

Aminoglycosides in Combination Therapy with β -Lactam Antibiotics for *Staphylococcus aureus* Endocarditis: A Systematic Review

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ABSTRACT

Background: There is no consensus as to whether aminoglycosides have a role in combination with β -lactams for the treatment of *Staphylococcus aureus* endocarditis.

Objective: To review the literature pertaining to the use of aminoglycosides in combination with β -lactams for *S. aureus* endocarditis.

Methods: A literature search was conducted in PubMed, EMBASE, and the Cochrane Database of Systematic Reviews (with various time frames, depending on the database). The search terms were “aminoglycoside”, “gentamicin”, “tobramycin”, “amikacin”, “netilmicin”, “streptomycin”, “staphylococcal”, and “endocarditis”; restrictions were set to identify only English-language articles describing research involving human subjects. The reference lists of all relevant articles identified in these searches were reviewed manually. All published reports of an aminoglycoside being given in combination with a β -lactam for the treatment of *S. aureus* endocarditis were reviewed to assess whether the results favoured combination therapy. A survey of the use of therapeutic drug monitoring for aminoglycosides was also conducted.

Results: Twelve relevant articles were identified. Seven of the articles were categorized as presenting the highest quality of evidence (levels I and II), and only 1 of these favoured combination therapy, the outcome being time to clinical improvement in the subpopulation of intravenous drug users. The 5 articles with lower-quality (level III) evidence favoured the combination regimens but did not make comparisons with β -lactam monotherapy. Only 2 articles described therapeutic drug monitoring techniques with respect to aminoglycoside therapy.

Conclusion: Current evidence does not support the use of aminoglycosides for the treatment of *S. aureus* endocarditis.

Key words: aminoglycoside, β -lactam, staphylococcal, endocarditis

RÉSUMÉ

Historique : Il n'existe aucun consensus sur le rôle possible des aminosides administrés en association avec des β -lactamines dans le traitement de l'endocardite à *Staphylococcus aureus*.

Objectif : Passer en revue la littérature actuelle sur l'emploi des aminosides en association avec des β -lactamines dans le traitement de l'endocardite à *S. aureus*.

Méthodes : Une recherche bibliographique a été effectuée dans les bases de données PubMed, EMBASE et *Cochrane Database of Systematic Reviews* (sur diverses périodes, selon la base de données). Les termes utilisés pour la recherche étaient : « aminoside », « gentamicine », « tobramycine », « amikacine », « nétilmicine », « streptomycine », « staphylocoque » et « endocardite »; la recherche était limitée à des articles en anglais décrivant des études avec des humains. Un examen des bibliographies de tous les articles pertinents ainsi recensés a aussi été réalisé. Tous les rapports publiés faisant état de l'emploi d'un aminoside en association avec une β -lactamine dans le traitement de l'endocardite à *S. aureus* ont été examinés pour évaluer dans quelle mesure les résultats privilégiaient le traitement d'association. On a également examiné si on avait eu recours à la surveillance pharmacocinétique des aminosides.

Résultats : Douze articles pertinents ont été recensés. Sept de ces articles ont été classés comme présentant des données probantes de la plus haute qualité (niveaux I et II), et un seul d'entre eux privilégiait le traitement d'association, le paramètre d'évaluation étant le délai d'obtention d'une amélioration clinique dans la sous-population des usagers de drogue par voie intraveineuse. Les cinq articles présentant des données probantes de plus faible qualité (niveau III) privilégiaient le traitement d'association, mais ne faisaient aucune comparaison avec le traitement par une β -lactamine en monothérapie. Seulement deux articles ont décrit des méthodes de surveillance pharmacocinétique des aminosides.

Conclusion : Les données actuelles ne corroborent pas l'emploi des aminosides dans le traitement de l'endocardite à *S. aureus*.

Mots clés : aminoside, β -lactamine, staphylocoque, endocardite

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INTRODUCTION

Staphylococcus aureus is one of the leading causes of infective endocarditis.¹ Although health care contact has been increasingly implicated in *S. aureus* endocarditis, the conventional association has been with injection drug use and, as such, much of the existing literature on treatment modalities has selectively evaluated the intravenous drug user (IVDU) population.¹ Mortality rates among patients with *S. aureus* endocarditis are very high, ranging from 25% to 47% overall.² The mortality rate seems to be much lower in the IVDU population, with some studies suggesting a rate of less than 5%.^{3,4} Noteworthy distinctions in this population are the relatively young age of most patients (between 20 and 40 years old), the lower number of comorbidities, and the target for infection (typically the tricuspid valve). This propensity to affect the less hemodynamically important side of the heart may account for the less aggressive nature of the infection.^{5,6} Nonetheless, effective treatment strategies are desired to reduce both morbidity and mortality, as well as to limit the time and resources required to resolve the infection. Short-course treatment regimens are of particular interest for the IVDU population, among whom compliance with conventional long-course regimens presents an obstacle to effective treatment.

β -Lactam antimicrobials have long been a mainstay in the treatment of gram-positive infections such as methicillin-susceptible *S. aureus* endocarditis. Aminoglycoside antibiotics have been promoted as being useful to hasten and/or improve response to therapy when given in combination with β -lactams for the treatment of *S. aureus* endocarditis.⁷ The first suggestion of a benefit came from in vitro studies,^{8,9} which showed a synergistic relationship between penicillins and aminoglycosides, and from in vivo animal models of experimental infection.¹⁰⁻¹² Subsequently, numerous studies of various

designs and quality have examined the issue in human subjects. Three narrative reviews,^{6,13,14} as well as a recent meta-analysis,¹⁵ have come to equivocal conclusions regarding the benefit of adding aminoglycosides to β -lactam treatment. Interestingly, there continues to be disagreement over the value of combination therapy, as demonstrated by treatment guidelines for *S. aureus* endocarditis published by 3 major medical associations^{5,16,17} (see Table 1).

