthritis and the remainder were osteomyelitis (three acute and 48 chronic). Forty per cent of patients with chronic osteomyelitis had a prosthetic joint infection. All patients received intravenous loading doses of teicoplanin (6 mg/kg/12 h for three doses) followed by a maintenance regimen of 6 mg/kg/day. Three patients were managed with an alternate day regimen. Teicoplanin was administered either by daily visit to a specialist OHPAT nurse (25%) or by self/carer administration (75%), with weekly outpatient visits for monitoring purposes. We have assumed that medical outpatient follow-up would have been similar for all patients regardless of the exact treatment regimen.

In the early period of our OHPAT programme, few patients underwent teicoplanin TDM. As our experience evolved and evidence became available, however, TDM was increasingly used with the aim of achieving a trough level ≥10 mg/L for bone and joint infections. All these patients had a trough level of >10 mg/L on at least one occasion. Although a mean of two assays per patient was calculated, wide inter-patient variation in the use of TDM (only 60% of patients had levels performed; see Table 1) and subsequent alteration of the maintenance regimen was evident. Our early programme experiences described above and the length of treatment did not always account for this suboptimal practice.

The costs of teicoplanin administration (including associated consumables), a specialist OHPAT nurse and in-patient care were obtained from reliable sources within NHS Tayside; Scottish Health Services Costs, Information and Statistics Division, NHS Scotland (see www.show.scot.nhs/isd); the British National Formulary (BNF); and previous publications. The actual time associated with PIC line insertion was not costed, but we estimate this to take our nurse practitioner 40 min at an approximate cost of £10. We have not included this in our analysis. The intangible cost to the patients in terms of hypothetical time that may have been spent as an in-patient or at home with oral linezolid.
of inconvenience and discomfort in our experience is thought to be low and not worthy of consideration here (J. Morrison, personal communication). The cost of linezolid used in this paper is the UK hospital price, whereas a higher price of £445 for 10 tablets is quoted in the British National Formulary (community price). Linezolid in the UK is primarily prescribed by hospital pharmacies. For the purpose of the cost-minimization analysis (see Table 2), we did not correct for the three patients who received an alternate-day teicoplanin regimen, but assumed that all patients received once-daily therapy.

### Discussion

This study clearly shows that parenteral teicoplanin, delivered by a specialist outpatient service, is associated with lower financial costs compared with either ‘traditional’ in-patient care or hypothetical oral linezolid therapy. The cost-minimization analysis is most sensitive to the length of in-patient stay and to the cost of the antimicrobial therapy. The cost of delivering alternate-day or thrice-weekly teicoplanin through the ambulatory service would also further reduce total costs. Although outpatient oral linezolid therapy has notably lower costs than in-patient care, it is more expensive than once-daily ambulatory teicoplanin. We estimate that a 32% reduction in the acquisition cost of linezolid, from £67 to £46 per day, would be required to achieve cost-equivalence. We have assumed that medical outpatient follow-up, including haematological and biochemical monitoring, would have been the same for both ambulatory groups.

Indeed, the emerging experience of adverse events with long-term linezolid treatment does suggest the need to observe for thrombocytopenia by regular weekly full blood count monitoring.\(^{26,27}\) This is essential in PJIs, which require protracted periods of antibiotic therapy. The analysis does not account for differing patient travel costs, indirect costs (e.g. the number of work days lost) and intangible costs (e.g. the inconvenience to the patient). Nevertheless, it is unlikely that any differences for these costs would outweigh the financial cost differential between ambulatory teicoplanin and outpatient linezolid therapy. In addition, we have previously shown that management by our OHPAT service is associated with high patient satisfaction\(^{28}\) and good clinical outcomes.\(^{23}\)

The value of TDM for teicoplanin has recently been reviewed.\(^{25}\) For patients with bacteraemia or osteomyelitis, there is clear evidence\(^{24}\) of a relationship between trough serum concentrations of \(\geq 10\) mg/L and favourable clinical outcome.\(^{17,24}\) Furthermore, tailoring the teicoplanin regimen according to serum concentrations may be a more cost-effective strategy compared with fixed dosing.\(^{29}\) Our own experience, and that of others, has revealed significant inter-individual variation in trough teicoplanin concentration\(^{25}\) and has highlighted the opportunity to maintain satisfactory levels with less frequent dosing. Alternate-day or thrice-weekly regimens, therefore, are likely to be used increasingly in the future\(^{17}\) and may lead to additional cost savings. Indeed, using this more targeted approach resulted in an estimated saving of £170000 per annum in one study.\(^{25}\)

