Clinical management of *Staphylococcus aureus* bacteraemia

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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, irremovable focus. Beyond this, the best drugs, dose, mode of delivery, and duration of therapy are uncertain, a situation compounded by emerging *S aureus* strains that are resistant to old and new antibiotics. We discuss the consequences on clinical practice, and how these findings define the 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.[1] In the UK, around 12 500 cases of *S aureus* bacteraemia (SAB) are voluntarily reported each year,[2] associated with a mortality of about 30%.[3]

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.[4–8] 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.[9] 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.[10–13] 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.[9]

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.[19–21] 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.[9]

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.[24] Three prospective studies have shown that not removing an infected intravenous catheter is the strongest independent risk factor for SAB relapse.[10,13,22] Early surgical intervention in *S aureus* endocarditis (SAE), particularly the early removal of infected prosthetic heart valves, improves outcome,[25,26] and not removing *S aureus*-infected prosthetic joints is strongly associated with treatment failure.[27,28] Some patients (10–40%)[11,29] 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.[16,30–32]

Should all patients with SAB have echocardiography?

SAB is a major risk factor for endocarditis, particularly in those with abnormal or prosthetic valves.[16] Studies published before the advent of echocardiography suggested that around 60% of patients with SAB had endocarditis,[9] 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.[33] 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.[34–36] Transoesophageal echocardiography

	Design	Location	Patients	Study definition of poor outcome	Factors associated with poor outcome
Jensen et al[10] (2002)	Prospective, single-centre cohort	Denmark	278	Death	Uneradicated focus; septic shock; total daily dose of dicloxacillin sodium <4 g; age ≥60 years
Lesens et al[14] (2003)	Prospective, two centres	France	166	Death by 3 months after the start of effective antibiotic therapy	Acute complication due to *Staphylococcus aureus*; old age; Charlson[15] weighted index of comorbidity score of ≥3
Fowler et al[11] (2003)	Prospective, single-centre cohort	USA	724	Complicated disease* at baseline, attributable mortality, embolic stroke, or recurrent infection	Community acquisition; skin examination suggesting the presence of acute systemic infection; positive blood culture at follow-up (48–96 h); persistent fever after 72 h of therapy
Chang et al[12] (2003)	Prospective, multicentre cohort	USA	448	Recurrent SAB after completion of anti-staphylococcal antibiotic therapy	Native-valve endocarditis; liver cirrhosis
Chang et al[16] (2003)	Prospective, multicentre cohort	USA	505	Diagnosis of endocarditis (by 1994 modified Duke's criteria)[17]	Prior native-valve disease; prosthetic valve; persistent bacteraemia; intravenous drug use; unidentifiable portal of entry; history of prior endocarditis; community acquisition; non-white race
Turnidge et al[18] (2009)	Prospective, multicentre cohort	New Zealand and Australia	1994	30-day all-cause mortality	Old age; sepsis syndrome; pneumonia/empyema; device-associated infection with a secondary focus; left-sided endocarditis; treatment of MSSA with a glycopeptide

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

	Simple SAB	Catheter-related SAB	Uncomplicated SAB	Complicated SAB
Fowler et al[22] (1998)	(1) TOE on day 5–7 of therapy, negative for vegetations and predisposing valvular abnormalities (2) Negative surveillance blood culture 2–4 days after beginning appropriate antibiotic therapy and removal of focus (3) Removable focus of infection (4) Clinical resolution (afebrile and no localising complaints attributable to metastatic staphylococcal infection within 72 h of initiating therapy and removal of focus) (5) No indwelling prosthetic devices	..	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	(1) Endocarditis according to Duke criteria[17] (2) Extracardiac deep source of infection (eg, mediastinitis and osteomyelitis)
Jenkins et al[23] (2008)	..	Definite: catheter-tip culture grew >15 colonies of *Staphylococcus aureus* 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	Isolation of *S aureus* 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
Naber et al[9] (2009)	..	..	(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	Absence of any of the features of uncomplicated SAB

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

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

was also superior to transthoracic echocardiography for the diagnosis of prosthetic valve endocarditis,[37] and infections of pacemaker leads and other intra-cardiac devices.[33]

