Combination Antibiotic Therapy for Infective Endocarditis

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Despite the availability of new and potent antibiotics, modern echocardiography, and advanced surgical techniques, infective endocarditis (IE) is still associated with high morbidity and mortality rates. Use of synergistic antibiotic combinations is an appealing way to optimize therapy for IE. This review focuses on evidence-based recommendations for combination antimicrobial therapy for IE due to the most common etiologic pathogens. Few proven synergistic approaches for the treatment of IE have been globally demonstrated via in vitro models, experimental IE models, and human clinical trials, except for IE due to enterococci. Novel approaches, such as short-course aminoglycoside therapy and double–β-lactam combination therapy, appear to be promising for treatment of enterococcal IE. Short-course combination therapy involving agents with activity against the cell wall (CWAs) and aminoglycosides is highly effective for IE caused by viridans group streptococci. Although synergistic combination therapy with CWAs-aminoglycosides remains widely used by clinicians for *Staphylococcus aureus* IE, few definitive human data exist that demonstrate the clinical benefit of such an approach.

Despite the availability of new and potent antibiotics, modern echocardiography, and advanced surgical techniques, infective endocarditis (IE) is still associated with high morbidity and mortality rates. For example, the most common organisms that cause IE, such as viridans streptococci, staphylococci, and enterococci, are associated with mortality rates of 4%–16%, 25%–47%, and 15%–25%, respectively [1]. The use of synergistic antibiotic combinations is an appealing way to optimize therapy for IE, especially when IE is due to resistant or relatively resistant organisms (e.g., methicillin-resistant staphylococci). Identification of synergistic antibiotic combinations with rapid bactericidal effects should potentially yield lower rates of morbidity associated with sepsis syndromes, ongoing valvular damage, periannular extension, and metastatic abscess formation. In this review, we focus on evidence-based recommendations for combination antimicrobial therapy for IE due to the most common etiologic pathogens.

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IN VITRO SUSCEPTIBILITY TESTING TO DEFINE SYNERGY

Identification of in vitro susceptibility tests that define "synergy" remains a contentious issue, particularly because there is no universally accepted methodology. Moreover, the linkage between the presence of in vitro synergy and enhanced clinical outcomes in IE has been essentially limited to enterococcal IE [2]. One widely used synergy assay system is the broth microdilution checkerboard technique, which defines synergy in 2-dimensional, serial 2-fold dilutions of drug combinations over wide antibiotic ranges. Such checkerboard tests define a synergistic interaction when calculated fractional inhibitory concentration (FIC) or fractional bactericidal concentration indices are $\leqslant 0.5$. The checkerboard technique has the advantage of being read at a single time point (usually at 24 h of incubation). However, these tests have the disadvantage of being somewhat labor intensive, with visual end points (i.e., in FIC indices) that may not be sharp. This technique also does not measure the rapidity of the bactericidal impact of antibiotic combinations.

Another popular technique for defining in vitro synergy is the time-kill curve method, in which antibiotics (alone or in combinations) are incorporated into broth tubes that contain organisms, after which subcultures are serially obtained during a 24-h incubation period. Quantitative counts in the antibiotic-containing tubes are compared with those from growth con-

trols. For time-kill curves, a differential decrease in counts of $\geq$2 $\log_{10}$/cfu caused by the drug combination compared with the most active single drug in the combination after 24 h will define a "synergistic combination." The advantage of this synergy technique is that it provides data on the rapidity of synergistic killing compared with single agents, and it also provides overall bactericidal information. The major disadvantage of this technique involves choosing the optimal antibiotic concentrations to be tested. Some experts advise the use of single drugs (alone and in combination), each at sub-MIC concentrations, to divulge synergy optimally. Others argue that the drug concentrations to be used should be based on readily achievable serum levels. It should be pointed out that, when compared directly, in experimental IE, the time-kill assay predicts bacteriologic outcome better than the checkerboard system [3].