The role of aminoglycosides in combination therapy for the treatment of *S. aureus* endocarditis is unclear and controversial. The primary objective of this systematic review was to amalgamate all of the evidence from human subjects that has been reported in the English language, to answer the question of whether aminoglycosides indeed have a role in such combination therapy. Given that aminoglycoside use is commonly a focus of therapeutic drug monitoring, whereby measured drug concentrations are used to individualize doses, a secondary objective was to assess if and how therapeutic drug monitoring of aminoglycoside therapy was incorporated into the published trials.

METHODS

A literature search was conducted within PubMed (1949 to the present), EMBASE (1980 to the present), and the Cochrane Database of Systematic Reviews, using the following search terms: “aminoglycoside”, “gentamicin”, “tobramycin”, “amikacin”, “netilmicin”, “streptomycin”, “staphylococcal”, and “endocarditis”. The objective of the search was to identify studies that specifically assessed aminoglycosides in combination with β -lactams for the treatment of *S. aureus* endocarditis. The search was limited to articles written in English, involving only human subjects. The reference lists of relevant articles identified by these searches were reviewed manually. Only articles that assessed therapy in patients with methicillin-sensitive *S. aureus* were

Table 1. Recent Treatment Guidelines for Native-Valve, Methicillin-Sensitive *Staphylococcus aureus* Endocarditis

British Society for Antimicrobial Chemotherapy ¹⁶	European Society of Cardiology ¹⁷	American Heart Association ⁵
Flucloxacillin 2 g IV q4–6h for at least 4 weeks	Oxacillin 8–12 g/day IV (q6–8h) for at least 4 weeks*	Nafcillin or oxacillin 12 g/day IV (q4–6h) for 6 weeks†
	PLUS	WITH OR WITHOUT
	Gentamicin 3 mg/kg daily IV (q8–12h) for 3–5 days (maximum 240 mg/day)	Gentamicin 3 mg/kg daily IV or IM (q8–12h) for 3–5 days

*Two weeks for IV drug users.

†Two weeks for patients with uncomplicated right-side infective endocarditis.



included, and susceptibility to methicillin can be assumed for all references to *S. aureus* in this review.

Articles were categorized by quality of evidence, using the rating scale of the US Preventive Services Task Force.¹⁸ Articles that were not directly relevant to the objective of the review but that provided supplemental information regarding the topic of the review have been included as “other evidence”. The following data elements were extracted from each of the included articles: study design, population, drug regimens used, outcome measures, use of therapeutic drug monitoring for aminoglycosides, and number of subjects. Summaries of these aspects of the articles^{7,15,19-28} are presented in Tables 2 and 3.

RESULTS

Level I Evidence

Level I evidence is defined as evidence from at least one properly conducted randomized controlled trial (RCT).

Meta-analysis

The single recently published meta-analysis examining the role of aminoglycosides in combination with β -lactams for the treatment of bacterial endocarditis caused by gram-positive cocci represents the highest level of evidence on this topic.¹⁵ Four RCTs and one prospective comparative trial were included in the meta-analysis; 4 of these studies investigated endocarditis caused by *S. aureus* infection^{7,19,21} and were thus also included in our own systematic review. The fifth trial examined endocarditis due to viridans streptococci²⁹ and was therefore not included in our systematic review. Trials included in the meta-analysis were RCTs or prospective comparative trials comparing combination therapy with a β -lactam and an aminoglycoside for the treatment of bacterial endocarditis caused by gram-positive cocci, using effectiveness and/or death as outcome measures. Case reports, reviews, guidelines, and epidemiologic, retrospective, experimental, laboratory, and noncomparative studies were excluded.

The primary outcome for this meta-analysis¹⁵ was the effectiveness of the regimen, defined by resolution of clinical, laboratory, and imaging findings suggestive of active endocarditis, after completion of therapy and during the defined follow-up period. Secondary outcome measures included treatment success without surgery, death, nephrotoxicity, and occurrence of relapse. The method for selecting the trials was described well and is reproducible. The authors

employed the Jadad scoring system³⁰ to weight the results of each of the RCTs included in the meta-analysis, according to study quality. The mean quality score was 2.5 (out of a maximum 5 points), with 2 of the trials scoring 2 points and the other 2 trials scoring 3 points. The 4 trials that investigated *S. aureus* endocarditis were included in our systematic review and are described in greater detail later in this article.

With the exception of nephrotoxicity, which occurred less often in the monotherapy arm (odds ratio [OR] 0.38, 95% confidence interval [CI] 0.16–0.88, $p = 0.024$), no significant differences were found between the monotherapy and combination therapy arms in terms of treatment success (the primary outcome) or any of the secondary outcomes. A separate analysis of only the trials that examined patients with *S. aureus* infection also found no significant differences in treatment success (OR 1.27, 95% CI 0.47–3.43) or mortality (OR 0.69, 95% CI 0.26–1.86) between the treatment arms.

Summary: While this meta-analysis represents the highest level of evidence available for addressing this issue, it is limited by the relatively small number of included trials and the small total number of subjects. The meta-analysis provided no evidence that aminoglycosides increase regimen effectiveness when added to β -lactam therapy, but there was evidence of an increased risk of nephrotoxicity.