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.[31] 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.[38] 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.[39]

	Design	Findings	Conclusions
Bayer et al[31] (1987)	Prospective study of 72 adults with SAB All had two-dimensional echocardiography	16 patients had endocarditis, 18% detected by echocardiography alone (no clinical stigmata) Predictors of endocarditis: no primary focus, community acquisition, metastatic lesions, valvular lesions on echocardiography	All cases of community-acquired SAB should have echocardiography
Fowler et al[38] (1997)	Prospective study of 103 adults with SAB who had TTE and TOE	7 (7%) had clinical evidence of endocarditis TTE diagnosed 7 patients with endocarditis TOE diagnosed 26 (1 false positive)	TOE is more sensitive for the diagnosis of endocarditis than TTE and should be considered for all patients with SAB
Rosen et al[39] (1999)	Cost-effectiveness analysis of TOE for line-associated SAB Frequency of events estimated from published case series and their own institution	Showed immediate TOE cost-effective when compared with empirical short (14 days) or long (28 days) therapy	Supports use of TOE in defining treatment length
Blyth et al[40] (2002)	Mixed retrospective and prospective study of adherence to Fowler's 1998 SAB management guidelines[22]	98 cases studied 38 (41%) received inadequate antibiotic therapy: non-significant increase in recurrence in this group (5 of 38 *vs* 1 of 55) TTE done in 24 and TOE in 10 TOE changed management in 2 patients only	Management guidelines for SAB are frequently ignored and shortened treatment common May cause more disease relapse Limited evidence to suggest TOE adds little to management and TTE is adequate in most patients with SAB
Pigrau et al[32] (2003)	Retrospective review of short course (10–14 days) antibiotics for line-related SAB and the role of TOE in management	87 patients; endocarditis in three (3·4%) TOE failed to detect any new cases of endocarditis if no signs and risk factors present	TOE may not be mandatory in those without risk factors who respond quickly to treatment
Van Hal et al[30] (2005)	Retrospective comparison of diagnostic yield of TTE and TOE in patients with SAB	125 patients: 22 with endocarditis by Duke's criteria;[37] endocarditis associated with no primary focus and community source 18 had vegetations detected by TTE, the rest had embolic phenomena 2 had vegetation detected by TOE alone.	No embolic signs and normal TTE makes endocarditis very unlikely Investigators suggest that there is a subgroup of SAB patients who do not require TOE, although high-risk patients still do
Sullenberger et al[41] (2005)	Retrospective review of 176 adults with SAB	64 had TOE and TTE; new vegetations found in 9 (14%) by TOE; patients with endocarditis were significantly older than those without; no other risk factors found	TOE more sensitive than TTE and should be considered for all patients with SAB

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

***Table* 3: Studies of the use of routine echocardiography for SAB**

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.[30] 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).[42,43] 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.[45] 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).[43]

Observational studies suggest that vancomycin does not sterilise blood as quickly as β-lactams, resulting in persistent SAB,[20,21,46] 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.[12,13,18,47,48] 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.[49]

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.[50] However, glycopeptide intermediate susceptibility *S aureus* (GISA) and susceptible strains with a subpopulation of bacteria (typically around one organism per 10^5–10^6 bacteria) within the intermediate susceptibility range (so-called hetero-GISA) are important emerging clinical problems.[51] The criteria for defining intermediate susceptibility

