Antimicrobials for right-sided endocarditis in intravenous drug users: a systematic review

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Background: Right-sided endocarditis (RSE) is a serious complication of intravenous drug use. We sought to systematically review the evidence for obtaining clinical cure with antimicrobials in intravenous drug users (IVDUs) with isolated native valve RSE.

Search strategy: We applied broad search strategies in the following databases: MEDLINE (1966–2006), EMBASE (1980–2006) and Cochrane CENTRAL Register (2006, Issue 3). Hand searching was performed on selected peer-reviewed journals and relevant citation lists were screened. No restrictions were set on language and type of publication.

Selection criteria: We included randomized controlled trials that evaluated clinical and microbiological cure using single or combination antibiotic regimens for the treatment of isolated native valve bacterial RSE. Clinical and microbiological cure and failure outcomes were evaluated between 2 weeks and 6 months after completion of therapy. Quality assessment of relevant studies was performed using an objective scoring scale.

Results: We identified seven randomized controlled trials, one comparing single antimicrobial therapies, four comparing combination with single therapy and two studies comparing combination therapies. Short-course therapy was present in at least one arm in three studies, but only one study compared short- and long-course therapy. No statistically significant benefit was demonstrated between any antimicrobial therapy and all studies were scored as having a moderate to severe risk of bias.

Conclusions: Randomized trial evidence does not support one antimicrobial regimen over another in the treatment of RSE in IVDUs.

Keywords: antibiotics, treatment, IVDUs

Introduction

Endocarditis is a serious complication of intravenous drug use, with an incidence ranging from 1% to 5% per year.\textsuperscript{1–10} Right-sided endocarditis (RSE) occurs commonly in this population,\textsuperscript{2,3,9,11–17} almost exclusively involves the tricuspid valve,\textsuperscript{2,3,14,15,18} and has a high frequency of recurrence.\textsuperscript{7,8,10} Staphylococcus aureus is the most common aetiological organism in intravenous drug users (IVDUs).\textsuperscript{2,3,9,12,13,15,18,19}

It is generally accepted that in uncomplicated RSE, that is without pericardial abscess formation or metastatic infection, a 4–6 week course of tailored antimicrobial therapy effective against the causative organism results in high cure rates.\textsuperscript{1,3,4,9,17,20–25} Given the low likelihood of adherence to a 4 week course of antimicrobials among IVDUs, shorter courses of therapy, that is treating with a combination of \(\beta\)-lactam and an aminoglycoside for 2 weeks with or without an aminoglycoside, have become an accepted standard.\textsuperscript{26–33}

It is important for clinicians to be familiar with the evidence upon which current practice is based. Given the variability of treatment regimens for endocarditis, we sought to review the clinical trial evidence in the treatment of RSE in IVDUs. This included assessing the evidence for short versus long duration antimicrobial treatment as well as differences between monotherapy and combination therapy.
Methods

Eligibility criteria

We included published and unpublished randomized controlled trials on adult inpatients with suspected native valve RSE who were IVDUs. RSE was defined as clinical evidence of infection with two or more blood cultures or positive echocardiographic findings demonstrating involvement of the right-sided structures of the heart. We excluded patients with extrapulmonary metastatic complications of endocarditis and patients with concurrent left-sided endocarditis.

Short-course therapies were defined as ≤2 weeks and long-course therapies as >2 weeks. No restrictions were set on route of administration or single versus combination therapy. A minimum follow-up of 2 weeks but not more than 6 months after the completion of antimicrobial therapy was required.

Outcomes

The primary outcome was complete cure, both clinical and microbiological, after completion of therapy until the end of the follow-up period. Clinical cure was defined as the disappearance of clinical signs or symptoms of infection including improvement on radiographic assessment. Microbiological cure was specified in the presence of negative blood cultures. Failure was defined for all patients not achieving clinical or microbiological cure, therefore requiring modification or discontinuation of the assigned therapy or resulting in death.