MECHANISM OF SYNERGY

Among the common pathogens responsible for IE, the mechanism of bactericidal synergy has been delineated only for enterococci. Enterococci are relatively resistant to penicillin G and ampicillin (with mean MICs of ~2 μg/mL), with each agent yielding a bacteriostatic effect [4]. In combination with gentamicin or streptomycin, penicillin G and ampicillin facilitate the intracellular uptake of the aminoglycoside, which causes the subsequent bactericidal effect against the enterococci. In the absence of these agents, there is little intracellular uptake of the aminoglycosides.

There is a close correlation between enterococcal susceptibility or resistance to aminoglycosides in vitro with the following outcomes: in vitro bactericidal synergy in combination with penicillin or ampicillin; microbiologic efficacy in experimental enterococcal IE; and clinical outcome in clinical enterococcal IE [2, 5, 6]. Of note, recent data from Asseray et al. [7] demonstrate that in vitro susceptibility or resistance to gentamicin (but not to amikacin) will accurately predict microbiologic outcomes in experimental enterococcal IE. Aminoglycoside resistance in enterococci (usually related to the presence of aminoglycoside-modifying enzymes) is highly prevalent among enterococci (e.g., among ~40% of isolates to gentamicin [8, 9]), which severely limits therapeutic options for IE. In particular, an MIC of streptomycin of $\geq$2000 μg/mL or an MIC of gentamicin of $\geq$500 μg/mL for enterococci is considered to be high-level resistance, and strains exhibiting such MICs predictably fail to be synergistically killed by combinations of aminoglycosides plus penicillin, ampicillin, or vancomycin [9].

Recent data have demonstrated the potential for in vitro and in vivo synergy against enterococci with combinations of third-generation cephalosporins and ampicillin on the basis of global saturation of distinct penicillin-binding proteins (PBPs; see the Enterococci section below) [10–12]. Combinations of aminoglycosides plus either penicillin or ampicillin also synergistically kill viridans group streptococci (VGS). Although the synergistic mechanism against VGS is not well understood, it does not appear to depend on facilitated aminoglycoside uptake [13].

For staphylococci, combinations of agents with activity against the cell wall (CWAs) plus aminoglycosides or possibly rifampin exert bactericidal synergy against both coagulase-positive and coagulase-negative strains; however, the mechanisms of such synergy are poorly defined. The addition of rifampin to regimens of CWAs for synergy remains controversial: there are conflicting data on synergy as well as antagonism in such combinations. Some investigators believe that the main impact of CWA-rifampin combinations for staphylococcal infections relates to the prevention of the emergence of rifampin resistance [14]. Moreover, some studies have suggested that the in vivo synergistic mechanism of CWA-aminoglycoside combinations involves the diverse metabolic and growth characteristics of the bacterial population in the cardiac vegetations. The high titers of organisms in vegetations (sometimes reaching 10^9–10^{10} of viable bacteria per gram) suggest that bacteria have reached maximum population densities and a state of reduced metabolic activity and cell division within these lesions. Thus, an additional factor that may play a role in the in vivo mechanism of synergy is the potential for the individual CWA and aminoglycoside to act in different phases of bacterial metabolic activity and cell division within the vegetations [15].

IN VITRO SYNERGY AGAINST PATHOGENS COMMONLY RESPONSIBLE FOR IE

Studies of Antibiotic Combinations that Demonstrate In Vitro Synergy

In many published in vitro studies, combinations of antibiotics have demonstrated synergistic activities against the pathogens that commonly cause IE. We have reviewed pivotal published studies on combinations that have demonstrated in vitro synergy. Selected aspects of such studies are discussed below.

Enterococci. Therapy for enterococcal IE has classically depended on the bactericidal activity of the combination of CWAs and aminoglycosides. Moellering et al. [16] were among the first investigators to demonstrate synergy of penicillin G and gentamicin against enterococci (30 of 30 enterococcal strains). Numerous studies then followed, reconfirming such in vitro synergy [17, 18]. Because of concerns about the nephrotoxic effects of high, sustained serum levels of aminoglycosides, subsequent in vitro studies focused on defining a minimum aminoglycoside concentration required to maintain synergistic activity. Matsumoto et al. [19] showed that regimens including a sustained penicillin G concentration of $\geq$5 μg/mL plus either 3 or 5 μg/mL of gentamicin were equally synergistic in vitro.