Although the primary aim of this study was not to evaluate teicoplanin TDM, the analysis of our experience has revealed that we have consistently used loading doses (6 mg/kg/12 h
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for three doses) and have managed to achieve a serum trough concentration of at least 10 mg/L, on at least one occasion in all patients who had levels performed. Our mean duration of therapy was 38 days, which is in keeping with current management recommendations. 4 – 6 Although all patients were deemed to be ‘clinically improved’ or ‘cured’ at the time of outpatient discharge (follow-up microbiological data were not available for most patients), we appear to be inconsistent regarding the use of adjunctive rifampicin (10%) and in the use of intravenous–oral switch therapy (5%). In addition, we performed teicoplanin levels on a mean of two occasions, but often in situations where a level of 10 mg/L had already been established. The reasons for this are likely to be multifactorial and may reflect: repeated monitoring, albeit unnecessarily, to ensure adequate serum concentration; uncertainty about the exact role of teicoplanin TDM and our ‘evolving experience with use of this regimen in real life practice’; concerns about adherence in self-administering patients; or a rising serum creatinine level.

To date we have not had an OHPAT protocol for the use of teicoplanin in bone and joint infections. This evaluation stimulated a recent multidisciplinary audit meeting during which a protocol for future OHPAT teicoplanin use was developed (see Scheme 1a and b). This formalizes our once-daily regimen (Scheme 1a) and also thrice-weekly regimen (Scheme 1b), which is proving very attractive and valuable in older, less ambulant patients with chronic bone infection. Since its introduction 2 months ago our experience in all five patients (at the time of completing this paper) has been to obtain optimal levels with this regimen (D. Nathwani, personal observation). The protocol was based on the presented analysis, pertinent published literature17,24,25,29 and our current and previous teicoplanin experience. The new protocol will be subjected to a continuing audit and quality assurance programme and, when necessary, amended according to new published evidence and our ongoing experiences. We would value hearing from and sharing experience with others who have embarked upon similar or even alternative regimens.

In the absence of a definitive evidence-based antimicrobial strategy for managing bone and joint infections, we have shown that teicoplanin therapy delivered by an established OHPAT service and our current and previous teicoplanin experience has been to obtain optimal levels with this regimen (D. Nathwani, personal observation). To date we have not had an OHPAT protocol for the use of teicoplanin in bone and joint infections. This evaluation stimulated a recent multidisciplinary audit meeting during which a protocol for future OHPAT teicoplanin use was developed (see Scheme 1a and b). This formalizes our once-daily regimen (Scheme 1a), which is proving very attractive and valuable in older, less ambulant patients with chronic bone infection. Since its introduction 2 months ago our experience in all five patients (at the time of completing this paper) has been to obtain optimal levels with this regimen (D. Nathwani, personal observation). The protocol was based on the presented analysis, pertinent published literature17,24,25,29 and our current and previous teicoplanin experience. The new protocol will be subjected to a continuing audit and quality assurance programme and, when necessary, amended according to new published evidence and our ongoing experiences. We would value hearing from and sharing experience with others who have embarked upon similar or even alternative regimens.

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Table 2. Cost-minimization analysis of bone and joint infections treated with teicoplanin (OHPAT) compared with in-patient care and outpatient oral linezolid

<table>
<thead>
<tr>
<th>Based on 55 episodes of bone/joint infection</th>
<th>In-patient care</th>
<th>Intravenous teicoplanin (OHPAT)</th>
<th>Oral linezolid</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of therapy (days, mean)</td>
<td>38</td>
<td>38</td>
<td>38</td>
</tr>
<tr>
<td>Dosing regimen</td>
<td>6 mg/kg (~400 mg) 12 h for 3 doses, then 6 mg/kg once daily</td>
<td>39 × £38.30 = £1493.70</td>
<td></td>
</tr>
<tr>
<td>Drug cost per treatment episode (BNF prices)</td>
<td>38 × £0.74 × 0.1 = £2.81</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drug cost for adjunctive oral rifampicin per treatment episode (10% of all treatment episodes)</td>
<td>39 × £0.76 = £29.64</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cost of intravenous consumables/preparation/administration</td>
<td>£15.50</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cost for hepsal/saline flushes</td>
<td>£25.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cost of PIC line</td>
<td>£38 × 0.25 = £95.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cost of daily outpatient nurse visits (25% of all treated episodes)</td>
<td>£5 × 0.75 = £3.75</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cost of weekly nurse visits (75% of all treated episodes)</td>
<td>£25 × 2 = £50.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cost of two (mean) teicoplanin assays</td>
<td>£38 × £300 = £11400</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cost of care per mean episode of infection</td>
<td>£1749.15</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>£2546.00</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

a Hypothetical setting, BNF price.