	Design	Patients studied	Main findings	Conclusions
Iannini and Crossley[85] (1976)	Retrospective case-note review of SAB with removable focus only Minimum 8 weeks of follow-up required	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)	No relapse or recurrence or endocarditis reported	Short course (10–14 days) IV therapy is probably safe for SAB with removable source
Mylotte and McDermott[81] (1987)	Prospective case series of catheter-associated SAB	28 cases None developed endocarditis or metastatic complications Mortality 21%	22 of 28 patients given ≤14 days antibiotics with no evidence of recurrence	≤14 days of antibiotics adequate for catheter-associated uncomplicated SAB
Mylotte et al[86] (1987)	Prospective case series of all SAB with literature review	114 cases: 33 (29%) with MRSA; 38 (33%) catheter-related Mortality 32% Most given ≥14 days of therapy	Low incidence of endocarditis (n=2) and metastatic infection (n=1)	Suggest 14 days of therapy acceptable for catheter-related SAB as incidence of secondary complications low
Ehni and Reller[87] (1989)	Prospective case series of catheter-associated SAB with 3 months of follow-up	13 patients with catheter-associated SAB given <15 days of IV antibiotics (range 0–14 days) 3 patients given oral antibiotics after 2·5–9 days of IV antibiotics	Only 1 patient relapsed with endocarditis (treated with 9 days of IV then 6 days of oral therapy)	Short-course IV antibiotic therapy is safe for those with simple catheter-associated SAB
Raad and Sabbagh[19] (1992)	Retrospective case review plus review of published studies of antibiotic duration for SAB	55 cases and 6 published studies (total 141 episodes of SAB analysed)	Late recurrence in 3 of 19 who had <10 days IV antibiotics *vs* 0 of 27 given >10 days IV therapy Persistent fever or bacteraemia after 3 days of therapy best predictor of recurrent disease	Minimum effective duration of therapy for SAB is 10 days
Jernigan and Farr[83] (1993)	Meta-analysis of short course IV antibiotics (<15 days) Only included studies with <15 days IV treatment (ie, no comparison with longer duration)	11 studies (only 1 RCT)[84] Only 4 studies with adequate follow-up to assess recurrence Data from 132 patients analysed No control group	Pooled complication rate 24%, mortality 15% Late complications 6·1% (95% CI 2·0–10·2)	Investigators suggest the data are flawed by bias and statistical imprecision and optimum duration of therapy remains unknown They suggest a controlled trial is required
Malanoski et al[88] (1995)	2-year retrospective case-note review of catheter-associated SAB with median 3 months of follow-up	55 patients 42 had no early complications: 3 treated with <10 days of IV antibiotics; 18 given 10–14 days of IV antibiotics; 21 received 16–43 days of IV antibiotics	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 <10 days of therapy relapsed	Uncomplicated catheter-associated SAB can be safely treated with 10–15 days of IV antibiotics as long as the catheter is rapidly removed
Fowler et al[22] (1998)	Prospective study of effect of specialist infectious diseases advice on outcome from SAB 3 months of follow-up Bacterial typing to distinguish recurrence from re-infection	244 enrolled Recommended 1 week IV for simple SAB, 2 weeks for uncomplicated SAB and 4–6 weeks for complex SAB	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	Infectious disease advice on the management of SAB can improve outcome Indirect evidence that 7 days of IV antibiotics may be sufficient for simple, catheter-associated infection
Zeylemaker et al[89] (2001)	Retrospective review analysing relation between duration of antibiotics for catheter-associated SAB and outcome	49 patients with 1 year of follow-up Antibiotic duration: 5, no treatment; 4, 1–7 days; 25, 7–14 days; 15, >14 days	24 (49%) patients had complications; 14 (29%) died No significant relation between duration of treatment and outcome	High complication rate, but no relation with duration of therapy Suggest 7–14 days of IV therapy may be adequate for uncomplicated catheter-associated SAB
Blyth et al[40] (2002)	Mixed retrospective and prospective study of adherence to Fowler 1998 SAB management guidelines[22]	98 cases 41% not treated according to guidelines Recurrence rate higher if not given adequate therapy (5 of 38 *vs* 1 of 55)	28 received shortened antibiotic therapy with a non-significant increase in recurrence	Fowler's 1998 treatment guidelines[22] may be adequate Duration of treatment shorter than recommended may result in increased risk of relapse
Jensen et al[10] (2002)	Prospective multicentre study of all types of SAB. 3 months of follow-up	278 cases. Mortality 34% Recurrence 12% Death associated with un-eradicated focus, septic shock, >60 years, and using <4 g daily dicloxacillin	Duration of treatment <14 days also associated with deaths (but unclear whether deaths occurring before 14 days were removed from the analysis)	Defining and removing focus critical to outcome, and high-dose β-lactam also important Relevance of duration of treatment to outcome uncertain
Pigrau et al[32] (2003)	Retrospective review of short-course (10–14 days) antibiotics for catheter-related SAB	87 patients 64 uncomplicated and followed for ≥3 months	Endocarditis in three (3·4%) No relapses or recurrences	10–14 days adequate for uncomplicated catheter-related SAB
Chang et al[16] (2003)	Prospective multicentre study; 6 months of follow-up of all patients Analysed 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