Data sources and search strategy

We searched the electronic databases: MEDLINE (1966 to August 2006), EMBASE (1980 to August 2006), Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library 2006, Issue 3) and multiple grey literature resources including Biosis Preview, clinical-trials.gov and controlled-trials.com (meta-RCTs). Hand searching of 11 major scientific general internal medicine, infectious disease and cardiology journals, and abstracts from the Interscience Conference on Antimicrobial Agents and Chemotherapy (1995–2006) was performed. The reference lists of all relevant studies, references citing relevant studies, major guidelines and review papers were also screened for the abstracts of conference proceedings and additional published or unpublished studies. We contacted experts in the field, and the first author of each included study to help locate unpublished and ongoing trials or complementary information on their own trials.

Study identification, data extraction and quality assessment

Three reviewers (BN, DY and DK) independently inspected the titles and abstracts of identified citations and excluded studies that were not relevant. The reviewers then independently assessed the eligibility of potentially relevant studies by applying inclusion and exclusion criteria. Data extraction was performed on included studies using a pre-piloted standardized form. Major data fields incorporated descriptive data on the patient population, interventions used (antibiotic type, dose, route and duration) and primary and secondary outcomes as previously defined. Authors were contacted to clarify details or provide additional information.

Included trials were assessed for quality according to the following characteristics: appropriate randomization, allocation concealment, blinding and adequate follow-up. We defined a high risk for bias when three or more of these criteria were not met, medium risk when one or two were not met and low risk when all criteria were met. Any discordance in study identification, extraction and quality assessment was resolved accordingly by reviewers using a consensus process.

Data analysis

Statistical analysis was performed on a modified intention to treat basis (ITT) restricting our efficacy analysis to those who completed a full course of treatment and follow-up. Non-compliance is intrinsic to this study population and assessing outcomes in a true intention to treat analysis would be an arduous task. Given the need for early empirical therapy for suspected RSE, we permitted for the exclusion of ineligible patients post-randomization. Relative risks (RRs) and corresponding 95% confidence intervals (CIs) were calculated and compared between antibiotic regimens to estimate the strength of the treatment effect. When the number of events was ‘0’ in any arm, a value of ‘0.5’ was assigned to permit for RR calculations.

We planned to calculate an $I^2$ value as a measure of heterogeneity for each outcome analysis. The $I^2$ index denotes a percentage of variation across trials that is due to heterogeneity rather than by chance alone. In the absence of clinical heterogeneity, a $\chi^2$ test at 10% level of significance was decided upon to determine whether a meta-analysis could be justified. We planned pooled estimates of treatment effect to be analysed using fixed and random effect models when similar interventions were applied to similar populations across studies. A sensitivity analysis was performed to examine the robustness of the pooled estimate as appropriate.

Results

Search results and study characteristics

Using our search strategy, we obtained 544 citations from MEDLINE, 710 citations from EMBASE and 181 citations from Cochrane CENTRAL databases, of which 10 studies were considered potentially eligible. Full manuscripts were obtained for all potentially eligible studies. After applying eligibility criteria, we excluded one non-randomized trial and two randomized prospective studies (see below). Ultimately, seven randomized controlled studies meeting our inclusion criteria were included for efficacy analysis (Figure 1), with a pooled total of 227 participants.

All seven studies were single-centre trials, three conducted in hospitals in Spain and four in tertiary care centres in the United States. Participants were adult IVDUs diagnosed with methicillin-susceptible S. aureus (MSSA) in at least two positive blood cultures, with clinical, radiographic and/or echocardiographic findings consistent with RSE as per the inclusion criteria. Antimicrobial regimens in competing treatment arms were predominately administered intravenously, and only occasionally orally or intramuscularly.