Because of increasing prevalences of *Enterococcus faecalis* isolates with high-level resistance to aminoglycosides (HLRAg), Mainardi et al. [10] explored the potential synergistic interaction between 2 β-lactams against enterococci. In 50 clinical strains of *E. faecalis,* a bactericidal synergistic effect between amoxicillin and cefotaxime was seen in most strains with use of a disk diffusion assay. In 48 of 50 strains, the MIC of amoxicillin decreased from 0.25–1 μg/mL to 0.01–0.25 μg/mL in the presence of only 4 μg/mL of cefotaxime. The authors speculated that the synergy could be explained by the partial saturation of PBPs 4 and 5 by amoxicillin at a low concentration (0.06 μg/mL), combined with the total saturation of PBPs 2 and 3 by cefotaxime at 4 μg/mL. Thus, PBPs 2 and 3 may not be essential β-lactam binding targets, but they may participate in building the cell wall when other PBPs (like 4 and 5) become inactivated [10]. Furthermore, with use of vancomycin-aminoglycoside–resistant *Enterococcus faecium* strains, Brandt et al. [11] combined amoxicillin and imipenem and showed a bactericidal synergistic effect. These investigators also postulated a similar synergy mechanism (i.e., the saturation of different PBPs).

Gavalda et al. [12] studied 10 strains of *E. faecalis* with HLRAg to further characterize the potential synergy between ampicillin and ceftriaxone. A reduction of the MIC of ampicillin by 2–8-fold was observed with a fixed concentration of 4 μg/mL of ceftriaxone. Also, all 10 strains were found to have a ⩾2-log decrease (in cfu/mL) in time-kill studies that used the combination of ampicillin (1–2 μg/mL) and ceftriaxone (5–60 μg/mL). At a higher concentration of ampicillin (>2 μg/mL), the synergistic effects were not as impressive.

Staphylococcus aureus. Although earlier studies from the 1960s demonstrated in vitro efficacy of penicillin G against *S. aureus,* the emergence of penicillinase-producing strains made semisynthetic penicillinase-resistant penicillins (e.g., methicillin, nafcillin, and oxacillin) the treatment of choice. Although these penicillins displayed different pharmacokinetic characteristics and yielded quantitatively different in vitro bactericidal effects, their in vivo activity in experimental IE models appeared to be equivalent to each other [20]. The combination of nafcillin and gentamicin has been studied extensively in vitro and in vivo, and a close correlation has been observed between in vitro synergy and enhanced in vivo outcomes in experimental IE documented in most investigations [15].

Coagulase-negative staphylococci (CoNS). CoNS (specifically, coagulase-negative *Staphylococcus epidermidis*) are responsible for the majority of cases of prosthetic valve endocarditis (PVE). Such strains usually exhibit high-level resistance to nafcillin and oxacillin, as well as resistance to the cephalosporin and carbapenem classes. This latter fact is not always reflected by routine in vitro susceptibility tests because of the frequent heterotypic expression of β-lactam and carbapenem resistance by *S. epidermidis,* in which only a small number of slowly growing cells in a colony exhibit the resistance phenotype. Frequencies of semisynthetic penicillin resistance have been reported to be as high as 63%–80% among strains of *S. epidermidis* recovered from patients with prosthetic valve IE; thus, combination therapy has been recommended for the treatment of such infections [21].

There have been several in vitro studies demonstrating a synergistic interaction in combinations of vancomycin, gentamicin, and rifampin against CoNS. Yu et al. [22], who used a 3-dimensional microtiter checkerboard method, found that the aforementioned triple-antibiotic combination had synergistic activity against 7 of 10 *S. epidermidis* isolates recovered from patients with documented PVE. However, the authors defined "synergy" as having an FIC index of <1.0 instead of ⩽0.5, as described above. In addition, they observed that vancomycin plus rifampin had a mean FIC index of >1.0, whereas gentamicin plus rifampin has a mean FIC index of <1.0.

In a series of in vitro studies by Archer et al. [23], the frequency of inducing rifampin resistance was much lower when rifampin was used in combination with other agents, without the presence of true synergy. Thus, the antimicrobial activity of rifampin was maintained by the prevention of emergence of rifampin-resistant mutants in the presence of a second or third agent.