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	Design	Patients studied	Main findings	Conclusions
(Continued from previous page)				
Johnson et al[13] (2003)	Retrospective review of compliance with standard therapy with analysis of relapse predictors	226 cases; 171 (76%) no removable focus; 33% mortality; 23% recurrence rate (24 of 104 patients assessed)	88% recurrences occurred within 90 days Bacteraemia >2 days, vancomycin treatment, failure to remove focus, all predicted relapse Duration of IV therapy did not predict relapse	Further evidence of the inferiority of vancomycin and the importance of removing catheters early Investigators suggest duration of IV therapy should be subject to a controlled trial
Fatkenheuer et al[90] (2004)	Retrospective review of 229 episodes of SAB with 1 year of follow-up	Mortality 37·6% Death associated with pneumonia, age >60 years, and known focus	Treatment duration assessable in 160 87 (54%) received less than 14 days of antibiotics No association with poor outcome	Evidence that duration of IV therapy (<14 days) does not influence outcome
Khosrovaneh et al[91] (2005)	Prospective study of SAB associated with soft-tissue infection Follow-up median 75 days	50 patients. 16% mortality and 6% incidence of relapse/metastatic infection 10 (20%) had bacteraemia >1 day	13 (26%) patients switched from IV to oral within 14 days (median 7 days)	Low complication rate suggests short-course IV followed by oral therapy might be safe for simple soft-tissue infection with SAB
Thomas and Morris[92] (2005)	Prospective study of catheter-associated SAB with 8 weeks of follow-up Bacterial typing to distinguish relapse from re-infection	276 cases 9% mortality 4% proven deep relapse 91 (33%) given <10 days IV antibiotics	No relation between relapse and duration of therapy	Suggest catheter-associated SAB generally benign and short-course IV therapy should be further examined by a controlled trial
Kreisel et al[47] (2006)	Retrospective case series in those surviving initial treatment for SAB 1 year of follow-up	397 cases 17% recurrence (bacterial typing not done to exclude re-infection)	HIV, diabetes, and MRSA predicted recurrence; duration of therapy <14 days did not	Suggest short-course IV therapy may be as effective as long course
Ghanem et al[93] (2007)	Retrospective review of patients with catheter-associated SAB with cancer 3 months of follow-up	91 cases 40% complications: 19% intravascular (thrombosis most common) and 21% extra-vascular (mostly septic shock with death) Mortality 19%	Relapse independently associated with renal failure Data on duration of treatment given, but not analysed against outcome	Patients with cancer and line-associated SAB may be more likely to suffer complications Longer duration IV therapy may be indicated in this group
Jenkins et al[23] (2008)	Retrospective review of the effect of an infectious diseases consultation service on the outcome of patients with SAB in USA	234 cases: 100 with consultation; 134 without consultation Consultation patients had more echocardiograms and were treated with IV antibiotics for longer	35 (26%) non-consultation patients got <11 days IV antibiotics Fewer complications in the consultation patients (13% vs 22%; p=0·09) No consultation or short duration of therapy was not significantly associated with poor outcome	Infectious disease consultations improve adherence to guidelines (and lengthens treatment), but whether this improves outcome is uncertain
Walker et al[48] (2009)	Retrospective case-control study of relapsed SAB (no bacterial typing) in Oxford, UK Compared adherence to standard treatment guidance and effect on outcome	Bacterial relapse in 40 (2·1%) of 1870 SAB cases, occurring 8–84 days after start of treatment	Glycopeptide therapy for meticillin-susceptible SAB independently associated with relapse Duration of therapy not associated with relapse	Low recurrence rate if remove focus and use β-lactams Controlled trials are required to address the optimum duration of therapy

