Clinical management of Staphylococcus aureus bacteraemia

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Abstract

Staphylococcus aureus bacteraemia is one of the most common serious bacterial infections worldwide. In the UK alone, around 12 500 cases each year are reported, with an associated mortality of about 30%, yet the evidence guiding optimum management is poor. To date, fewer than 1500 patients with S aureus bacteraemia have been recruited to 16 controlled trials of antimicrobial therapy. Consequently, clinical practice is driven by the results of observational studies and anecdote. Here, we propose and review ten unanswered clinical questions commonly posed by those managing S aureus bacteraemia. Our findings define the major areas of uncertainty in the management of S aureus bacteraemia and highlight just two key principles. First, all infective foci must be identified and removed as soon as possible. Second, long-term antimicrobial therapy is required for those with persistent bacteraemia or a deep, irreprovable focus. Beyond this, the best drugs, dose, mode of delivery, and duration of therapy are uncertain, an agenda for future clinical research.

Introduction

Staphylococcus aureus is an important cause of serious community and health-care-associated infections worldwide. In a study of 6697 bloodstream infections from 59 hospitals in the USA, S aureus was the most common bacterial isolate, accounting for 23% of all episodes, and was more strongly associated with death than any other bacterial pathogen. In the UK, around 12 500 cases of S aureus bacteraemia (SAB) are voluntarily reported each year, associated with a mortality of about 30%. Surprisingly little evidence is available to guide the management of SAB. Current UK and US treatment guidelines suggest that uncomplicated SAB should be treated for a minimum of 14 days, and for 4–6 weeks if there is a deep infection focus. To date, fewer than 1500 patients have been enrolled in 16 randomised controlled trials (RCTs) investigating SAB antimicrobial therapy. Much of our current practice is therefore based on clinical experience and observational studies; consequently, discrepant views of how to manage SAB abound. We review the evidence behind the key clinical decisions in the management of SAB and define the agenda for future clinical research.

How should SAB be defined?

A clinically significant bacteraemia, or bloodstream infection, is usually defined as the isolation of bacteria from one or more peripheral venous blood-culture samples collected from a patient with associated relevant symptoms and signs of systemic infection. Prospective studies including 1809 SAB episodes considered only 27 (1-5%) to be due to contamination. Given the severity of disease associated with SAB, particularly the risk of metastatic complications, the isolation of S aureus from blood culture should always be considered clinically significant.

Further categorisation of SAB is needed to determine optimum management. Prospective studies have identified baseline predictors of complicated disease, disease recurrence, or death from SAB (table 1). These and other studies have found that persistent bacteraemia (positive blood cultures ≥3 days after starting effective antimicrobial therapy) is the strongest predictor of complicated disease. Consequently, duration of bacteraemia has formed the basis for several different attempts to define SAB severity (table 2), although these have not been universally accepted.

Is identification and removal of the focus of infection important?

Expert opinion has long been that optimum management of SAB requires adequate antimicrobial therapy and, where possible, the removal or drainage of potential foci of infection. Three prospective studies have shown that not removing an infected intravascular catheter is the strongest independent risk factor for SAB relapse. Early surgical intervention in S aureus endocarditis (SAE), particularly the early removal of infected prosthetic heart valves, improves outcome, and not removing S aureus-infected prosthetic joints is strongly associated with treatment failure. Some patients (10–40%) have no identifiable focus of infection at presentation or after initial investigations. Case series have reported covert endocarditis to be more likely in these individuals.

Should all patients with SAB have echocardiography?

SAB is a major risk factor for endocarditis, particularly in those with abnormal or prosthetic valves. Studies published before the advent of echocardiography suggested that around 60% of patients with SAB had endocarditis, and long-term antimicrobial therapy (4–6 weeks) was given to most patients with SAB in that era. Transthoracic echocardiography has been extensively compared with transoesophageal echocardiography for infective endocarditis of any cause. These investigations confirmed that transoesophageal echocardiography detected a higher proportion of valve vegetations than did transthoracic echocardiography, particularly if the vegetations were small (<5 mm) and were on the aortic or mitral valves.

Transoesophageal echocardiography
was also superior to transthoracic echocardiography for the diagnosis of prosthetic valve endocarditis, and infections of pacemaker leads and other intra-cardiac devices.

Studies on the role of echocardiography in SAB management are summarised in table 3. Initial studies suggested transthoracic echocardiography detected around 20% of cases of SAE unsuspected by clinical signs. One influential prospective study reported that transoesophageal echocardiography detected SAE in 103 (19%) cases after a negative transthoracic echocardiogram and concluded transoesophageal echocardiography should be considered in all patients with SAB.

This view was supported by an economic analysis, which suggested that transoesophageal echocardiography was a cost-effective way to shorten antimicrobial therapy for patients who presented with clinically uncomplicated catheter-associated SAB.

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**Table 1: Prospective studies that have identified independent risk factors for complicated disease, disease recurrence, or death from SAB**

<table>
<thead>
<tr>
<th>Design</th>
<th>Location</th>
<th>Patients</th>
<th>Study definition of poor outcome</th>
<th>Factors associated with poor outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jensen et al</td>
<td>Prospective, single-centre cohort</td>
<td>Denmark</td>
<td>278</td>
<td>Death</td>
</tr>
<tr>
<td>Lesens et al</td>
<td>Prospective, two centres</td>
<td>France</td>
<td>166</td>
<td>Death by 3 months after the start of effective antibiotic therapy</td>
</tr>
<tr>
<td>Fowler et al</td>
<td>Prospective, single-centre cohort</td>
<td>USA</td>
<td>724</td>
<td>Complicated disease* at baseline, attributable mortality, embolic stroke, or recurrent infection</td>
</tr>
<tr>
<td>Chang et al</td>
<td>Prospective, multicentre cohort</td>
<td>USA</td>
<td>448</td>
<td>Recurrent SAB after completion of anti-staphylococcal antibiotic therapy</td>
</tr>
<tr>
<td>Chang et al</td>
<td>Prospective, multicentre cohort</td>
<td>USA</td>
<td>505</td>
<td>Diagnosis of endocarditis (by 1994 modified Duke's criteria)**</td>
</tr>
<tr>
<td>Tumidge et al</td>
<td>Prospective, multicentre cohort</td>
<td>New Zealand and Australia</td>
<td>1994</td>
<td>30-day all-cause mortality</td>
</tr>
</tbody>
</table>

*Defined as a site of infection remote from the primary focus caused by haematogenous seeding (eg, endocarditis or vertebral osteomyelitis) or extension of infection beyond the primary focus (eg, septic thrombophlebitis or abscess). SAB=*Staphylococcus aureus* bacteraemia. MSSA=meticillin-sensitive *S aureus*.