Randomized Controlled Trials

Three RCTs assessing combination therapy with aminoglycosides for the treatment of staphylococcal endocarditis have been conducted since 1979, all of which examined gentamicin in combination with antistaphylococcal β -lactams.^{7,19,20} Two of these studies included only IVDUs,^{19,20} one of which examined only cases of right-sided endocarditis.²⁰

The earliest study included 24 IVDUs with *S. aureus* endocarditis and assessed 25 episodes of the disease.¹⁹ Twenty (80%) of these episodes represented right-sided involvement alone. A penicillinase-resistant β -lactam given alone at a dosage of 12 g/day for 4 weeks was compared with the same dosage given in combination with gentamicin 80 mg every 8 h for the first 2 weeks. All drugs were given intravenously. The β -lactams were oxacillin, penicillin G, and cephalothin. The outcome measures were time to defervescence, bacteriologic failure or relapse, congestive heart failure, valve replacement, and death. Follow-up beyond the treatment period was not reported. No difference was found in any of the outcome measures other than time



Table 2. Summary of Articles Included in Systematic Review of Combination Therapy with β -Lactam Antibiotics for *Staphylococcus aureus* Endocarditis

Study Description	Population	Drug Regimens	Duration of Post-Treatment Follow-Up	Aminoglycoside Therapeutic Drug Monitoring	<i>n</i>
Level I evidence					
Meta-analysis ¹⁵	RCTs or prospective comparative studies evaluating aminoglycosides in combination with β -lactams for treatment of gram-positive cocci endocarditis	NA	NA	NA	5 trials: 4 RCTs ^{7,19,20,29} and 1 comparative study ²¹ 394 ITT patients* 261 clinically evaluable patients*
RCT ¹⁹	IVDUs with <i>S. aureus</i> endocarditis	Oxacillin OR oxacillin + penicillin OR oxacillin + cephalothin OR cephalothin 12 g/day x 4 weeks WITH OR WITHOUT Gentamicin 80 mg q8h x 2 weeks (route not specified for any of the drugs, but presumed to be IV)	Not reported	No	24 (25 episodes)
RCT ⁷	IVDUs and non-IVDUs with <i>S. aureus</i> endocarditis	Nafcillin 1.5–2 g IV q4h x 6 weeks WITH OR WITHOUT Gentamicin 1 mg/kg IV or IM q8h x 2 weeks	1 month	Not	78
RCT ²⁰	IVDUs with isolated tricuspid valve methicillin-sensitive <i>S. aureus</i> endocarditis	Cloxacillin 2 g IV q4h x 14 days WITH OR WITHOUT Gentamicin 1 mg/kg IV q8h x 7 days	6 months	No	90
Level II-2 evidence					
Prospective comparative trial ²¹	Cases of endocarditis or bacteremia due to <i>S. aureus</i> † in IVDUs and non-IVDUs	Oxacillin, nafcillin, cephalosporin (singly or sequentially) 12 g/day x 4–6 weeks WITH OR WITHOUT Gentamicin 4.5 mg/kg daily x 7 days or more (begun up to 48 h after primary agent)	Not reported	No	50 (subgroup)
Level II-3 evidence					
Retrospective comparative trial ²²	IVDUs and non-IVDUs with <i>S. aureus</i> endocarditis	Penicillin, methicillin, or nafcillin x 6 weeks AND gentamicin 3–5 mg/kg daily x 2–3 weeks OR penicillin, methicillin, nafcillin, cephalothin, vancomycin x 6 weeks	None	No	40
Retrospective comparative trial ²³	IVDUs and non-IVDUs with <i>S. aureus</i> endocarditis	β -Lactam WITH OR WITHOUT Aminoglycoside	Last treatment effect described 31 days after treatment stopped	No	76 (subgroup)

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Table 2. continued

Study Description	Population	Drug Regimens	Duration of Post-Treatment Follow-Up	Aminoglycoside Therapeutic Drug Monitoring	n
Level III evidence					
Prospective noncomparative trial ²⁴	IVDUs with right-sided <i>S. aureus</i> endocarditis	Nafcillin 1.5 g IV q4h OR vancomycin 30 mg/kg IV daily q8–12h AND tobramycin 1 mg/kg IV q8h x 2 weeks	Up to 2 months	Yes	51 (53 episodes)
Prospective noncomparative trial ²⁵	IVDUs with right-sided <i>S. aureus</i> endocarditis	Cloxacillin 2 g IV q4h AND amikacin 7.5 mg/kg IV q12h x 2 weeks	6 months	Yes	72
Case study ²⁶	<i>S. aureus</i> endocarditis unresponsive to methicillin treatment	Methicillin 2 g IV q4h x 8 days, increased to 3 g IV q4h x 4 days, changed to 18 g/day continuous infusion AND gentamicin 80 mg IV q8h (discontinued after 4 weeks)	Patient followed until death occurred on second course of combination therapy	Not	1
Other evidence					
Randomized open trial ²⁷	IVDUs with right-sided <i>S. aureus</i> endocarditis	Cloxacillin 2 g IV q4h AND gentamicin 1.5 mg/kg IV q8h for 2 weeks OR Teicoplanin 10 mg/kg IV q12h (days 1–3), 6 mg/kg IV q12h (days 4–7), 7 mg/kg IV q24h (days 8–28)	2–4 weeks	Not	14
Randomized open trial ²⁸	IVDUs with right-sided <i>S. aureus</i> endocarditis	Cloxacillin 2 g IV q4h AND gentamicin 1.5 mg/kg IV q8h x 14 days OR Glycopeptide (vancomycin 500 mg IV q6h OR teicoplanin 12 mg/kg q24h with loading dose of 24 mg/kg) AND gentamicin 1.5 mg/kg IV q8h x 14 days	12 weeks	Not	31

RCT = randomized controlled trial, NA = not applicable, ITT = intention to treat, IVDU = intravenous drug user.