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

Table 4: **Observational studies on optimum duration of therapy for SAB**

laboratory detection methods, and in-vitro MIC thresholds to predict clinical success or failure are contentious.[50]

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).[52] A recent international case series found hetero-VISA in 29% (19 of 65) of MRSA isolated from patients with endocarditis.[53] 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[53–55] and poorer clinical outcomes[56,57] 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.[58,59] It is possible that reduced vancomycin susceptibility is associated with reduced virulence.[60,61] 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.[62–64]

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

(semisynthetic second-generation cephalosporin) and ceftazidime (third-generation cephalosporin with enhanced Gram-negative activity), which have both been associated with treatment failure in small case series.[65,66]

The most robust efficacy data exist for cefazolin, a first-generation cephalosporin widely used in the USA. A non-randomised comparison of vancomycin with cefazolin for the treatment of 123 haemodialysis-dependent patients with meticillin-susceptible SAB reported vancomycin therapy (median serum trough concentration 14 µg/mL [IQR 11·6–18·5]) was an independent risk factor for treatment failure (odds ratio [OR] 3·5 [95% CI 1·2–13·5], adjusted for the retention of haemodialysis access).[67] However, cefazolin treatment may fail in patients with a deep focus of infection and high bacterial loads,[68] possibly due to cefazolin-hydrolysing β-lactamases,[69,70] and some recommend avoiding cefazolin in such patients.[68,70]

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 penicillin 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.[76] 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 endovascular *S aureus* infections failed teicoplanin therapy compared with one of four patients with equivalent infections given vancomycin.[77]

In 1994, an analysis of published and unpublished data concluded that teicoplanin 6 mg/kg every 24 h was probably as effective as vancomycin for most *S aureus* infections, with the exception of endocarditis and septic arthritis when 12 mg/kg every 24 h may be required.[78] Furthermore, predose serum teicoplanin concentrations of less than 20 mg/L have been associated with treatment failure in SAB with endocarditis, and therapeutic drug monitoring has been recommended if using teicoplanin to treat SAB with a deep, 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 teicoplanin 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.[24] 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 intravenous therapy for any form of SAB: 11 adults with SAB were assigned to either 2 weeks or 4 weeks of intravenous 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.[81,85–87] 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.[19]

Even shorter courses may be effective. Fowler and colleagues[22] 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.[40] 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.[89] 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,[10,88] 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.[93]

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.[4,5,8,94] 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).[43,95–97]

Is oral therapy as effective as intravenous therapy?

Two RCTs indicate some oral antibiotics are as effective as those given intravenously.[98,99] 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).[98] 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.[99] 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,[100] and 18 adults with cancer with SAB,[101] 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 SAE with a mean of 10 days of intravenous antibiotics, followed by 4 weeks of oral dicloxacillin with probenecid.[102] 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.[91]

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,[110,111] 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 1·27 [95% CI 0·47–3·42]), but aminoglycosides were significantly associated with