**Table 2: Proposed definitions of SAB disease**

<table>
<thead>
<tr>
<th>Simple SAB</th>
<th>Catheter-related SAB</th>
<th>Uncomplicated SAB</th>
<th>Complicated SAB</th>
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<tr>
<td>Fowler et al (1998)</td>
<td>(1) TOE on day 5–7 of therapy, negative for vegetations and predisposing valvular abnormalities</td>
<td>...</td>
<td>One or more of the following: (1) Predisposing valvular abnormalities (more than mild regurgitation) but no vegetations shown by TOE (2) Positive surveillance blood culture (3) Superficial, non-removable focus of infection (4) Persistent signs of infection after 72 h of antibiotic therapy</td>
</tr>
<tr>
<td>Jenkins et al (2008)</td>
<td>Definite: catheter-tip culture grew &gt;15 colonies of <em>Staphylococcus aureus</em> or inflammation was present at the insertion site, and no alternative source of infection identified Probable: catheter in place at the time of bacteraemia, and no alternative focus identified Negative blood culture 2–4 days after starting treatment, and no distal focus</td>
<td>...</td>
<td>(1) Catheter-associated infection (with the catheter removed) (2) Defervescence within 72 h of starting therapy (3) Sterile follow-up blood culture (4) Normal TOE (5) No prosthetic material in any joint or vessel (6) No clinical signs suggestive of metastatic infection</td>
</tr>
<tr>
<td>Naber et al (2009)</td>
<td>...</td>
<td>Isolation of 5 aures from blood 2–4 days after starting treatment and either spread of infection, infection involving a prosthesis not removed within 4 days, or evidence of endocarditis</td>
<td></td>
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</table>

SAB=*Staphylococcus aureus* bacteraemia. TOE=transthoracic echocardiography. TTE=transthoracic echocardiography.

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*Defined as a site of infection remote from the primary focus caused by haematogenous seeding (eg, endocarditis or vertebral osteomyelitis) or extension of infection beyond the primary focus (eg, septic thrombophlebitis or abscess). SAB=*Staphylococcus aureus* bacteraemia. MSSA=meticillin-sensitive *S aureus*.
Others have argued that transthoracic echocardiography alone may be sufficient to exclude endocarditis in most patients with SAB. 32,40 A retrospective comparison of the diagnostic yields of transthoracic and transoesophageal echocardiography in 125 adults with SAB (18% had endocarditis) found the probability of left-sided native-valve endocarditis was less than 2% after a normal transthoracic echocardiography if no embolic phenomena were present. 32 These investigators concluded that transthoracic echocardiography can exclude SAE in low-risk patients.

**Are glycopeptides equivalent to β-lactams for the treatment of SAB?**

Two trials, involving 47 intravenous drug users with right-sided *S aureus* endocarditis, showed poorer outcomes in those given either teicoplanin or vancomycin (19 [68%] of 28 failed therapy) versus cloxacillin (one [5%] of 19 failed therapy). 20,21,46 A third trial compared teicoplanin with flucloxacillin for the treatment of SAB and other sterile-site infections and was stopped early after six (67%) of nine patients given teicoplanin failed treatment compared with one (11%) of nine given flucloxacillin, although the teicoplanin dose (200 mg once daily) was probably subtherapeutic. 44 A fourth trial compared teicoplanin and netilmicin with flucloxacillin and netilmicin in 21 patients with SAB and reported no difference in outcomes in the 18 patients assessed. 28 The poor responses to teicoplanin may be partly explained by the use of low doses (<5 mg/kg daily). 44,45 However, unfavourable results were also observed in the more recent trial, which used a higher dose (24 mg/kg during the first 24 h, then 12 mg/kg daily). 45

Observational studies suggest that vancomycin does not sterilise blood as quickly as β-lactams, resulting in persistent SAB, 20,21,28 and there is substantial evidence that vancomycin treatment of SAB, whether meticillin susceptible or resistant, is an independent risk factor for disease recurrence and death. 22,23,28,48 Use of empirical vancomycin therapy in intravenous drug users with meticillin-susceptible SAE was associated with higher attributable mortality, even if patients were switched from vancomycin once sensitivities were available. 22

The reduced clinical efficacy of vancomycin may be associated with emergent strains with higher minimum inhibitory concentration (MIC). High-level resistance (vancomycin MIC >8 μg/mL) due to acquisition of the vanA gene has been reported but remains rare. 49 However, glycopeptide intermediate susceptibility *S aureus* (GISA) and susceptible strains with a subpopulation of bacteria (typically around one organism per 10⁵–10⁶ bacteria) within the intermediate susceptibility range (so-called hetero-GISA) are important emerging clinical problems. 51