Outcome assessment procedures and follow-up periods were slightly different between trials but met our minimum requirements. All studies consistently applied clinical assessments and blood cultures at 2–4 weeks after completion of therapy, although the total follow-up period varied between 2 weeks and 6 months. Routine transthoracic echocardiography and chest radiography were performed at the completion of therapy in the Ribera 1996 study. Additional clinical assessments, standard laboratory investigations, blood cultures, chest radiography and
Studies comparing single antimicrobial therapies

A single study by Greenman et al.\textsuperscript{35} evaluated long-course monotherapy between two cephalosporins. The authors randomized 54 IVDUs, of which 32 had \textit{S. aureus} endocarditis. Sixteen patients were randomized to im cephalosporin ceftaroline (1 g every 12 h) and 16 to iv cefapirin (2 g every 4 h) for 4 weeks. There were three patients in each group with left-sided cardiac involvement. The specific outcomes for the isolated RSE subgroup were not reported and therefore a modified ITT efficacy analysis was not performed. The RR for failure of ceftaroline compared with cefapirin was 0.25 (0.031-1.99), and both therapies were considered similar in terms of cost-effectiveness.\textsuperscript{35}

Studies comparing combination versus single antimicrobial therapy

Four studies compared combination versus single therapy: (i) Ribera et al.\textsuperscript{31} compared short-course therapies, (ii) Fortun et al.\textsuperscript{29} and (iii) Abrams et al.\textsuperscript{20} compared short- with long-course therapy, and (iv) Markowitz et al.\textsuperscript{36} compared long-course therapies. All antimicrobials were administered intravenously.

In the Ribera 1996 study, cloxacillin (2 g every 4 h for 2 weeks) and gentamicin (1 mg/kg every 8 h for 1 week) were compared with cefapirin (2 g every 4 h for 2 weeks). There were 45 participants randomized to each arm. The outcome of clinical or microbiological cure was observed in 31 patients receiving short-course combination therapy (cloxacillin and gentamicin) and 34 patients receiving short-course cloxacillin alone. Therefore, the observed RR of failure for cloxacillin and gentamicin compared with cloxacillin alone was 1.27 (95% CI 0.65–2.49). After randomization, four patients in the combination therapy arm and three patients in the single therapy arm were found to have left-sided endocarditis. Using the modified ITT method, the RR for failure of cloxacillin and gentamicin was 1.31 (95% CI 0.38–4.53).

In the Fortun 1995 study, short-course combination therapy with cloxacillin (2 g every 4 h) and gentamicin (1.5 mg/kg every 8 h) for 2 weeks was compared with long-course single therapy with teicoplanin (10 mg/kg/12 h on days 1–3, 6 mg/kg/12 h on days 4–7 and 7 mg/kg/24 h on days 8–28). Seven of nine patients randomized to cloxacillin and gentamicin, and two of seven patients randomized to the teicoplanin arm were clinically and microbiologically cured. The RR of failure for cloxacillin and gentamicin compared with teicoplanin was 0.31 (95% CI 0.08–1.15).

The Abrams 1979 study randomized 37 IVDUs, of which 20 patients had RSE requiring therapy with a penicillinase-resistant penicillin (oxacillin) for 4 weeks. Ten patients were randomized to receive oxacillin monotherapy (12 g/day) and 10 patients to combination therapy with the addition of gentamicin (80 mg every 8 h) for the first 2 weeks. Combination therapy with gentamicin was just as effective as 4 weeks of oxacillin alone with no clinical or microbiological failures in either group (RR 1.0, 95% CI 0.02–45.64).

Markowitz et al.\textsuperscript{31} investigated 3 weeks of trimethoprim/sulfamethoxazole (320/1600 mg every 12 h) compared with 3 weeks of vancomycin (1 g every 12 h). Among their population of 228 IVDUs, 101 were diagnosed with \textit{S. aureus} infection and met eligibility criteria. Fifteen patients were ultimately diagnosed with tricuspid MSSA endocarditis, of which four of seven patients receiving trimethoprim/sulfamethoxazole compared with one of eight patients receiving vancomycin demonstrated clinical or microbiological failure (RR 4.57, 95% CI 0.66–31.89).