	Design	Patients studied	Main findings	Conclusions
Chambers et al[95] (1988)	Case series of IVDUs with uncomplicated right-sided *Staphylococcus aureus* endocarditis treated with either nafcillin *vs* vancomycin both in combination with tobramycin for 2 weeks	53 of 127 cases of right-sided endocarditis were eligible for inclusion (50 received nafcillin, 3 vancomycin)	47 of 50 patients treated with nafcillin cured 1 of 3 patients treated with vancomycin cured	Selected patients with *S aureus* endocarditis can be treated safely and effectively with a 2-week course of nafcillin plus tobramycin
Tortes-Tortosa et al[96] (1994)	Case series of IVDUs with right-sided MSSA endocarditis and a good prognosis (normal renal function, no extra-pulmonary foci of infection)	72 of 139 cases of right-sided endocarditis were eligible for inclusion	67 of 72 patients cured 4 required lengthening of treatment, 1 died	Administration of cloxacillin and amikacin for 14 days is effective therapy of right-sided endocarditis in IVDU
Ribera et al[97] (1996)	Open-label RCT of IVDUs with right-sided MSSA endocarditis Patients received 2 weeks of cloxacillin alone or with gentamicin for the first week	74 of 90 cases of right-sided endocarditis were eligible for inclusion (38 cloxacillin alone; 36 cloxacillin in combination with gentamicin)	Treatment successful in 34 of 38 patients treated with cloxacillin alone and 31 of 36 patients treated with cloxacillin in combination with gentamicin. Overall cure, 88% Gentamicin associated with trend towards increased renal failure (14% *vs* 8%; p>0·2)	A penicillinase-resistant penicillin used as single-agent therapy for 2 weeks is effective for most patients with isolated tricuspid endocarditis caused by MSSA Adding gentamicin does not seem to provide any therapeutic advantages
Fortun et al[43] (2001)	Open-label RCT in IVDUs with right-sided MSSA endocarditis Patients received 2 weeks of cloxacillin or vancomycin or teicoplanin with gentamicin	31 patients (11 cloxacillin, 10 vancomycin, 10 teicoplanin)	Patients cured: all 11 on cloxacillin; 6 of 10 on vancomycin (3 clinical failures, 1 microbiological relapse); 7 of 10 on teicoplanin (1 clinical failure, 2 microbiological relapses) Relative risk for treatment failure with glycopeptide-based regimen, 1·54 (95% CI 1·12–2·12; p=0·03)	A 14-day course of vancomycin or teicoplanin plus gentamicin is ineffective in right-sided endocarditis because it is associated with a high rate of clinical and microbiological failure

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**

	Design	Patients studied	Main findings	Conclusions
Watanakunakorn and Baird[103] (1977)	Retrospective case-series analysis of patients with SAE treated with appropriate backbone antibiotics with or without gentamicin	40 cases: 14 on nafcillin, 13 on penicillin G, 9 on meticillin, 3 on cefalotin, 1 on vancomycin 15 patients also treated with gentamicin	Overall mortality: 40% in patients treated both with and without gentamicin	Use of gentamicin in addition to a penicillin in the therapy of SAE should be considered a new therapy of unproven benefit
Abrams et al[104] (1979)	Randomised comparison of β-lactam with or without gentamicin for treatment of SAE	25 IVDUs with SAE: 12 on β-lactam, 13 on β-lactam and gentamicin	No deaths or treatment failures in either group	Single-drug therapy with a β-lactam antibiotic is adequate in IVDUs with SAE
Korzeniowski and Sande[105] (1982)	Randomised comparison of nafcillin for 6 weeks either alone or combined with gentamicin for the first 2 weeks in SAE	48 IVDUs: 24 on nafcillin, 24 on nafcillin and gentamicin 30 non-IVDUs: 11 on nafcillin, 19 on nafcillin and gentamicin	Gentamicin associated with more rapid resolution of bacteraemia but a higher incidence of azotaemia	The addition of gentamicin does not alter morbidity or mortality
Cosgrove et al[106] (2009)	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 SAB	236 patients: 120 on daptomycin, 116 on standard treatment	Patients who received initial low-dose gentamicin more commonly had decreased creatinine clearance (22% *vs* 8%; p=0·005)	Initial low-dose gentamicin as part of therapy for SAB and native-valve infective endocarditis is nephrotoxic and should not be used routinely
Hughes et al[107] (2009)	Retrospective non-randomised comparison of patients receiving continuous infusion or intermittent infusion oxacillin treatment for MSSA endocarditis	107 patients: 78 on continuous and 29 on intermittent oxacillin 63 received additional gentamicin, 44 did not	Patients receiving gentamicin defervesced more quickly (2 *vs* 4 days) No difference observed in cure or mortality Acute kidney injury similar between patients who received synergistic gentamicin (18% *vs* 7%; p=0·1)	Continuous oxacillin is an effective alternative to intermittent oxacillin for the treatment of MSSA endocarditis No benefit associated with synergistic gentamicin use and a trend towards higher rates of mortality and acute kidney injury
Levine et al[108] (1991)	RCT of vancomycin with or without rifampicin for 28 days in MRSA endocarditis	42 patients with MRSA endocarditis: 34 with right-sided endocarditis, 8 with left-sided endocarditis 22 treated with vancomycin alone, 20 treated with vancomycin plus rifampicin	Vancomycin group: 4 failures and 2 deaths Median duration of bacteraemia 7 days Vancomycin plus rifampicin group: 2 failures and 1 death Median duration of fever 9 days No significant differences in any outcome between groups	The addition of rifampicin to vancomycin does not seem to be beneficial
Reidel et al[109] (2008)	Retrospective cohort study of SAE cases treated with and without addition of rifampicin	84 cases, 42 treated with rifampicin-containing regimens	Patients who received rifampicin more commonly had left-sided endocarditis and more commonly received gentamicin, but otherwise were similar Rifampicin was associated with longer duration of bacteraemia, lower survival rates, more frequent drug interactions, and hepatotoxicity	Clinicians should undertake a careful risk–benefit assessment before adding rifampicin to standard antibiotic treatment of native-valve SAE