**Streptococcus viridans* and *Streptococcus bovis* were the causative organisms in 67 and 51 of the ITT and clinically evaluable patients, respectively.

†Report included an indication that blood samples were drawn for determination of drug concentrations, but no mention of pharmacokinetic analysis and/or therapeutic drug monitoring.

‡Only the results for endocarditis are summarized here.

to defervescence, which was 0.3 days longer for the combination-therapy arm (6.6 vs 6.3 days). No episodes of renal dysfunction were observed, and no statistical analysis was reported.

The second study included 48 IVDUs and 30 non-IVDUs, all of whom had right- and/or left-sided *S. aureus* endocarditis.⁷ Thirty (63%) of the IVDUs but only 3 (10%) of the non-IVDUs had exclusively right-sided endocarditis. Patients were randomly assigned to receive nafcillin monotherapy 1.5–2 g IV every 4 h for 6 weeks or the same dosage given in combination with gentamicin 1 mg/kg IV or IM every 8 h for the first 2 weeks. Penicillin G 20 IV MU/day was substituted for nafcillin if the organism was shown to be susceptible

(minimum inhibitory concentration less than 0.1 mg/mL). The authors stated 3 outcomes of interest: improved clinical and bacteriologic response (as demonstrated by duration of bacteremia and fever), decreased morbidity and mortality, and adverse effects associated with combination therapy. Patients were followed for 1 month after discharge from hospital. No significant difference was observed between the experimental and control arms in terms of duration of bacteremia or time to defervescence when the entire study sample was analyzed as a group. However, the mean duration of bacteremia (\pm standard deviation) was shorter in the subgroup of IVDUs with right-sided disease who were receiving combination therapy



Table 3. Summary of Outcome Measures and Conclusions

Study Description	Outcome Measures (as Stated a priori)	Outcome Measures Reported	Combination Favoured
Level I evidence			
Meta-analysis ¹⁵	Primary: regimen effectiveness as measured by clinical, laboratory, and imaging findings after completion of therapy and during follow-up Secondary: treatment success without the need for surgical repair of affected valve(s), death, nephrotoxicity, occurrence of relapse	As stated a priori	No
RCT ¹⁹	None stated	Time to defervescence, bacteriologic failure or relapse, congestive heart failure, valve replacement, death	No
RCT ⁷	Duration of bacteremia and fever, morbidity, death, "risks" associated with combination therapy (time to abacteremia, defervescence, and normalized leukocyte count shortened in IVDU subpopulation)	Duration of leukocytosis, outcome (defined by microbiologic or clinical assessment, telephone contact via friends, loss of contact, relapse, aortic valve replacement), complications (including congestive heart failure, brain abscess, joint destruction, subarachnoid bleeding, myocardial infarction, osteomyelitis, reinfection, surgery required), cause of death, toxicity (including renal dysfunction, neutropenia, eosinophilia, and rash)	Yes/No
RCT ²⁰	Primary: death, continued clinical or microbiologic evidence of active infection after 2 weeks of therapy, relapse of staphylococcal infection Secondary: duration of fever, complications during treatment (e.g., renal failure)	As stated a priori	No
Level II-2 evidence			
Prospective comparative trial ²¹	NA	Time to defervescence, complications, No death (outcome measures reported for relevant subgroup)	No
Level II-3 evidence			
Retrospective comparative trial ²²	None stated	Time to defervescence, death, renal toxicity	No
Retrospective comparative trial ²³	None stated	Death, clinical effect (defervescence and improvement in general condition) complications (emboli, cardiac incompen-sation), renal toxicity	No (embolic complications greater in combination group)
Level III evidence			
Prospective noncomparative trial ²⁴	Continued clinical or microbiologic evidence of active infection	Nephrotoxicity	Yes*
Prospective noncomparative trial ²⁵	Continued clinical or microbiologic evidence of active infection, relapse	Death, toxic serum levels of aminoglycoside (amikacin), nephrotoxicity, neutropenia	Yes*
Case study ²⁶	NA	Serum bactericidal activity	Yes*
Other evidence			
Randomized open trial ²⁷	Cure (defined by microbiologic and clinical response), clinical failure (defined by no response or worsening during treatment), microbiologic failure or relapse (determined microbiologically)	Duration of symptoms, duration of fever, adverse effects (rash, nephrotoxicity, hepatotoxicity)	Yes†
Randomized open trial ²⁸	Cure (defined by microbiologic and clinical response), clinical failure (defined by persistence of fever, progression of infiltrates, and/or new pulmonary embolisms), microbiologic failure or relapse (determined microbiologically)	Death, adverse effects (rash, nephrotoxicity)	Yes†

RCT = randomized controlled trial, IVDU = intravenous drug user, NA = not available or not applicable.

*No comparator arm.

†Comparator arm not relevant to the focus of this review (i.e., not single-agent β-lactam therapy).