The criteria for defining intermediate susceptibility,
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<th>Patients studied</th>
<th>Main findings</th>
<th>Conclusions</th>
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<tr>
<td>Iannini and Crossley® (1976)</td>
<td>Retrospective case-note review of SAB with removable focus only Minimum 8 weeks of follow-up required</td>
<td>29 cases (22 line-associated) Treatment range: 3–21 days IV antibiotics 15/29 patients IV antibiotics alone for mean 12.7 days 14 patients received mean 8.4 days IV then mean 8.4 days oral Mean follow-up of 12 weeks (range 2 months to 6 years)</td>
<td>No relapse or recurrence or endocarditis reported</td>
</tr>
<tr>
<td>Mylotte and McDermott® (1987)</td>
<td>Prospective case series of catheter-associated SAB</td>
<td>28 cases None developed endocarditis or metastatic complications Mortality 31%</td>
<td>22 of 28 patients given &lt;14 days antibiotics with no evidence of recurrence</td>
</tr>
<tr>
<td>Mylotte et al® (1987)</td>
<td>Prospective case series of all SAB with literature review</td>
<td>114 cases: 33 (29%) with MRSA, 38 (33%) catheter-related Mortality 12% Most given ≥14 days of therapy</td>
<td>Low incidence of endocarditis (n=2) and metastatic infection (n=1)</td>
</tr>
<tr>
<td>Ehni and Reller® (1980)</td>
<td>Prospective case series of catheter-associated SAB with 3 months of follow-up</td>
<td>13 patients with catheter-associated SAB given &lt;15 days of IV antibiotics (range 0–14 days) 3 patients given oral antibiotics after 2.5–9 days of IV antibiotics</td>
<td>Only 1 patient relapsed with endocarditis (treated with 3 days of IV then 6 days of oral therapy)</td>
</tr>
<tr>
<td>Raad and Sabbagh® (1992)</td>
<td>Retrospective case review plus review of published studies of antibiotic duration for SAB</td>
<td>55 cases and 6 published studies (total 141 episodes of SAB analysed)</td>
<td>Late recurrence in 3 of 19 who had &lt;10 days IV Antibiotics vs 0 of 27 given &gt;10 days IV therapy Persistent fever or bacteraemia after 3 days of therapy best predictor of recurrent disease</td>
</tr>
<tr>
<td>Jernigan and Farr® (1993)</td>
<td>Meta-analysis of short course IV antibiotics (&lt;15 days)</td>
<td>11 studies (only 1 RCT) Only 4 studies with adequate follow-up to assess recurrence Data from 132 patients analysed</td>
<td>Pooled complication rate 24%, mortality 15% Late complications 6.1% (95% CI 2.0–10.2)</td>
</tr>
<tr>
<td>Malanoski et al® (1995)</td>
<td>3-year retrospective case-note review of catheter-associated SAB with median 3 months of follow-up</td>
<td>55 patients 42 had no early complications: 3 treated with &lt;10 days of IV antibiotics; 18 given 10–14 days of IV antibiotics; 21 received 16–43 days of IV antibiotics</td>
<td>3 recurrences, all within 2 months of stopping therapy Relapse 0% if 10–14 days IV antibiotics vs 4.7% if longer 2 of 3 patients given &lt;10 days of therapy relapsed</td>
</tr>
<tr>
<td>Fowler et al® (1998)</td>
<td>Prospective study of effect of specialist infections diseases advice on outcome from SAB 3 months of follow-up Bacterial typing to distinguish recurrence from re-infection</td>
<td>244 enrolled Recommended 1 week IV for simple SAB, 2 weeks for uncomplicated SAB and 4–6 weeks for complex SAB</td>
<td>Advice followed in 112 (45.9%) Failure to follow advice strongly associated with relapse (but not death), relapse rate 10% Failure to remove catheter greatest risk of relapse Short duration of therapy not associated with poor outcome</td>
</tr>
<tr>
<td>Zeylemaker et al® (2001)</td>
<td>Retrospective review analysing relation between duration of antibiotics for catheter-associated SAB and outcome</td>
<td>40 patients with 1 year of follow-up Antibiotic duration: 5, no treatment; 4, 1–7 days; 25, 7–14 days; 15, &gt;14 days</td>
<td>24 (49%) patients had complications; 14 (29%) died No significant relation between duration of treatment and outcome</td>
</tr>
<tr>
<td>Blyth et al® (2002)</td>
<td>Mixed retrospective and prospective study of adherence to Fowler 1998 SAB management guidelines®</td>
<td>98 cases 41% not treated according to guidelines Recurrence rate higher if not given adequate therapy (5 of 38 vs 1 of 55)</td>
<td>28 received shortened antibiotic therapy with a non-significant increase in recurrence</td>
</tr>
<tr>
<td>Jensen et al® (2002)</td>
<td>Prospective multicentre study of all types of SAB 3 months of follow-up</td>
<td>278 cases. Mortality 34% Recurrence 12% Death associated with un-eradicated focus, septic shock, &gt;60 years, and using &lt;4 g daily dicloxacillin</td>
<td>Duration of treatment &lt;14 days also associated with deaths (but unclear whether deaths occurring before 14 days were removed from the analysis)</td>
</tr>
<tr>
<td>Pigau et al® (2003)</td>
<td>Retrospective review of short-course (10–14 days) antibiotics for catheter-related SAB</td>
<td>87 patients 64 uncomplicated and followed for ≥3 months</td>
<td>Endocarditis in three (3.4%) No relapses or recurrences</td>
</tr>
</tbody>
</table>
| Chang et al® (2003) | Prospective multicentre study; 6 months of follow-up of all patients Analyzed factors that predicted relapse Used bacterial typing to define relapse vs re-infection | 505 enrolled, 448 analysed Relapse rate 9.4%, occurring after median 36 days of stopping treatment | Valvular heart disease, liver cirrhosis, vancomycin therapy each predicted relapse Duration of IV therapy not associated with relapse | Suggests vancomycin not as effective as β-lactams Provides evidence that duration of IV therapy (>10 days minimum) does not influence relapse (Continues on next page)
Table 4: Observational studies on optimum duration of therapy for SAB