Studies comparing combination antimicrobial therapies

Two studies compared combination therapies: (i) Fortun et al.\textsuperscript{30} compared short-course iv therapies and (ii) Heldman et al.\textsuperscript{24} compared long-course oral and iv therapies.

In the Fortun 2001 study, 11 patients were randomized to combination therapy with cloxacillin (2 g every 4 h) and gentamicin (1.5 mg/kg every 8 h), 11 patients to combination therapy with vancomycin (500 mg every 6 h) and gentamicin (1.5 mg/kg every 8 h), and 12 patients to combination therapy with teicoplanin (24 mg/kg for 1 day, then 12 mg/kg every 24 h) and gentamicin (1.5 mg/kg every 8 h). All patients had culture proven MSSA and received a short-course of therapy for 2 weeks. All 11 patients randomized to cloxacillin and gentamicin, 6 patients randomized to vancomycin and gentamicin and 7 randomized to teicoplanin and gentamicin were cured. Therefore, the observed RR of failure for cloxacillin and gentamicin compared with vancomycin and gentamicin was 0.10 (95% CI 0.01–1.68), and compared with teicoplanin and gentamicin was 0.13 (95% CI 0.01–2.26). The RR of failure comparing cloxacillin and gentamicin with any glycopeptide and gentamicin was 0.12 (95% CI

Figure 1. Flow chart detailing study selection.
<table>
<thead>
<tr>
<th>Study</th>
<th>Population randomized&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Intervention (I)</th>
<th>Comparison (C)</th>
<th>Outcomes&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Follow-up</th>
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<td><strong>Studies comparing single therapies</strong></td>
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<td>Greenman et al.&lt;sup&gt;35&lt;/sup&gt;</td>
<td>IVDUs with clinical suspicion for endocarditis (n = 54)</td>
<td>im ceforanide 1 g every 12 h × 4 weeks</td>
<td>iv cefapirin 2 g every 4 h × 4 weeks</td>
<td>clinical and microbiological cure/failure, time to defervescence, adverse events and MIC testing</td>
<td>initial visit, daily during Rx, then 2–6 weeks (mean 3.5 weeks) after completed Rx</td>
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<td><strong>Studies comparing combination to single therapy</strong></td>
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<td>Ribera et al.&lt;sup&gt;31&lt;/sup&gt;</td>
<td>IVDUs with suspected RSE (n = 90)</td>
<td>iv cloxacillin 2 g every 4 h × 2 weeks and iv gentamicin 1.5 mg/kg every 8 h × 2 weeks</td>
<td>iv cloxacillin 2 g every 4 h × 2 weeks</td>
<td>clinical and microbiological cure/failure and adverse events</td>
<td>initial visit, during Rx, then 2 weeks, 1 month, 3 months and 6 months after completion of Rx</td>
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<tr>
<td>Fortun et al.&lt;sup&gt;29&lt;/sup&gt;</td>
<td>IVDUs with suspected RSE (n = 16)</td>
<td>iv cloxacillin 2 g every 4 h and iv gentamicin 1.5 mg/kg every 8 h × 2 weeks</td>
<td>iv teicoplanin 10 mg/kg/12 h on days 1–3, 6 mg/kg/12 h on days 4–7, 7 mg/kg/24 h on days 8–28</td>
<td>clinical and microbiological cure/failure, time to defervescence, MIC testing and adverse events</td>
<td>initial visit, during Rx, then 2–4 weeks after completion of Rx</td>
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<td>Abrams et al.&lt;sup&gt;20&lt;/sup&gt;</td>
<td>IVDUs with clinical suspicion for bacterial endocarditis (n = 37)</td>
<td>iv penicillinase-resistant penicillin 12 g/day × 4 weeks and iv gentamicin × 2 weeks</td>
<td>iv penicillinase-resistant penicillin 12 g/day × 4 weeks</td>
<td>clinical and microbiological cure/failure, time to defervescence, CHF, valve replacement and adverse events</td>
<td>unclear of timing of follow-up (i.e. after completion of therapy)</td>
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<td>Markowitz et al.&lt;sup&gt;36&lt;/sup&gt;</td>
<td>IVDUs hospitalized with suspected &lt;i&gt;S. aureus&lt;/i&gt; bacteraemia (n = 228)</td>
<td>iv trimethoprim/sulfamethoxazole 320/1600 mg every 12 h × 3 weeks</td>
<td>iv vancomycin 1 g every 12 h × 3 weeks</td>
<td>clinical and microbiological cure/failure, time to defervescence, leucocytosis, length of hospitalization and adverse events</td>
<td>initial visit, during Rx, and at 30 or more days after completion of Rx</td>
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<td><strong>Studies comparing combination therapies</strong></td>
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<tr>
<td>Fortun et al.&lt;sup&gt;30&lt;/sup&gt;</td>
<td>IVDUs with suspected RSE (n = 34)</td>
<td>iv cloxacillin 2 g every 4 h and iv gentamicin 1.5 mg/kg every 8 h × 2 weeks</td>
<td>iv vancomycin 500 mg every 6 h or teicoplanin 24 then 12 mg/kg daily and iv gentamicin 1.5 mg/kg every 8 h × 2 weeks</td>
<td>clinical and microbiological cure/failure, time to defervescence, MIC testing and adverse events</td>
<td>initial visit, during Rx, and for at least 12 weeks after completion of Rx</td>
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<tr>
<td>Heldman et al.&lt;sup&gt;24&lt;/sup&gt;</td>
<td>IVDUs with a fever (n = 573)</td>
<td>iv oxacillin 2 g every 4 h × 4 weeks and iv gentamicin 2 mg/kg every 8 h × 5 days</td>
<td>po ciprofloxacin 750 mg every 12 h and po rifampicin 300 mg every 12 h × 4 weeks</td>
<td>clinical and microbiological cure/failure and adverse events</td>
<td>initial visit, during Rx, and day 35 after completion of Rx</td>
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<sup>a</sup>Only patients with a diagnosis of RSE who completed treatment and follow-up were included in the efficacy analysis. All infections in the efficacy analysis were caused by methicillin-susceptible <i>S. aureus</i>.