(2.6 ± 0.9 vs 3.6 ± 1.3 days). In the broader subgroup of IVDUs with infection on both sides or either side of the heart, combination therapy also significantly decreased time to defervescence (median 3 vs 7 days) and duration of leukocytosis (6.7 ± 6.5 vs 11.7 ± 6.6 days). No significant difference in mortality or morbidity was observed, with reported complications including congestive heart failure, brain abscess, joint destruction, subarachnoid bleeding, myocardial infarction, osteomyelitis, reinfection, and requirement for surgery. There was a trend toward increased mortality in the combination-therapy arm, driven by patients in the non-IVDU subgroup, but no deaths were attributed to aminoglycoside toxicity. Using the reported results and a 2×2 table, we performed a simple statistical calculation and found that renal dysfunction was significantly higher in the combination arm than in the monotherapy arm of the non-IVDU subgroup (11/19 [58%] vs 1/11 [9%]; 49% absolute increase in risk; 95% CI 21% to 77%). However, no difference in this outcome was found when the entire study sample was assessed.

The most recent RCT,²⁰ published in 1996, included 90 IVDUs with right-sided *S. aureus* endocarditis. This study compared the efficacy of short-course monotherapy and short-course combination therapy with an aminoglycoside. Patients were randomly assigned to receive cloxacillin 2 g IV every 4 h for 14 days, alone or in combination with gentamicin 1 mg/kg IV every 8 h for the first 7 days. Patients were followed for 6 months after the end of treatment. Three primary outcomes were assessed: death during treatment, continued clinical or microbiologic evidence of active infection after 2 weeks of therapy, and relapse of staphylococcal infection. To account for the fact that some exclusion criteria were applied after randomization, as per study protocol, the authors performed 2 analyses: an intention-to-treat analysis assessing all of the patients by the group to which they had been assigned (90 patients) and an efficacy analysis assessing only patients remaining after the exclusion criteria had been applied (74 patients). The type of analysis did not alter the absolute numbers of patients attaining primary outcomes. No significant differences were observed for any of the outcomes listed. Although the incidence of renal failure was not listed as an outcome, no significant difference was found between combination and monotherapy groups.

Summary: Aminoglycosides have not been shown to influence mortality when added to β -lactam therapy, nor have they been shown to significantly influence other outcome measures in the overall populations

evaluated. In a single study, aminoglycosides were shown by subgroup analysis to significantly decrease duration of bacteremia among IVDUs with right-sided disease and to decrease time to defervescence and duration of leukocytosis among all IVDUs. In the same study, use of aminoglycosides was associated with an increased incidence of renal dysfunction in the non-IVDU subgroup. Another study suggested that short-course monotherapy may be adequate for treatment of IVDUs.

Level II-2 evidence

Level II-2 evidence is defined as evidence from well-designed cohort or case-control analytic studies, preferably from more than one centre or research group.

The single prospective comparative trial included in the meta-analysis described earlier was also found to provide relevant information for the current systematic review, albeit only from a subgroup analysis. Rajashekaraiah and others²¹ studied 104 cases of bacteremia and endocarditis due to *S. aureus* in IVDUs and non-IVDUs, looking specifically at the difference in outcomes between sensitive and tolerant bacterial strains, where tolerance refers to minimum bactericidal concentration or minimum inhibitory concentration of at least 16. Results summarizing the influence of the type of therapy on the clinical course of the 50 patients with endocarditis were also reported. Patients were divided into groups according to type of treatment received, defined as single agent (oxacillin, nafcillin, cephalosporin), combination (gentamicin added to the initial agent up to 48 h after the start of therapy), or other (gentamicin added to the initial agent 48 h or more after the start of therapy). The distribution of IVDUs and non-IVDUs in the various treatment groups is unclear from the published report. No significant differences in complications or mortality rate were noted between patients receiving monotherapy and those receiving combination therapy, although a significant difference in febrile response was observed: 7 (44%) of 16 patients in the combination-therapy arm and 8 (89%) of 9 patients in the single-therapy arm were febrile for up to 10 days ($p < 0.05$). More of the patients in the combination therapy arm than in the single-therapy arm had "tolerant" organisms, although this difference did not reach statistical significance. Overall, it appeared that the addition of an aminoglycoside to the primary antimicrobial therapy offered no clinically important benefit.

Summary: This single prospective comparative trial did not show any significant clinical benefit from the



addition of aminoglycoside to β -lactam therapy, including time to defervescence.

Level II-3 Evidence

Level II-3 evidence is obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments could also be regarded as level II-3 evidence.

Two retrospective comparative trials examined the use of aminoglycosides in *S. aureus* endocarditis. The first trial reported on the results of endocarditis therapy in a mixed population of IVDUs and non-IVDUs with *S. aureus* endocarditis who were treated with a single antimicrobial agent or a combination including gentamicin.²² Single-agent therapy was given for 6 weeks and included one of the following intravenously administered agents: penicillin G 10–20 MU/day; methicillin, nafcillin, or cephalothin 6–12 g/day; or vancomycin 2 g/day. Combination therapy consisted of penicillin, methicillin, or nafcillin at the same dosages and duration as cited for single-agent therapy, plus gentamicin 3–5 mg/kg IV daily, given for the first 2 or 3 weeks. In an unspecified number of cases, patients were stepped down to oral antibiotics during the last 2 or 3 weeks of therapy. Twenty-five patients received single-agent therapy, and 15 patients had gentamicin added. Clinical response was measured by duration of fever at the first and second week of antimicrobial therapy. In the single-agent and combination therapy groups, 66.7% and 61.5%, respectively, had persistent fever during the first week of therapy, whereas 31.6% and 20.0%, respectively, had persistent fever during the second week of therapy. These differences were not statistically significant. However, it is unclear whether fever had to persist throughout the second week for this effect to be reported. The mortality rate was 40% in both groups. It should be noted that the study population was heterogeneous not only in terms of the valves infected but also in terms of age and underlying conditions, which may explain the high mortality rate overall.