<table>
<thead>
<tr>
<th>Design</th>
<th>Patients studied</th>
<th>Main findings</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Johnson et al(^{48}) (2003)</td>
<td>Retrospective review of compliance with standard therapy with analysis of relapse predictors</td>
<td>226 cases; 171 (76%) no removable focus; 33% mortality; 23% recurrence rate (24 of 104 patients assessed)</td>
<td>88% recurrences occurred within 90 days. Bacteraemia &gt;2 days, vancomycin treatment, failure to remove focus, all predicted relapse. Duration of IV therapy did not predict relapse.</td>
</tr>
<tr>
<td>Fatkenheuer et al(^{90}) (2004)</td>
<td>Retrospective review of 229 episodes of SAB with 1 year of follow-up</td>
<td>Mortality 37.6% Death associated with pneumonia, age &gt;60 years, and known focus</td>
<td>Treatment duration assessable in 160 87 (54%) received less than 14 days of antibiotics No association with poor outcome</td>
</tr>
<tr>
<td>Khosrovaneh et al(^{91}) (2005)</td>
<td>Prospective study of SAB associated with soft-tissue infection Follow-up median 75 days</td>
<td>50 patients. 16% mortality and 6% incidence of relapse/metastatic infection 10 (20%) had bacteraemia &gt;1 day</td>
<td>13 (26%) patients switched from IV to oral within 14 days (median 7 days)</td>
</tr>
<tr>
<td>Thomas and Morris(^{92}) (2005)</td>
<td>Prospective study of catheter-associated SAB with 8 weeks of follow-up Bacterial typing to distinguish relapse from re-infection</td>
<td>276 cases 9% mortality 4% proven deep relapse 91 (33%) given &lt;10 days IV antibiotics</td>
<td>No relation between relapse and duration of therapy</td>
</tr>
<tr>
<td>Kreisel et al(^{49}) (2006)</td>
<td>Retrospective case series in those surviving initial treatment for SAB 1 year of follow-up</td>
<td>397 cases 17% recurrence (bacterial typing not done to exclude re-infection)</td>
<td>HIV, diabetes, and MRSA predicted recurrence; duration of therapy &lt;14 days did not</td>
</tr>
<tr>
<td>Ghanem et al(^{93}) (2007)</td>
<td>Retrospective review of patients with catheter-associated SAB with cancer 3 months of follow-up</td>
<td>91 cases 40% complications: 19% intravascular (thrombosis most common) and 21% extra-vascular (mostly septic shock with death) Mortality 19%</td>
<td>Relapse independently associated with renal failure Data on duration of treatment given, but not analysed against outcome</td>
</tr>
<tr>
<td>Jenkins et al(^{94}) (2008)</td>
<td>Retrospective review of the effect of an infectious diseases consultation service on the outcome of patients with SAB in USA</td>
<td>234 cases: 100 with consultation; 134 without consultation Consultation patients had more echocardiograms and were treated with IV antibiotics for longer</td>
<td>25 (26%) non-consultation patients got &lt;11 days IV antibiotics Fewer complications in the consultation patients (13% vs 22%, p=0.05) No consultation or short duration of therapy was not significantly associated with poor outcome</td>
</tr>
<tr>
<td>Walker et al(^{95}) (2009)</td>
<td>Retrospective case-control study of relapsed SAB (no bacterial typing) in Oxford, UK Compared adherence to standard treatment guidance and effect on outcome</td>
<td>Bacterial relapse in 40 (2 1%) of 1870 SAB cases, occurring 8–84 days after start of treatment</td>
<td>Glycopeptide therapy for meticillin-susceptible SAB independently associated with relapse Duration of therapy not associated with relapse</td>
</tr>
</tbody>
</table>

SAB=Staphylococcus aureus bacteraemia. IV=intravenous. RCT=randomised controlled trial. MRSA=meticillin-resistant S aureus.

A 20-year study of meticillin-resistant S aureus (MRSA) clinical isolates (60% from blood) from Detroit, USA, reported the proportion with heterogeneous vancomycin intermediate susceptibility (hetero-VISA) increasing from 2·2% (1986–1993) to 8·3% (2003 and 2007). A recent international case series found hetero-VISA in 29% (19 of 65) of MRSA isolated from patients with endocarditis. Some studies have even reported that S aureus isolates with vancomycin MIC in the susceptible range (1–2 μg/mL) are associated with persistent SAB and poorer clinical outcomes than isolates with MIC of 1 μg/mL or less. However, two large studies from Taiwan and the USA did not identify any effect of reduced vancomycin susceptibility and outcome. It is possible that reduced vancomycin susceptibility is associated with reduced virulence. There are no data to show that alternative antibiotics (eg, linezolid or daptomycin) are superior to vancomycin in treatment of GISA. Indeed, several studies have reported an association between decreased vancomycin susceptibility and decreased susceptibility to these drugs.

**Are cephalosporins as effective as penicillins for the treatment of SAB?**

Cephalosporins are often considered for the treatment of SAB in patients who are intolerant of penicillins and when longer-acting antimicrobials are needed for ease of administration. Despite substantial anecdotal experience of their use in the treatment of SAB, little published evidence exists to confirm their efficacy. No comparative RCTs have been done, but prospective observational studies suggest that most of the commonly used cephalosporins may be as effective as penicillins for the treatment of SAB. The exceptions may be for cefonicid laboratory detection methods, and in-vitro MIC thresholds to predict clinical success or failure are contentious.
success (>90%) has been reported for ceftriaxone, 73–75 due to cefazolin-hydrolysing β-lactamases, 69,70 and some
associated with treatment failure in small case series.65,66
Deep focus of infection and high bacterial loads,64 possibly
due to cefazolin-hydrolysing β-lactamases,62,63 and some
recommend avoiding cefazolin in such patients.66
There are concerns that third-generation cephalosporins
(cefotaxime and ceftriaxone) might be less effective
against S aureus than penicillins because of higher MIC. Limited
clinical data suggest that these fears may be unfounded. Cefotaxime was used to treat 16 adults with SAB (13 were catheter associated) and all showed a
prompt clinical response to therapy.71 Furthermore, cefotaxime treatment of 90 patients with serious S aureus
disease (mostly respiratory and skin and soft-tissue infections) resulted in a 97% cure.72 Similar treatment
success (>90%) has been reported for ceftriaxone,73–75 although no case series of ceftriaxone use for SAB alone
have been published, and there are few data on the use of these agents in the treatment of complicated disease.