Animal Models of IE

Experimental animal models can be an invaluable tool to bridge the gap between the artificial environment of an in vitro system on the one hand and the complicated in vivo milieu within a human host on the other. Experimental IE has been studied extensively in both rats and rabbits by establishing intracardiac vegetations via insertion of a polyethylene catheter across the aortic or tricuspid valves. When the etiologic organism is injected intravenously into catheterized animals, IE is reproducibly established. This model has been used to study both disease pathogenicity and the response to antimicrobial therapy. In particular, this model allows facile comparisons of treatments with single-agent versus combination-therapy regimens, with respect to bacterial killing and/or clearance from target tissues.

As noted above, numerous investigations have confirmed the superior in vivo synergistic efficacy of CWAs in combination with aminoglycosides compared with single-drug regimens in experimental IE due to VGS, *S. aureus,* CoNS, and enterococci. These studies have been summarized in detail by Fantin et al. [24]. We address 2 selected aspects of such studies below: (1) synergy dose strategies, and (2) enterococcal synergy with double–β-lactam regimens.

Synergy dosing strategies. As noted in the Enterococci section above, achievable aminoglycoside levels required for synergistic killing of enterococci and VGS appear to be con-

siderably lower than those needed to reliably kill susceptible gram-negative pathogens (e.g., 1–5 μg/mL vs. 5–10 μg/mL, respectively [6]). In addition, the impact of antibiotic dosing intervals on synergistic killing of pathogens responsible for IE remains of critical importance. For example, in experimental IE due to VGS or enterococci, data suggest that levels of CWAs should be maintained above the MIC throughout the dosing interval to prevent the loss of efficacy. This has been linked to the time-dependent killing features of such agents, as well as the lack of any substantial postantibiotic effect of penicillin G, with or without aminoglycosides, particularly for VGS and enterococci [24].

There has been extensive controversy about the optimal dose interval for the aminoglycoside component of the CWA-aminoglycoside synergistic regimens for IE due to common gram-positive pathogens. As noted by Fantin et al. [24], some of the variability in the therapeutic outcomes of experimental IE treated with combination therapy undoubtedly relates to variations in the aminoglycoside dose intervals used. For staphylococci and enterococci, it appears that lengthening the interval between each aminoglycoside dose reduces in vivo efficacy; this has been putatively linked to the requirement for simultaneous presence of the CWA and the aminoglycoside for maximal efficacy in murine pneumonitis and thigh infection models ("sigmoidal dose-response curve" [25]). This relationship is particularly important given the lack of significant postantibiotic effects, as noted above.

***Double–β-lactam combination therapy for* E. faecalis.** In a rabbit aortic valve IE model, Join-Lambert et al. [26] demonstrated that a combination of 2 β-lactam agents (amoxicillin and cefotaxime) yielded an enhanced in vivo effect against HLAgR *E. faecalis* strains, but only for a low-dose amoxicillin regimen. These in vivo observations were consistent with the in vitro findings of Mainardi et al. [10]. Brandt et al. [11], in a similar in vivo study, found that this same combination yielded both in vitro and in vivo synergy in experimental IE. Of note, other double-CWA combinations, such as ampicillin plus vancomycin, were not synergistic in vivo. It should be emphasized that the double–β-lactam strategy for experimental IE has been evaluated in relatively few enterococcal strains to date.

CLINICAL TRIALS

Table 1 summarizes the largest studies of combination therapy for humans with IE due to common pathogens [27–42].