<sup>b</sup>Clinical and microbiological failure includes the outcomes of mortality, persistent infection or complications, relapse and re-infection.
Two patients developed extrapulmonary infection within the first 48 h of therapy (one in the vancomycin and gentamicin arm, and one in the teicoplanin and gentamicin arm). A modified ITT analysis to exclude these patients did not markedly affect RR values.

The Heldman 1996 study had broad inclusion criteria and randomized all IVDUs with a fever (n = 573) to 4 weeks of either oxacillin (2 g iv every 4 h) and gentamicin (2 mg/kg iv every 8 h for the first 5 days), or oral ciprofloxacin (750 mg every 12 h) and rifampicin (300 mg every 12 h). Among the 95 patients with isolated RSE, 45 patients in the parenteral therapy group and 40 patients in the oral therapy group were eligible for analysis, and only 20 and 19, respectively, completed treatment and follow-up. Three documented treatment failures were observed in the parenteral therapy arm compared with one failure from non-compliance in the oral therapy arm. The calculated RR for failure was 2.85 (95% CI 0.32–25.07) for parenteral therapy compared with oral therapy.

After acceptable post-randomization exclusions, the number of patients lost to follow-up did not constitute more than 20% of the population available for efficacy analysis in six of seven studies. Poor follow-up was achieved in the Heldman study, where 85 patients with isolated RSE could potentially be included in the efficacy analysis, of which 41 were lost to follow-up, distributed equally between study arms.

Excluded studies

We excluded one non-randomized trial, and two randomized prospective studies that did not meet eligibility criteria. The excluded non-randomized trial performed by Espinosa et al. showed that short-course cloxacillin and gentamicin therapy compared with long-course historic controls had similar cure rates.