Frimodt-Moller and others²³ retrospectively analyzed 119 cases of penicillin-resistant *S. aureus* endocarditis from sites across Denmark over a 6-year period (1976–1981) and assessed the effect of antibiotic treatment on infection outcome. IVDUs and non-IVDUs were included in the study, and patients with infections of any of the heart valves were included. Seventy-six patients who had been treated for at least 3 days with either a combination of a β -lactam and an aminoglycoside or a β -lactam alone were assessed for death,

clinical effect (defined as decrease in temperature and improvement in general condition), and complications (including emboli or “cardiac incompenation”). Although the mortality rate during treatment was high for both groups (47% and 57% for combination and monotherapy, respectively), the difference between the groups was not significant. A greater incidence of embolic complications in the group receiving combination therapy was the only significant difference observed (47% versus 34%; $p < 0.05$).

Summary: In 2 retrospective comparative trials, there was no decrease in mortality rate or time to defervescence with the addition of aminoglycosides to β -lactam therapy. One of these studies found more embolic complications with the addition of aminoglycosides, a novel finding not reported in earlier trials.

Level III Evidence

Level III evidence is represented by the opinions of respected authorities, based on their clinical experience; by descriptive studies and case reports; and by reports of committees.

Prospective Noncomparative Studies

Two prospective noncomparative trials assessed the efficacy of short-course combination therapy in IVDUs with uncomplicated right-sided *S. aureus* endocarditis, each using a different combination regimen.

The first study evaluated consecutive patients admitted to hospital with suspected staphylococcal endocarditis.²⁴ Fifty-one patients (representing 53 episodes of endocarditis) met the inclusion criteria (including IV drug use) and completed treatment for *S. aureus* endocarditis with one of two 2-week treatment regimens. Fifty patients were treated with nafcillin 1.5 g IV every 4 h and tobramycin 1 mg/kg IV every 8 h, and 3 patients were given vancomycin 30 mg/kg IV per day in 2 or 3 divided doses, along with the same dose of tobramycin. Patients were followed for as long as 6 weeks after the end of therapy, and cure was defined as eradication of *S. aureus* from the blood at 4 weeks after the end of therapy (microbiologic cure) or absence of signs or symptoms of endocarditis for 2 months (clinical cure). Of the 50 patients treated with nafcillin plus tobramycin, 47 met the criteria for cure (43 microbiologic, 4 clinical). The other 3 patients had relapses, with positive blood culture results for *S. aureus* within 6 to 12 days after stopping treatment. The results of this trial represent the earliest evidence



supporting short-course combination therapy for IVDUs with *S. aureus* endocarditis.

A second study evaluated a different antistaphylococcal combination consisting of cloxacillin 2 g IV every 4 h plus amikacin 7.5 mg/kg every 12 hours for a total of 14 days.²⁵ Notably, this trial was specifically designed to have stricter inclusion criteria than the trial conducted by Chambers and others,²⁴ to increase the certainty of the diagnosis of endocarditis. This was accomplished through the exclusion of patients with *S. aureus* bacteremia but without evidence of endocardial lesions. Of 139 patients evaluated for endocarditis, 72 patients were eligible for inclusion, of whom 71 completed the 2-week treatment regimen (one patient died of respiratory distress syndrome on the 10th day of treatment). Patients were followed for as long as 6 months after discharge and were assessed for cure or treatment failure, measured clinically and microbiologically, as well as for relapse and death. Cure was achieved in 67 patients, and an extension of the treatment period was required for 4 patients.

Summary: In 2 prospective comparative trials, short-course (2-week) combination therapy with an aminoglycoside and a β -lactam yielded a high success rate in IVDUs with *S. aureus* endocarditis.

Case Study

A single case study examined the late addition of gentamicin to therapy for a 55-year-old man with a diagnosis of aortic-valve *S. aureus* endocarditis for whom primary methicillin treatment was failing.²⁶ Gentamicin 80 mg IV every 8 h was added on day 14 of IV methicillin therapy, which had been increased over the 14 days from 2 g every 4 h to 18 g/day via continuous infusion. In vitro studies demonstrated synergistic action between the 2 antimicrobials, with enhancement of serum bactericidal activity. The patient's fever and leukocytosis resolved over the next 5 days, and he remained well over the subsequent 4 weeks, during which time the combination therapy was continued. About 2 weeks after discontinuation of the therapy, the patient was readmitted for acute cardiac compensation, and the combination therapy was restarted. The patient underwent aortic valve replacement and died postoperatively of mediastinal hemorrhage. Preoperative blood culture results had been negative, and samples of the aortic valve tissue and vegetations were sterile. Microscopic sections and smears also showed no sign of active infection.

Summary: A single case study demonstrated microbiologic response to combination therapy with an

aminoglycoside when methicillin treatment alone was deemed to be failing.

Other Evidence

Two additional prospective, randomized, open trials that assessed aminoglycosides in combination with β -lactams were identified.^{27,28} These trials included comparator arms that did not directly provide information relevant to the original question upon which this review is based. For this reason, these trials are not amenable to classification according to the rating scale employed for this review, although they represent an important component of the literature on aminoglycoside combination therapy for *S. aureus* endocarditis. Only the results pertaining to combinations of aminoglycoside and β -lactam are described here.

In the first trial, 16 patients were randomly assigned to the treatment groups, but only 14 were included in the final evaluation.²⁷ A regimen of cloxacillin 2 g IV given every 4 h in combination with gentamicin 1.5 mg/kg IV given every 8 h, both for a total of 2 weeks, was compared with a changing-dose regimen of teicoplanin administered intravenously. Eight patients were assigned to combination therapy, 7 of whom were cured. The remaining patient required an additional week of treatment. Culture of blood samples showed no evidence of microbiologic failure.