VGS. The largest experience of combination therapy in IE has been generated for VGS IE. For penicillin G–susceptible strains of VGS (MIC, ≤0.1 μg/mL), high cure rates (95%–98%) were demonstrated in a clinical case series during the 1970s that involved a 4-week course of intravenously administered penicillin G [43]. Although in vitro studies have demonstrated synergy with the combination of penicillin G plus streptomycin or gentamicin, such combination therapy has not been definitively established as being more effective than penicillin G or ceftriaxone alone in human trials [27]. It appears that the major advantage of combination therapy in VGS IE is the ability to shorten the course of treatment for uncomplicated infection from 4–6 weeks to 2 weeks (short-course therapy). For example, studies by Wilson et al. [27] yielded cure rates of 98% for a short-course combination regimen of penicillin G and streptomycin. Moreover, Francioli et al. [28] showed that a 2-week course of once-daily ceftriaxone plus netilmicin was equivalent to a 2-week course of penicillin G (daily divided dose) and gentamicin (daily divided dose). A recent study by Sexton et al. [32] yielded a similar cure rate of 96% for both a 2-week course of once-daily ceftriaxone plus once-daily gentamicin and a regimen of ceftriaxone alone administered once-daily for 4 weeks. It should be emphasized that the dose used for once-daily dosing of gentamicin was 3 mg/kg, which is substantially lower than the 5–7 mg/kg per day used for gram-negative enteric infections. The other major advantage of the short-course, once-daily ceftriaxone-aminoglycoside regimen is its applicability to outpatient treatment strategies [28, 32].

Although there have not been any definitive, large-scale, comparative clinical trials, the American Heart Association (AHA; Dallas, TX) has advocated combination therapy regimens for VGS IE caused by penicillin-resistant VGS (i.e., strains with an MIC of penicillin of ≥0.1 μg/mL to ≤0.5 μg/mL). For such strains, the AHA recommends that gentamicin be given for the first 2 weeks of a 4-week course of penicillin G or ampicillin. For VGS with an MIC of penicillin of >0.5 μg/mL or infections with *Abiotrophia* species ("nutritionally variant" strains), a standard regimen of a combination of ≥4 weeks of penicillin G or ampicillin plus gentamicin should be used—similar to the treatment used for enterococcal IE [4].

S. aureus. The benefit of combination therapy with a CWA and aminoglycosides has not been definitively established by human clinical trials of *S. aureus* IE. In nonaddicts with left-sided IE due to *S. aureus*, Korzeniowski and Sande [33] reported a more rapid clearance of bacteremia but a higher rate of nephrotoxicity, without a reduction in mortality in the combination therapy group (nafcillin and gentamicin) versus the nafcillin-alone group. Current AHA recommendations advise provision of aminoglycosides in combination with CWAs only for the first 3–5 days of therapy in patients with left-sided native valve IE due to *S. aureus*. This latter recommendation is based solely on the potential for more-rapid bacteremia clearance. Although this recommendation is supported by the AHA guidelines, there are no specific studies to confirm the enhanced efficacy of such an approach with regard to improved outcome,

Table 1. Clinical outcomes reported in selected studies of combination treatment for infective endocarditis (IE) due to common pathogens.

Reference	Study period or year of publication	Pathogen	Combination regimen	No. of episodes of IE	Valve(s) involved	Comments
Wilson et al. [27]	1972–1979	VGS	Pen + Stm	91	MV/AV	Two-week course of therapy; no cases of relapse
Francioli et al. [28]	1995	VGS	Ctri + Net	48	MV/AV	Short-course (2-week) therapy with single daily doses had outcome similar to 4-week courses [29–31]
Sexton et al. [32]	1992–1995	VGS	Ctri + Gm vs. Ctri	51	MV/AV	Short-course (2-week) combination therapy had outcome similar to 4-week monotherapy
Korzeniowski et al. [33]	1982	SA	Naf + Gm vs. Naf	19	TV	No differences observed
			Naf + Gm vs. Naf	15	MV/AV	Naf + Gm was superior to Naf alone for bacteremia clearance
Watanakunakorn et al. [34]	1961–1975	SA	CWA + Gm vs. CWA	40	MV/AV/TV	No differences observed
Abrams et al. [35]	1976–1977	SA	CWA + Gm vs. CWA	25	TV	No differences observed
Dworkin et al. [36]	1989	SA	Cpfx (po) + Rif (po)	14	TV	100% Cure rate in 10 assessable patients
Chambers et al. [37]	1983–1987	SA	Naf + Tm	50	TV	94% Cure rate for short-course (2-week) therapy
Heldman et al. [38]	1990–1993	SA	Cpfx (po) + Rif (po) vs. Oxa + Gm	85	TV	Cure rates, 95% vs. 88%
Ribera et al. [39]	1988–1993	SA	Clox vs. Clox + Gm	90	TV	Cure rates, 92% vs. 94%
Fortun et al. [40]	2001	SA	Clox + Gm vs. Vm or Teic + Gm	31	TV	Cure rates, 100% vs. 60%–70%
Olaison et al. [41]	1995–1999	E	CWA + AG	93	MV/AV	82% Cure rate with shortened duration of AG therapy (median, 15 days)
Gavalda et al. [42]	2001	E	Amp + Ctri or Ctax	20	MV/AV	100% Cure rate