Is teicoplanin as effective as vancomycin?
Vancomycin and teicoplanin are the first-line therapy
for MRSA bacteraemia and for those with serious
cellulitis allergy. Teicoplanin is not licensed for use in
the USA, and comparisons are complicated by the
suboptimum dosing of teicoplanin in early studies. An
RCT of 21 patients with serious S aureus infections (13 SAB; six with a deep focus) compared teicoplanin
(400 mg daily) with vancomycin (1 g twice daily) and reported similar proportions cured for each drug.74 An
RCT compared teicoplanin (12 mg/kg in the first 24 h, 6 mg/kg for the next 24 h) with vancomycin (15 mg/kg
every 12 h) for serious Gram-positive infections and was
stopped early after six of eight patients with complicated
does not have an irremovable focus.78,79 A recent
systematic review and meta-analysis that compared the
efficacy and safety of vancomycin versus teicoplanin for
various Gram-positive infections concluded that
treatment was non-inferior to vancomycin when
comparing all-cause mortality and clinical or
microbiological failure, but that vancomycin was
associated with a higher incidence of nephrotoxicity and
red-man syndrome.80

What is the optimum duration of therapy for SAB?
50 years ago, two-thirds of SAB were associated with
endocarditis, and long-term (>4 weeks) intravenous
therapy was thought mandatory.75 Intravascular catheters
are now the most common source of SAB,81 and the risks
of endocarditis and disease recurrence are low, provided
the source is removed.82 This has prompted use of much
shorter courses of antibiotics, particularly for catheter-associated SAB.83

Only one published RCT has examined the duration of
intraavenous therapy for any form of SAB: 11 adults
with SAB were assigned to either 2 weeks or 4 weeks of
intraavenous therapy.84 One patient in the 2-week group
developed endocarditis compared with none in the
4-week group. The remaining evidence comes from
observational studies (table 4). Small case series in the
1980s indicated that 10–14 days of intravenous therapy
for uncomplicated catheter-associated SAB was
associated with very low numbers of secondary
complications.85–88 In 1992, an analysis of published
data and a retrospective case series concluded that
fewer than 10 days of intravenous antibiotics may be
associated with an increased risk of recurrence, but
10–14 days of intravenous therapy was safe for most
cases of catheter-associated SAB.79

Even shorter courses may be effective. Fowler and
colleagues22 reported the clinical consequences of the
variable adherence to SAB treatment guidelines, which
included the recommendation to treat uncomplicated,
catheter-associated SAB with 7 days of intravenous
antibiotics. These and other investigators, who tested
similar recommendations, did not report a worse
outcome in this group. In addition, 7 days of intravenous
therapy was reported to be safe and effective in a
retrospective review of 49 patients with uncomplicated
catheter-associated SAB. However, the possibility that
patients chosen to receive short courses are a highly
selected subgroup with better underlying prognosis
cannot be excluded, a selection bias that cannot be
adequately adjusted for in statistical models (particularly
with such small numbers). Furthermore, two studies
reported increased complications in those receiving
fewer than 14 days of intravenous therapy,89,90 and a review
of patients with catheter-associated SAB and cancer
found that this group had a high rate of complications
that might necessitate long-term therapy.91
Long-term intravenous treatment (>4 weeks) remains standard practice for patients who have left-sided SAE, an irremovable primary focus, metastatic infection, or persistence of bacteraemia after catheter removal.43,53,54 Such patients are at high risk of treatment failure, disease recurrence, and death.11,12 but there is little evidence that long-term therapy (>4 weeks) is superior to shorter courses. Some studies suggest that a 2-week intravenous course might be adequate in the treatment of right-sided endocarditis (table 5).43,55-57

Is oral therapy as effective as intravenous therapy?

Two RCTs indicate some oral antibiotics are as effective as those given intravenously.58,59 The first compared oral fleroxacin plus rifampicin against conventional intravenous therapy with a β-lactam or glycopeptide in 104 adults with SAB (55 with catheter-associated infection, 35 with bone or joint infection).58 Patients with left-sided endocarditis were excluded. The second trial compared oral ciprofloxacin plus rifampicin versus standard intravenous therapy in 85 intravenous drug users with right-sided endocarditis, 65% of whom had HIV.59 The proportions of patients who achieved clinical and microbiological cure were similar in both treatment groups (around 80%) and in both trials. Those receiving oral antibiotics were discharged from hospital significantly earlier than those given intravenous therapy.

Whether oral antibiotics after an initial period of intravenous therapy are non-inferior to continuous intravenous therapy remains little tested. Two case series described 35 adults with SAE,60 and 18 adults with cancer with SAB,61 successfully treated intravenously followed by oral antibiotics. Complete cure was achieved in those with endocarditis by a mean of 16 days of intravenous therapy followed by a mean of 26 days of oral therapy (30 of 35 received oral dicloxacillin, or cloxacillin alone). Patients in the second study received a mean of 9 days of intravenous therapy followed by 25 days of oral therapy; only one patient relapsed. A further study described the successful treatment of nine patients with SAB with a mean of 10 days of intravenous antibiotics, followed by 4 weeks of oral dicloxacillin with probenecid.62 In a prospective study of 50 patients with SAB associated with skin and soft-tissue infection, 13 (26%) were switched to oral therapy after a median of 7 days of intravenous antibiotics with no apparent increase in complications.63

Is combination antimicrobial therapy better than monotherapy?

Combining antimicrobials to enhance bacterial killing has long been used for the treatment of SAB, particularly SAE, but has never been shown to improve outcome (table 6). Synergy between β-lactams and gentamicin has been shown experimentally,100,101 but the evidence for clinical effectiveness in human beings is limited to one report of 78 patients with SAE in whom the addition of gentamicin to the first 2 weeks of nafcillin treatment reduced the time to defervescence and duration of bacteraemia by 1 day.105 A meta-analysis of four trials (210 patients) of a β-lactam, with or without an aminoglycoside for the treatment of native-valve SAE, found no significant benefit of aminoglycosides in terms of mortality (OR 0.69 [95% CI 0.26–1.86]) or treatment success (OR 1.177 [95% CI 0.47–3.42]), but aminoglycosides were significantly associated with complications.91