*b Costs obtained from Davey et al.19

c Direct cost per day per case in Orthopaedic ward in Dundee [data from Scottish Health Services Costs, ISD, Edinburgh, UK (www.show.scot.nhs.uk/isd)].
Audit of teicoplanin for home IV therapy

**Scheme 1a.** Protocol for once daily teicoplanin treatment of joint/skin/soft tissue infection
Teicoplanin: once daily dosing

- Teicoplanin 6 mg/kg intravenously for three doses (12 h apart)\(^{a,b}\)
- Round dose to nearest 100 mg

- 6 mg/kg teicoplanin intravenously once daily

- Before sixth dose check teicoplanin level

<table>
<thead>
<tr>
<th>Level (mg/L)</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;10</td>
<td>Increase dose to 9 mg/kg daily. Recheck levels after further 10 days</td>
</tr>
<tr>
<td>10–20</td>
<td>No dose adjustment required</td>
</tr>
<tr>
<td>20–30</td>
<td>No dose adjustment. Recheck levels after further 10 days</td>
</tr>
<tr>
<td>&gt;30</td>
<td>Decrease frequency of dosing—give same dose on alternate days. Recheck levels on a weekly basis</td>
</tr>
</tbody>
</table>

For protracted therapy: recheck levels at 6/52

Add rifampicin 600 mg once daily to regime if:
1. Prosthetic joint/implant in situ
2. Proven *Staphylococcus* spp. infection (MSSA, MRSA or MRSE)

Check for contraindications/interactions with rifampicin

\(^a\)If <70 kg, use teicoplanin 400 mg (not 6 mg/kg).
Use 6 mg/kg dose regimen for all patients >70 kg unless renal impairment.

\(^b\)If serum creatinine >150, calculate creatinine clearance.
If creatinine clearance >60 mL/min give 6 mg/kg (dose as above);
if <60 mL/min, contact pharmacist.

Creatinine clearance (mL/min) = \(140 - (\text{age in years}) \times (\text{weight in kg})\)

| Serum creatinine (\(\mu\)mol/L) | Multiply value \(\times 1.23\) if male patient |

Weekly blood monitoring: FBC, U&Es, LFTs, CRP.

**Scheme 1b.** Protocol for three times a week teicoplanin treatment of joint/skin/soft tissue infection
Teicoplanin: three times weekly dosing
Indication: where daily dosing as OHPAT not possible/feasible (following discussion with ID consultant/SpR)

- Teicoplanin 15 mg/kg intravenously once daily for three doses\(^a\)
- Round dose to nearest 100 mg

- Teicoplanin 15 mg/kg intravenously three times weekly (Mon, Wed, Fri)

- Before sixth dose check teicoplanin level

<table>
<thead>
<tr>
<th>Levels</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>10–20</td>
<td>No dose adjustment</td>
</tr>
<tr>
<td>20–30</td>
<td>No dose adjustment. Recheck levels after further 10 days</td>
</tr>
<tr>
<td>&gt;30</td>
<td>Decrease frequency of dosing—give same dose twice weekly. Recheck levels on a weekly basis</td>
</tr>
</tbody>
</table>

For protracted therapy: recheck levels at 6/52

Add rifampicin 600 mg once daily to regime if:
1. Prosthetic joint/implant in situ
2. Proven staphylococcal spp. infection (MSSA, MRSA or MRSE)

Check for contraindications/interactions with rifampicin

\(^a\)If serum creatinine >150, calculate creatinine clearance.
If creatinine clearance >60 mL/min give 15 mg/kg (dose as above);
if <60 mL/min, contact pharmacist.

Creatinine clearance (mL/min) = \(140 - (\text{age in years}) \times (\text{weight in kg})\)

| Serum creatinine (\(\mu\)mol/L) | Multiply value \(\times 1.23\) if male patient |

Weekly blood monitoring: FBC, U&Es, LFTs, CRP.
high-quality data, however, about its safety and clinical efficacy for bone and joint infections. An appropriately powered randomized controlled trial could, potentially, answer these important outstanding questions. Until these data are available we would recommend that more established cost-effective therapies, such as teicoplanin delivered through OHPAT, should continue to be used, and urge caution and close monitoring if linezolid is to be used for prolonged periods.30

References