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 6: **Comparative studies on combination antibiotic treatment in SAE**

nephrotoxicity (OR 2·63 [95% CI 1·14–6·25]).[112] 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.[106,113] Gentamicin is thus no longer routinely recommended for the treatment of *S aureus* native-valve endocarditis.[5]

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),[114] 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.[115] 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.[116,117] There are few other supportive data and possible efficacy must be balanced against the risks of hepatotoxicity.[118]

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.

Linezolid

No comparative trials of linezolid specifically for the treatment of SAB have been done, but several studies have investigated the used of linezolid for a range of Gram-positive infections, including subsets of patients with SAB. These studies have been included in two meta-analyses.[124,125] The first analysed data from 99 patients with SAB enrolled in five comparative trials of linezolid with vancomycin for severe staphylococcal infections, and found no evidence of differences in outcome with linezolid or vancomycin (OR for cure 1·16 [95% CI 0·5–2·65]).[124] The second included 12 controlled trials involving 6093 patients (255 had SAB), and found that linezolid was associated with greater chance of treatment success than a β-lactam or glycopeptide for the treatment of SAB (OR 2·07 [95% CI 1·13–3·78]), but was not associated with improved survival.[135] Linezolid was associated with a significant risk of drug-related thrombocytopenia (OR 11·72 [95% CI 3·33–37·57]), but not with any excess of adverse events overall.[125] Whether linezolid is effective in the treatment of SAE remains uncertain, although a review of published cases suggested acceptable cure, particularly when the bacteria have reduced glycopeptide susceptibility.[136]

Two recent trials provide additional supportive evidence of the use of linezolid for the treatment of SAB. The first randomly assigned 726 patients with catheter-related bloodstream infection to receive either linezolid or vancomycin.[137] 94 patients had SAB and, within this subset, linezolid showed similar responses (hazard ratio for death 0·70 [95% CI 0·34–1·44]), but the study could not exclude the possibility of large differences with such small numbers. The second study compared linezolid with or without a carbapenem, with vancomycin plus an aminoglycoside or rifampicin for the treatment of 35 patients with persistent MRSA bacteraemia despite at least 5 days of appropriate antibiotic therapy.[138] Linezolid was associated with a lower proportion of positive blood cultures after 72 h of therapy (75% *vs* 17%; p=0·006) and lower attributable mortality (13% *vs* 53%; p=0·03), but the study was small, not randomised, and seven of 16 patients treated with linezolid were switched to vancomycin because of thrombocytopenia.[138]

Daptomycin

Daptomycin is a novel cyclic lipopeptide antibiotic whose bactericidal activity and once-daily parenteral administration make it an attractive new therapeutic option.[139] The drug should not be used to treat pulmonary *S aureus* disease because its activity is inhibited by surfactant.[128] Data on the role of daptomycin in the treatment of SAB come from case reports, treatment registries, and one RCT.[140]

In 2006, Fowler and colleagues[113] reported the results from 246 adults with SAB, 39% (n=53) of whom had definite or possible endocarditis, randomly assigned to daptomycin (6 mg/kg every 24 h; n=124) or standard therapy (n=122) with either vancomycin or an anti-staphylococcal penicillin with gentamicin for the first 4 days of therapy. Those with left-sided endocarditis in the daptomycin group also received 4 days of gentamicin. There was no significant difference in treatment success between the two treatment groups (44·2% *vs* 41·7%, absolute difference 2·4%). However, the 95% CI (–10·2% to 15·1%) was wide, and does not exclude the possibility of a small (<15%) but nevertheless clinically important difference. Adverse events were more common in the standard therapy group, predominantly