<table>
<thead>
<tr>
<th>Design</th>
<th>Patients studied</th>
<th>Main findings</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chambers et al58 (1988)</td>
<td>Case series of IVDUs with uncomplicated right-sided</td>
<td>47 of 50 patients treated with nafcillin cured</td>
<td>Selected patients with S aureus</td>
</tr>
<tr>
<td></td>
<td>Staphylococcus aureus endocarditis treated with either</td>
<td>1 of 3 patients treated with vancomycin cured</td>
<td>endocarditis can be treated safely and</td>
</tr>
<tr>
<td></td>
<td>nafcillin vs vancomycin both in combination with</td>
<td></td>
<td>effectively with a 2-week course of</td>
</tr>
<tr>
<td></td>
<td>tobramycin for 2 weeks</td>
<td></td>
<td>nafcillin plus tobramycin</td>
</tr>
<tr>
<td>Tortes-Tortosa et al59</td>
<td>Case series of IVDUs with right-sided MSSA endocarditis</td>
<td>67 of 72 patients cured</td>
<td>Administration of cloxacillin and</td>
</tr>
<tr>
<td></td>
<td>and a good prognosis (normal renal function, no extra-</td>
<td>4 required lengthening of treatment, 1 died</td>
<td>amikacin for 14 days is effective therapy</td>
</tr>
<tr>
<td></td>
<td>pulmonary foci of infection)</td>
<td></td>
<td>of right-sided endocarditis in IVDU</td>
</tr>
<tr>
<td>Ribera et al60 (1996)</td>
<td>Open-label RCT of IVDUs with right-sided MSSA</td>
<td>Treatment successful in 24 of 38 patients</td>
<td>A penicillinase-resistant penicillin used in</td>
</tr>
<tr>
<td></td>
<td>endocarditis</td>
<td>treated with cloxacillin alone and 31 of 36</td>
<td>single-agent therapy for 2 weeks is</td>
</tr>
<tr>
<td></td>
<td>Patients received 2 weeks of cloxacillin alone or</td>
<td>patients treated with cloxacillin in combination</td>
<td>effective for most patients with isolated</td>
</tr>
<tr>
<td></td>
<td>with gentamicin for the first week</td>
<td>with gentamicin. Overall cure, 88%</td>
<td>tricuspid endocarditis caused by MSSA</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Gentamicin associated with trend towards increased</td>
<td>Adding gentamicin does not seem to provide any</td>
</tr>
<tr>
<td></td>
<td></td>
<td>renal failure (14% vs 8%; p=0.02)</td>
<td>therapeutic advantages</td>
</tr>
<tr>
<td>Fortun et al43 (2003)</td>
<td>Open-label RCT in IVDUs with right-sided MSSA</td>
<td>Patients cured all 11 on cloxacillin, 6 of 10</td>
<td>A 14-day course of vancomycin or</td>
</tr>
<tr>
<td></td>
<td>endocarditis</td>
<td>on vancomycin (3 clinical failures, 1 microbiological</td>
<td>teicoplanin plus gentamicin is ineffective</td>
</tr>
<tr>
<td></td>
<td>Patients received 2 weeks of cloxacillin or</td>
<td>relapse), 7 of 10 on teicoplanin (1 clinical failure,</td>
<td>in right-sided endocarditis because it is</td>
</tr>
<tr>
<td></td>
<td>vancomycin or teicoplanin with gentamicin</td>
<td>2 microbiological relapses)</td>
<td>associated with a high rate of clinical and</td>
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<td></td>
<td></td>
<td>Relative risk for treatment failure with</td>
<td>microbiological failure</td>
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<td></td>
<td></td>
<td>glycopeptide-based regimen, 1:54 (95% CI</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>1·12–2·12; p=0·03)</td>
<td></td>
</tr>
</tbody>
</table>

IVDU=intravenous drug user. MSSA=meticillin-sensitive S aureus. RCT=randomised controlled trial.

Table 5: Case series and controlled trials supporting shortened duration of treatment in right-sided Staphylococcus aureus endocarditis
nephrotoxicity (OR 2.63 [95% CI 1.14–6.25]). A recent analysis of 236 patients with SAB (77% had endocarditis) randomly assigned to daptomycin or standard therapy plus gentamicin for the first 4 days, found that gentamicin was an independent predictor of clinically significant renal toxicity without any observed benefit. Gentamicin is thus no longer routinely recommended for the treatment of S aureus native-valve endocarditis.

Fluoroquinolones, rifampicin, and fusidic acid are also commonly used in the combination therapy of SAB, although there is little evidence to support their routine use. An RCT compared the addition of levofloxacin to standard intravenous therapy in 381 adults with all forms of SAB (331 [87%] had a deep focus of infection), and found that levofloxacin did not improve outcome overall, or in any subgroup. An exploratory subgroup analysis found an improved outcome among those with a deep focus of infection who also received rifampicin, but confirmatory studies are lacking.

Fusidic acid adjunctive therapy has been used, particularly for SAB associated with bone and joint infection. Two recent reports suggest its usefulness in combination with linezolid for the treatment of complicated SAB in cases in which there is reduced susceptibility to vancomycin. There are few other supportive data and possible efficacy must be balanced against the risks of hepatotoxicity.

**What is the role of the newer antimicrobials in the treatment of SAB?**

Several new antimicrobials may have important future roles in the management of SAB (table 7), although only linezolid and daptomycin have entered mainstream clinical practice.

### Table 6: Comparative studies on combination antibiotic treatment in SAE

<table>
<thead>
<tr>
<th>Design</th>
<th>Patients studied</th>
<th>Main findings</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Watanakunakorn and Baird (1977)</td>
<td>Retrospective case-series analysis of patients with SAE treated with appropriate backbone antibiotics with or without gentamicin</td>
<td>40 cases: 14 on nafcillin, 13 on penicillin G, 9 on meticillin, 3 on cefalotin, 1 on vancomycin</td>
<td>Overall mortality: 40% in patients treated both with and without gentamicin</td>
</tr>
<tr>
<td>Abrams et al (1979)</td>
<td>Randomised comparison of β-lactam with or without gentamicin for treatment of SAE</td>
<td>25 IVDUs with SAE: 12 on β-lactam, 13 on β-lactam and gentamicin</td>
<td>No deaths or treatment failures in either group</td>
</tr>
<tr>
<td>Korzeniowski and Sande (1982)</td>
<td>Randomised comparison of nafcillin for 6 weeks either alone or combined with gentamicin for the first 2 weeks in SAE</td>
<td>Gentamicin associated with more rapid resolution of bacteraemia but a higher incidence of azotaemia</td>
<td>The addition of gentamicin does not alter morbidity or mortality</td>
</tr>
<tr>
<td>Cosgrove et al (2009)</td>
<td>Subanalysis of patients with native-valve SAE who had been recruited to an RCT of daptomycin vs standard treatment (anti-staphylococcal penicillin or vancomycin plus initial gentamicin) for treatment of SAE</td>
<td>Patients receiving gentamicin more commonly had decreased creatinine clearance (22% vs 9%; p=0.003)</td>
<td>Initial low-dose gentamicin as part of therapy for SAB and native-valve infective endocarditis is nephrotoxic and should not be used routinely</td>
</tr>
<tr>
<td>Hughes et al (2009)</td>
<td>Retrospective non-randomised comparison of patients receiving continuous infusion or intermittent infusion oxacillin treatment for MSSA endocarditis</td>
<td>Patients receiving gentamicin defervesced more quickly (2 vs 4 days)</td>
<td>Continuous oxacillin is an effective alternative to intermittent oxacillin for the treatment of MSSA endocarditis</td>
</tr>
<tr>
<td>Levine et al (1991)</td>
<td>RCT of vancomycin with or without rifampicin for 28 days in MRSA endocarditis</td>
<td>Vancomycin group: 4 failures and 2 deaths</td>
<td>The addition of rifampicin to vancomycin does not seem to be beneficial</td>
</tr>
<tr>
<td>Reidel et al (2008)</td>
<td>Retrospective cohort study of SAE cases treated with and without addition of rifampicin</td>
<td>Patients who received rifampicin more commonly had left-sided endocarditis and more commonly received gentamicin, but otherwise were similar</td>
<td>Clinicians should undertake a careful risk-benefit assessment before adding rifampicin to standard antibiotic treatment of native-valve SAE</td>
</tr>
</tbody>
</table>