In the second trial, 34 patients were randomly assigned to the treatment group, and 31 were included in the final analysis.²⁸ Patients were assigned to receive IV therapy with either cloxacillin, vancomycin, or teicoplanin in combination with gentamicin for a total of 14 days. The cloxacillin dosage was 2 g every 4 h, and the gentamicin dosage was 1.5 mg/kg every 8 h. All 11 patients in the cloxacillin group were cured, with no relapse by the end of the 12-week follow-up period. No side effects were reported for this group.

Summary: Two additional prospective, randomized, open trials provided evidence of treatment success in patients treated with a combination of aminoglycoside and β -lactam; however, no comparisons were made with a control group.

Therapeutic Drug Monitoring of Aminoglycoside Therapy

Of the 11 clinical studies included in this review, only 2 used serum concentrations of aminoglycoside to guide dosing. Both of these studies^{24,25} were noncomparative trials classified as providing level III evidence. In the first of these trials,²⁴ samples were drawn for determination of serum peak and trough



concentrations of tobramycin, which was measured by radioimmunoassay; the sampling times were not reported, and achievement of steady-state conditions before monitoring was unclear. The mean peak serum concentration of tobramycin achieved after a dose of 1 mg/kg was 3.3 ± 1.0 mg/L (range: <1 to 5.7 mg/L; sampling time not reported). Trough concentrations were less than 1 mg/L in 45 of 54 samples. For 2 patients reported to have experienced 50% increases in serum concentrations of creatinine, to above-normal values (upper limit of normal, 130 mmol/L) on day 3, dosages were adjusted to achieve peak tobramycin concentrations of 3 to 4 mg/L. No reference supporting this concentration range was provided.

In the second trial,²⁵ amikacin treatment was monitored using serum concentrations of the drug. Monitoring was carried out as per “established procedures”,^{31,32} although sampling times were not described and observed concentrations were not reported. The thresholds for toxic peak and trough concentrations used in the trial were 35 mg/L and 10 mg/L, respectively. No thresholds for minimal effective concentrations were reported. The authors reported that no toxic serum concentrations were detected during the trial, although technical difficulties precluded the assessment of amikacin concentrations in 6 of the 72 patients.

There were indications in 4 of the other trials that serum concentrations for the respective aminoglycosides being investigated were measured during the study period.^{7,26-28} However, it is unclear to how these data were used. Pharmacodynamic assessments were described in these articles, although there was no reference to pharmacokinetic assessment and/or therapeutic drug monitoring. Pharmacodynamic assessments typically involved serum bactericidal titres before and after aminoglycoside doses.

DISCUSSION

The evidence included in this review was generated over a period of nearly 30 years. During that time, microbial susceptibility, therapeutics, and diagnostics for *S. aureus* endocarditis have all undergone significant changes that limit our ability to extrapolate results and draw conclusions for patients being treated today. For instance, some of the β -lactam antimicrobials used in the earlier trials (e.g., cephalothin) are not included in current treatment guidelines for *S. aureus* endocarditis. Also, the now widely adopted Duke Criteria for the Diagnosis of Infective Endocarditis³³ with proposed modifications³⁴ were published only within the last

13 years. Across all trials, as a function of both the difficulty of diagnosis and the lack of standardization, diagnostic certainty is open to various degrees of criticism, potentially casting suspicion on the results.

Methodologic quality in clinical trials has improved over the past 30 years, with greater attention being paid to controlling for sources of bias and confounding factors. The articles included in this review reflect this trend, with the more recent articles being more rigorously designed than the earlier ones. As might be expected for a subject for which the evidence has accumulated over a relatively long period, the quality of the combined evidence is imperfect; however, evaluating any pattern that is demonstrated can help in drawing conclusions. The summary of conclusions of individual studies (Table 3) is useful for this purpose. Perhaps the most significant critique of all of the included trials is lack of sufficient patient numbers to detect a clinically significant effect, if one exists. However, this factor is very difficult to address.

Following demonstration of a synergistic effect of combination therapy in both in vitro and in vivo animal studies, the first human data were published in the form of a case study,²⁶ which revealed only in vitro support for a synergistic relationship in combination therapy. Then, 2 retrospective comparative trials,^{22,23} a prospective comparative trial,²¹ and 2 randomized controlled trials^{7,19} evaluated the impact of the addition of an aminoglycoside to conventional primary β -lactam antimicrobial therapy. Only the study by Korzeniowski and Sande⁷ demonstrated any benefit with combination therapy (shortened time to abacteremia, defervescence, and normalized leukocyte count); however, this benefit was found only in the IVDU subpopulation and could be interpreted as strictly hypothesis-generating.

The investigators for the 2 subsequent noncomparative trials,^{24,25} which investigated combination therapy in the context of abbreviated treatment regimens, hypothesized that an antimicrobial combination that rapidly eradicates *S. aureus* might be effective in treatment regimens shorter than the conventional 4 to 6 weeks, particularly in patients with uncomplicated right-sided disease. A shortened treatment duration would also be particularly advantageous for the IVDU population. However, these trials did not have comparator arms, leaving unanswered the question of benefit with the specific addition of aminoglycoside to primary β -lactam therapy. Although combination therapy was deemed effective, the adequacy of short-course monotherapy with β -lactams remained unknown.