	Class	Mode of action	Antimicrobial spectrum	Pharmacology	Relevant clinical evidence
Linezolid	Oxazolidinone	Targets 50S ribosomal subunit	Bacteriostatic Active against MRSA and VRSA[119,120] Like clindamycin, inhibits the production of bacterial extracellular toxins[121]	100% oral bioavailability Excellent tissue penetration Use limited by long-term neurological and bone-marrow toxicity	Some evidence of superiority over vancomycin in treatment of MRSA pneumonia and skin and soft-tissue infection[122,123] Non-inferior to vancomycin for treatment of SAB in meta-analyses[124,125]
Daptomycin	Cyclic lipopeptide	Acts at the cytoplasmic membrane	Bactericidal Heteroresistance observed in vancomycin-heteroresistant strains[126,127] Development of resistance on treatment reported	Only available parenterally, but suitable for once-daily dosing	Non-inferior to vancomycin in MRSA bacteraemia and right-sided endocarditis[113] Not active in lung tissue[128]
Tigecycline	Glycylcycline	Modified tetracycline with activity against tetracycline-resistant strains	Bacteriostatic Active against MRSA and VRSA	Only available parenterally. Commonly causes mild side-effects (nausea)	Equivalent to vancomycin for the management of cSSSI[129,130] Low serum concentrations achieved may make it a poor choice for bacteraemia
Ceftobiprole	Cephalosporin	Activity against MRSA	Bactericidal Good activity against Gram-negative bacteria	Only available parenterally Well tolerated	Non-inferior to vancomycin in cSSSI[131,132]
Dalbavancin and telavancin	Glycopeptides	Activity against cell wall Telavancin also has cell-membrane activity	Bactericidal Active against MRSA and VRSA	Only available parenterally Dalbavancin has a very long half-life permitting once weekly dosing	Dalbavancin equivalent to linezolid in cSSSI[133] Phase 2 data for efficacy in SAB[134]

SAB=*Staphylococcus aureus* bacteraemia. MRSA=meticillin-resistant *S aureus*. VRSA=vancomycin-resistant *S aureus*. cSSSI=complicated skin and skin structure infection.

Table 7: **New antibiotics with potential to treat SAB**

gentamicin-related changes in renal function.[106] 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 *S aureus* infections (30% with SAB or SAE) treated with daptomycin, reported that clinical successes for SAB and SAE were 88% and 81%, respectively.[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.[64] Daptomycin treatment failures associated with increased MIC have been reported, primarily in association with deep, irremovable foci of *S aureus* infection.[142–145] Heterogeneous intermediate susceptibility to daptomycin may be induced in some strains of *S aureus* by prior vancomycin exposure,[146,147] although the mechanism and clinical relevance remains uncertain.[64] Currently, there seems to be a clinical association between reduced daptomycin susceptibility and VISA, but not hetero-VISA.[148–150]

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.[151] Healthy volunteers have tolerated doses of up to 12 mg/kg every 24 h for 14 days,[152] and drug registry data have suggested that doses of at least 8 mg/kg every 24 h are well-tolerated and effective.[150] Clinical trials investigating the safety and effectiveness of higher doses for the treatment of SAB or SAE are required.

***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 β-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.

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 *S aureus* should always be defined as clinically significant, given the intrinsic pathogenicity of *S aureus*, the high number and frequency of complications following SAB, and the rarity of *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,[10,13,22] 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). β-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,[153] 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

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 "echocardiography 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.

to be sufficient for most cases of uncomplicated, catheter-associated SAB, provided that the catheter has been removed and the risk of endocarditis is low. 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,[4–6,8] 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.[4–6,8] 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.[91,100–102] This approach is relatively widespread but with uncertain effect on outcome.[154] 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.[155]

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.[156,157] *S aureus* with reduced susceptibility to glycopeptides may be less virulent and cause less bacteraemic disease.[60]

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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