In one randomized trial by Korzeniowski in 1982, data on IVDUs were only available upon subgroup analysis. Both addicts and non-addicts with suspected endocarditis were randomized to either 6 weeks of nafcillin alone or 6 weeks of nafcillin in combination with gentamicin for the first 2 weeks. Of the 150 patients randomized, 42 addicts were included in the analysis, and only 21 and 19, respectively, completed treatment and follow-up. Three documented treatment failures were observed in the parenteral therapy arm compared with one failure from non-compliance in the oral therapy arm. The calculated RR for failure was 2.85 (95% CI 0.32–25.07) for parenteral therapy compared with oral therapy.

Quality of included studies

All studies were at moderate to high risk for bias based on our quality criteria (Table 3). The randomization process was not clearly reported in the Fortun 1995, Fortun 2001 and Abrams 1979 studies. Allocation concealment procedures were reported only in the Ribera 1996 and Heldman 1996 studies, which used sealed envelope protocols. The Abrams 1979, Heldman 1996 and Markowitz 1992 studies randomized patients based on a low threshold of clinical suspicion for endocarditis resulting in a large number of censored patients in the modified ITT analysis, potentially compromising the integrity of randomization. Only the Markowitz study blinded interventions to the participants or observers assessing outcomes, and reported sources of funding.
patients were cured in the daptomycin and standard therapy groups, respectively. There was no statistical significance between these treatment modalities.

**Pooling treatment effects**

Although short-course combination therapy with penicillinase-stable penicillin and gentamicin was found to be a common treatment arm in five of the seven included trials, the treatment effect for penicillinase-stable penicillin and gentamicin was not pooled and compared with all other therapies because of clinical heterogeneity.

**Discussion**

Current standard therapy for RSE due to MSSA is a 2 week course of a penicillinase-stable penicillin (oxacillin), with or without gentamicin.\(^{21,38}\) We sought to directly compare various combination agent therapies, combination with single agent therapy and single agent therapies.

We found two trials comparing different combination therapies, namely cell-wall-active agents, aminoglycosides and fluorquinolones. In the Fortun 2001 study, combination cloxacillin and gentamicin showed a trend towards benefit over combination teicoplanin therapy, and a significant benefit over combination vancomycin therapy.\(^{29,30}\) This is consistent with previous findings that vancomycin is less rapidly bactericidal in time–kill studies in vitro and in rat models,\(^{39}\) and non-comparative observational data showing moderate to high rates of failure with vancomycin therapy.\(^{40–43}\) The second study by Heldman et al.\(^ {24}\) evaluated the effect of combined ciprofloxacin and rifampicin therapy and concluded that it is not significantly different from cloxacillin and gentamicin. These results are consistent with a prospective study by Dworkin et al.\(^ {22}\) evaluating ciprofloxacin and rifampicin that showed complete cure in all 10 IVDUs treated for uncomplicated right-sided S. aureus endocarditis. However, the interpretation of the results from Heldman et al. is limited by the large subset of post-randomization patients excluded and lost to follow-up. Therefore, despite its theoretical benefit in high bactericidal activity, rapid penetration into vegetations and oral route of administration, routine fluoroquinolone use cannot be recommended based on the available evidence.

Four studies compared combination with single agent therapy. One study comparing cloxacillin and gentamicin with teicoplanin showed a non-significant effect.\(^ {29}\) This trial was insufficiently powered, and since different antibiotic classes were compared, it is difficult to delineate the magnitude of treatment effect attributed to synergism as opposed to antibiotic type. The Abrams 1979 and Ribera 1996 studies, comparing penicillinase-resistant penicillin and gentamicin with penicillinase-resistant penicillin alone showed no statistical difference, although the latter showed a non-significant trend towards benefit in the monotherapy arm. The outcome achieved with trimethoprim/sulfamethoxazole combination therapy was not significant compared with vancomycin monotherapy trending towards inferiority.