Interestingly, 2 subsequent randomized trials investigating the use of glycopeptides (vancomycin and teicoplanin) with and without aminoglycosides for the treatment of *S. aureus* endocarditis^{27,28} used short-course combinations of cloxacillin and gentamicin as control arms, suggesting the adoption of such short-course combinations as standard treatment regimens. Recognizing that the benefit of combination therapy with β -lactam and aminoglycoside remained theoretical, Ribera and others²⁰ conducted the most recently published RCT, with the goal of establishing whether a benefit actually exists, but the results of this trial were negative.

As illustrated in Table 3, with the exception of a single trial, all evidence with quality above level III has not favoured combination therapy with an aminoglycoside. The single exception originated from subgroup analysis, where the benefit of combination therapy with β -lactam and aminoglycoside was of questionable clinical importance. Interestingly, although the work from which these results were drawn studied a combination regimen that included 2 weeks of aminoglycoside treatment, the authors recommended that aminoglycosides be discontinued after clearance of bacteremia (3 to 5 days). This recommendation apparently reflects a balance between the expedited control of bacteremia with combination therapy demonstrated in the IVUD subpopulation and a desire to minimize aminoglycoside toxicity.⁷ The endocarditis guidelines cited in this review that mention the addition of aminoglycosides in their treatment recommendations^{5,17} each recommend a 3- to 5-day duration of therapy when the aminoglycoside is given in combination with conventional 4- to 6-week β -lactam therapy (see Table 1), despite the fact that this specific regimen has never been studied.

Although the evidence classified as level III or below favoured combination therapy, it is important to remember that in every case either there was no comparator arm or the comparator arm was not relevant to the focus of this review (i.e., it did not include a single-agent β -lactam). These trials simply demonstrate the adequacy of combination therapy but do not speak to the adequacy of single-agent β -lactam therapy.

Aminoglycosides are a common focus for therapeutic drug monitoring, whereby therapy can be tailored to the individual patient according to measured drug concentrations and pharmacokinetic principles. It is therefore surprising that there were so few references to therapeutic drug monitoring in the articles included in this systematic review. The treatment guidelines that

mentioned use of aminoglycosides in combination with β -lactams^{5,17} recommended doses but did not provide target peak and trough concentrations for dosage adjustments. Furthermore, no other evidence suggesting a “therapeutic range” for the treatment of *S. aureus* endocarditis was uncovered in the preparation of this review. A chapter on the therapeutic drug monitoring of aminoglycosides in an eminent tertiary pharmacokinetics reference published very recently³⁵ also did not yield any other specific information pertaining to the monitoring of aminoglycosides for this indication. On the basis of the available evidence, it is unclear how to incorporate therapeutic drug monitoring into therapy for *S. aureus* endocarditis.

It has been hypothesized that more rapid eradication of bacteria from the bloodstream and cardiac vegetations may decrease the possibility of metastatic complications, as well as lessening the degree of valvular destruction and dysfunction.⁷ Unfortunately, it is doubtful that a trial designed with adequate rigour to provide compelling support for this hypothesis will ever be conducted, for a number of reasons. Ultimately, showing a difference in a meaningful nonsurrogate measure, such as death, would be most desirable. This sort of benefit of combination therapy with aminoglycosides, if it exists, is likely small and would therefore be difficult to detect without a very large sample size. As outcome is profoundly influenced by certain patient characteristics such as age, location and extent of valvular infection and presence of cardiac comorbidities, seeking out a homogeneous patient group with uncomplicated disease, in whom the benefit may be most readily detectable, would limit the external validity of the results and the feasibility of patient recruitment.

Although the problem of diagnostic standardization has been addressed to some extent by the relatively recent adoption of the Duke Criteria for the Diagnosis of Infective Endocarditis,^{33,34} diagnosing this condition remains difficult. The diagnostic certainty for patients in the trials included in this review was variable, a common fault. To date, there appears to be no way to limit study inclusion to patients with diagnostic certainty, nor is it possible to assess cure or relapse with absolute certainty. Lastly, the primary patient population of interest adds another level of difficulty to all of the aforementioned problems. Adherence to treatment regimens and routine follow-up is problematic for the IVUD population and affects the number and integrity of the results. There is likely very little that can be done to control for this factor, which adds complexity to any



further studies. Given the significant obstacles to conducting a definitive trial in this area, it is hardly surprising that only 3 RCTs, all with significant limitations, have been published during the past 30 years.

Despite the recent publication of a meta-analysis on a related topic,¹⁵ we believe that the findings of our review are distinct in that we have included both comparative and noncomparative trials and addressed the question of aminoglycoside use specifically for *S. aureus* endocarditis.

The most compelling evidence to date does not support the addition of aminoglycosides to β -lactam therapy for the treatment of *S. aureus* endocarditis, in either short-course or conventional regimens, regardless of injection drug use status. It is unlikely that clinical trials providing a definitive conclusion on this matter will ever be conducted. Few human data are available to guide patient-tailored therapeutic drug monitoring and dosage adjustment for aminoglycosides used in combination for this indication. On the basis of these findings, we recommend against the routine addition of aminoglycosides to β -lactam therapy for *S. aureus* endocarditis, regardless of the source of infection or the valve involved. Although the degree of harm to which patients are exposed with short-course, low-dose aminoglycoside therapy for this indication is probably very small, the lack of any consistently demonstrated benefit makes the assumption of any degree of treatment risk unacceptable. Furthermore, aminoglycoside therapy is not without cost, in terms of drug acquisition, administration, and monitoring. The unproven benefits of aminoglycosides added to β -lactams do not warrant the cost of therapy.

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