SAE=Staphylococcus aureus endocarditis. RCT=randomised controlled trial. SAB=S aureus bacteraemia. MSSA=meticillin-sensitive S aureus. MRSA=meticillin-resistant S aureus. IVDU=intravenous drug user.
Table 7: New antibiotics with potential to treat SAB

<table>
<thead>
<tr>
<th>Class</th>
<th>Mode of action</th>
<th>Antimicrobial spectrum</th>
<th>Pharmacology</th>
<th>Relevant clinical evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Linezolid</td>
<td>Oxazolidine</td>
<td>Targets 50S ribosomal subunit</td>
<td>100% oral bioavailability</td>
<td>Some evidence of superiority over vancomycin in treatment of MRSA pneumonia and skin and soft-tissue infection&lt;br&gt;Non-inferior to vancomycin for treatment of SAB in meta-analyses</td>
</tr>
<tr>
<td></td>
<td>Cyclic lipopeptide</td>
<td>Acts at the cytoplasmic membrane</td>
<td>Bactericidal</td>
<td>Non-inferior to vancomycin in MRSA bacteraemia and right-sided endocarditis&lt;br&gt;Not active in lung tissue</td>
</tr>
<tr>
<td></td>
<td>Glycylcycline</td>
<td>Modified tetracycline with activity against tetraacycline-resistant strains</td>
<td>Bacteriostatic&lt;br&gt;Active against MRSA and VISA&lt;br&gt;Like clindamycin, inhibits the production of bacterial extracellular toxins&lt;br&gt;Activity against MRSA pneumonia and skin and soft-tissue infection</td>
<td>Equivalent to vancomycin for the management of cSSSI&lt;br&gt;Low serum concentrations achieved may make it a poor choice for bacteraemia</td>
</tr>
<tr>
<td></td>
<td>Cephalosporin</td>
<td>Activity against MRSA</td>
<td>Bactericidal&lt;br&gt;Good activity against Gram-negative bacteria&lt;br&gt;Non-inferior to vancomycin in cSSSI</td>
<td>Non-inferior to vancomycin in cSSSI&lt;br&gt;Well tolerated</td>
</tr>
<tr>
<td>Dalbavancin and telavancin</td>
<td>Glycopeptides</td>
<td>Activity against cell wall&lt;br&gt;Telavancin also has cell-membrane activity</td>
<td>Bactericidal&lt;br&gt;Active against MRSA and VISA</td>
<td>Dalbavancin equivalent to linezolid in cSSSI&lt;br&gt;Phase 2 data for efficacy in SAB</td>
</tr>
</tbody>
</table>

SAB=Staphylococcus aureus bacteraemia; MRSA=meticillin-resistant S. aureus; VISA=vancomycin-resistant S. aureus; cSSSI=complicated skin and skin structure infection.
gentamicin-related changes in renal function.\textsuperscript{29} Serum creatinine kinase increased in eight patients (7%) given daptomycin, which resulted in drug withdrawal in three patients, and there was a non-significant increase in microbiological failures in the daptomycin group (16% vs 10%; \( p=0.17 \)). Daptomycin MIC increased to the non-susceptible range in six of 19 patients with persistent or relapsing MRSA infection, all of whom had received vancomycin previously.

A post-marketing retrospective database of 1227 patients in the USA with \textit{S aureus} infections (30% with SAB or SAE) treated with daptomycin, reported that clinical successes for SAB and SAE were 88% and 81%, respectively.\textsuperscript{141} Multivariable analysis showed predictors of daptomycin treatment failure were endocarditis, bacteraemia, severe renal dysfunction, and diabetes mellitus.

The relation between prior vancomycin treatment, VISA, hetero-VISA, and increased daptomycin MIC is undetermined.\textsuperscript{64} Daptomycin treatment failures associated with increased MIC have been reported, primarily in association with deep, irremovable foci of \textit{S aureus} infection.\textsuperscript{142–145} Heterogeneous intermediate susceptibility to daptomycin may be induced in some strains of \textit{S aureus} by prior vancomycin exposure,\textsuperscript{146–148} although the mechanism and clinical relevance remains uncertain.\textsuperscript{64} Currently, there seems to be a clinical association between reduced daptomycin susceptibility and VISA, but not hetero-VISA.\textsuperscript{146–150}

Daptomycin is currently licensed to treat skin and soft-tissue infections at 4 mg/kg every 24 h and bacteraemia and endocarditis at 6 mg/kg every 24 h. An animal endocarditis model found that doses less than 6 mg/kg every 24 h were associated with the emergence of reduced susceptibility, and 10 mg/kg every 24 h produced superior bactericidal activity to 6 mg/kg every 24 h.\textsuperscript{211} Healthy volunteers have tolerated doses of up to 12 mg/kg every 24 h for 14 days,\textsuperscript{152} and drug registry data have suggested that doses of at least 8 mg/kg every 24 h are well-tolerated and effective.\textsuperscript{150} Clinical trials investigating the safety and effectiveness of higher doses for the treatment of SAB or SAE are required.