The addition of an aminoglycoside to a β-lactam for synergism in the treatment of bacterial endocarditis is mainly supported by in vitro, animal and non-comparative studies. It has not been verified subsequently by prospective trials, as reflected by our included studies.\(^ {29,31}\) It is important to note that staphylococcal resistance to aminoglycosides may reduce any benefit gained by using combination therapy.\(^ {26,44–50}\) The Abrams study included in this review found that adding gentamicin to a penicillinase-resistant penicillin did not lead to clinically important differences in clinical cure and mortality, although another study that was excluded from our analysis did show a faster time to defervescence and eradication of bacteremia.\(^ {20,51}\)

Additionally, a recent meta-analysis supports the lack of benefit.
in adding an aminoglycoside to β-lactams in the treatment of endocarditis due to Gram-positive cocci. Although such results may not be generalizable to IVDUs, these data suggest that the addition of an aminoglycoside for synergism may not be useful and should be used with caution to reduce nephrotoxicity.

We also sought to compare short duration with long duration antimicrobial therapy. Early prospective non-comparative studies did show potential for short duration therapy, but such studies were subject to bias and were not compared with a corresponding long-course regimen. Three of the seven clinical trials in this review evaluated short-course therapies in at least one study group, but only the Fortun 1995 study compared short-course with long-course therapy, showing no statistical difference. Differences in antimicrobial class and number of antibiotics in each study group preclude meaningful interpretation of these trials with respect to duration of therapy. Although the theoretical concern with short-course therapy has been relapse, this outcome could not be assessed because of low event rates.

Based on our results, we conclude that there is a need for a rigorous randomized control trial of antibiotic therapy for RSE in IVDUs. A comparison of a 2 week course of cloxacillin alone versus 2 weeks of cloxacillin and gentamicin would be of interest. Clinical and microbiological cure are important primary outcomes and it would be best to conduct the study in areas with a low incidence of community methicillin-resistant \( S. aureus \). Secondary outcomes should include time to defervescence, congestive heart failure, valve replacement and adverse events. Although randomization of participants who eventually fail to meet eligibility criteria should be anticipated, efforts to minimize this, such as early echocardiography, would be warranted in the protocol. Assuming a cure rate of 90% for RSE with standard therapy and a cure rate of 85% with cloxacillin alone, assuming a difference of 5% or less is equivalence, for an \( \alpha \) of 0.05 and 80% power, 537 participants would be needed in each study arm. Any study of IVDUs poses unique challenges including persistent drug use behaviour and addiction, non-compliance to medication and follow-up, and early self-discharge from hospital. Such behaviour leads to high rates of relapse and re-infection.

Differentiating between secondary outcomes such as relapse and re-infection is challenging. Among included studies in this review, relapse was defined as any positive culture after cessation of therapy. To differentiate re-infection from relapse, most studies have used a combination of clinical clues and microbiological techniques. For example, a history of intravenous drug use and recurrence of symptoms following a pre-specified disease-free interval after completing a course of therapy has been considered evidence of re-infection. Previous studies have defined relapse as documented eradication and subsequent recurrence of bacteremia using phage typing to compare strains. Any new trial being planned should include molecular typing methods such as PFGE to help differentiate relapse from re-infection.

Other directions in the study and management of IVDUs with RSE include the use of outpatient-based therapy, aggressive community-targeted services and perhaps concurrent use of rehabilitation programmes. Alternative antimicrobial therapies with the aim of lowering resistance, shortening duration of therapy and minimizing adverse events are needed. Given the absence of definitive randomized controlled trial evidence, short-course cloxacillin alone for RSE due to MSSA is reasonable. The addition of an aminoglycoside is not supported by the current literature. The AHA/ACC 2005 Guidelines are consistent with these suggestions, but perhaps the strength of their recommendations should be amended to class 1B given the quality of the available evidence. The results of our systematic review indicate a need for definitive randomized controlled trial evidence to guide therapy for RSE in IVDUs.

### References


Systematic review