**Discussion**

SAB is a common and serious infection worldwide, yet the evidence base for almost all aspects of its management is poor. We first examined the evidence on the definition of SAB and the need to identify the infection source and focus (panel). A single positive blood culture for \textit{S aureus} should always be defined as clinically significant, given the intrinsic pathogenicity of \textit{S aureus}, the high number and frequency of complications following SAB, and the rarity of \textit{S aureus} contamination of blood cultures. The finding should prompt immediate and careful clinical assessment to identify any site of invasion and deep-seated metastatic focus of infection. There is strong evidence to suggest that prompt removal or drainage of infected foci improves outcome,\textsuperscript{10,11,22} but much less certainty about defining a group of patients with uncomplicated disease that may be adequately treated with short courses of antibiotics. Whether transthoracic echocardiography or transoesophageal echocardiography should be a mandatory part of this assessment remains controversial. In many settings, transoesophageal echocardiography for all patients with SAB is impractical, and the current evidence suggests a pragmatic approach may be to consider the use of transthoracic echocardiography for all patients with SAB, unless the physician is satisfied that the source or foci of infection are identified and removed and the risk of endocarditis is low. A transoesophageal echocardiogram may be required in those at high risk of endocarditis (ie, with abnormal native heart valves or a prosthetic valve), signs of embolic phenomena, or if SAB persists with no identified focus of infection.

The optimum antimicrobial choice, duration, and route of delivery for the treatment of SAB were examined in the remaining questions (panel). \( \beta \)-lactam antibiotics are more effective than glycopeptides for treatment of meticillin-susceptible SAB, and the emergence of GISA or hetero-GISA threatens the role of glycopeptides in the treatment of MRSA bacteraemia. The superiority of alternative agents, such as linezolid and daptomycin, for the treatment of MRSA bacteraemia remains unproven. Resistance to both these agents emerged shortly after their introduction,\textsuperscript{215} and studies are required to determine whether their activity can be preserved or enhanced by increases in dose or by their use in combination with other antibiotics. There are insufficient data to determine whether cephalosporins are as effective as penicillins for the treatment of SAB, but they are probably more effective than vancomycin for the treatment of meticillin-susceptible SAB.

Little evidence exists to guide the best duration of SAB therapy: 10–14 days of intravenous therapy seems

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**Panel: Key clinical questions concerning the management of SAB**

1. How should SAB be defined?
2. Is identification and removal of the focus of infection important?
3. Should all patients with SAB have echocardiography?
4. Are glycopeptides equivalent to \( \beta \)-lactams for the treatment of SAB?
5. Are cephalosporins as effective as penicillins for the treatment of SAB?
6. Is teicoplanin as effective as vancomycin?
7. What is the optimum duration of therapy for SAB?
8. Is oral therapy as effective as intravenous therapy?
9. Is combination antimicrobial therapy better than monotherapy?
10. What is the role of the newer antimicrobials in the treatment of SAB?

SAB=Staphylococcus aureus bacteraemia.
So do we know how to manage SAB? Review of the evidence underscores two key principles. First, all infective foci should be identified and, where possible, removed. Second, long-term antimicrobial therapy is required for those with persistent bacteraemia or a deep, irremovable focus. Beyond this, most of the answers to the key clinical question are unknown. Even when randomised clinical trials have been done, their sample size has generally been small—and insufficient to show non-inferiority—and this lack of power may explain why findings have not been translated into clinical practice. The best way to manage SAB will remain unknown until the key clinical questions, defined above, have been addressed by large, rigorous RCTs.

**Contributors**
All authors helped formulate the clinical questions addressed. GT and ML searched the published work and wrote the first draft. All authors helped write the final draft.

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**References**

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**Search strategy and selection criteria**
Each key question was addressed by searching PubMed (July, 1965, to September, 2009) using the following MeSH search terms: “*Staphylococcus aureus* and (bacteraemia or blood stream infection)”. Further specific search terms, for example “echoendocardiography or cephalosporin”, were added, depending on the question. The search was limited to studies published in the English language. Bibliographies were hand-searched for secondary references. Studies were categorised by study design and the questions they purported to address. Two clinicians (GT and ML) independently reviewed each study, and disagreements with regard to inclusion or exclusion were resolved by consensus. A formal meta-analysis was not done because factors such as study design, disease definition, treatment modality, potential bias, and the extent to which investigators controlled for confounding were too heterogeneous across the studies to enable comparison.

Whether intravenous therapy can be shortened to 7 days, or replaced by oral antibiotics after initial intravenous treatment, is uncertain. Despite few data, most treatment guidelines recommend 4–6 weeks of intravenous antibiotic therapy for left-sided SAE, and equivalent courses may be required for patients with an irremovable or unidentified primary focus, haematogenous spread of infection, or persistence of bacteraemia after catheter removal.

Current guidelines suggest that patients with SAB should receive long-term intravenous therapy, necessitating protracted hospital stays. Tantalising evidence suggests that an initial intravenous phase of therapy followed by oral antibiotics may be as effective as long-term intravenous therapy and may allow earlier hospital discharge and reduced overall cost. This approach is relatively widespread but with uncertain effect on outcome. RCTs are required in this area to counter the potential for selection bias.

The benefits of adding other antimicrobials to β-lactam or glycopeptide core therapy remain unproven. Risk of renal toxic effects may outweigh the possible benefits of synergistic aminoglycosides for the treatment of SAB with or without endocarditis.

Finally, the clinical outcome from SAB is influenced by the dynamic relation between antibiotic exposure and *S aureus* genotype, virulence, and antibiotic susceptibility. *S aureus* associated with either higher incidence of SAB, persistent SAB, or metastatic dissemination and death have been associated with selected genotypes and particular virulence phenotypes. *S aureus* with reduced susceptibility to glycopeptides may be less virulent and cause less bacteraemic disease.


Review


150 Moise PA, Hershberger E, Arndo-Groton MI, Lamp KC. Safety and clinical outcomes when utilizing high-dose (> or = 8 mg/kg) daptomycin therapy. Ann Pharmacother 2009; 43: 1211–19.