NOTE. AG, aminoglycoside; Amp, ampicillin; AV, aortic valve; Clox, cloxacillin; Cpfx, ciprofloxacin; Ctax, cefotaxime; Ctri, ceftriaxone; CWA, agent with activity against cell walls; E, enterococci; Gm, gentamicin; MV, mitral valve; Naf, nafcillin; Net, netilmicin; Oxa, oxacillin; Pen, penicillin; Rif, rifampin; SA, *Staphylococcus aureus;* Stm, streptomycin; Teic, teicoplanin; Tm, tobramycin; TV, tricuspid valve; VGS, viridans group streptococci; Vm, vancomycin.

reduction in metastatic complications, or mitigation of valvular damage.

Initial studies of combination therapy for right-side native valve IE due to *S. aureus* focused on the addition of 2 weeks of gentamicin therapy to a standard 4-week course of nafcillin. These investigations failed to show any microbiologic or clinical improvement in outcome associated with the addition of the aminoglycoside [33–35]. Subsequent studies from San Francisco General Hospital (California) confirmed the excellent efficacy of 2-week courses of nafcillin plus tobramycin, as well as 4-week courses of predominantly orally administered ciprofloxacin plus rifampin, for treatment of right-side IE due to *S. aureus* [36, 37]. The high efficacy rates for short-course parenteral and oral combination therapy for right-side IE due to *S. aureus* have been confirmed in other, more recent investigations [38]. Of note, a recent study by Ribera et al. [39] showed that short-course parenteral cloxacillin monotherapy yielded clinical outcomes comparable to combined β-lactam–aminoglycoside therapy. In addition, Fortun et al. [40] compared short-course therapy for right-side *S. aureus* endocarditis with combinations of cloxacillin plus gentamicin versus a glycopeptide (teicoplanin or vancomycin) plus gentamicin, and they confirmed the relative ineffectiveness of glycopeptide-based regimens.

PVE. In a retrospective study by Karchmer et al. [14] of 75 episodes of PVE due to *S. epidermidis*, the enhanced efficacy of combination antibiotic regimens was evaluated. Collectively, therapy with vancomycin-based regimens was more effective than β-lactam–based regimens, with improved cure rates of 81% versus 50%, respectively ($P = .055$); the improved efficacy of vancomycin regimens was undoubtedly related to the high prevalence of methicillin resistance among PVE isolates. The addition of rifampin and/or an aminoglycoside to vancomycin therapy improved the cure rates to 90%, compared with a cure rate of 50% for vancomycin alone ($P = .06$). Although these data have not been prospectively confirmed, most experts sug-

gest that therapy for PVE due to methicillin-resistant strains of *S. epidermidis* should include vancomycin in combination with rifampin and an aminoglycoside.

Enterococci. Recently, Olaison and Schadewitz [41] conducted a 5-year (1995–1999) nationwide prospective study in Sweden in which 881 definite episodes of IE were identified, 93 (11%) of which were caused by enterococci. Although current AHA guidelines for treatment of enterococcal IE have recommended combined treatment with penicillin G or ampicillin plus an aminoglycoside for a total duration of 4–6 weeks [4], these investigators evaluated the clinical outcomes when the total duration of aminoglycoside therapy was reduced. This approach was driven by the fact that aminoglycoside toxicity mostly affects the elderly population, the prime target group for enterococcal IE. Although no direct restriction on the duration of aminoglycoside therapy was specified, study patients had a median total duration of antibiotic therapy of 42 days, with a median of 15 days of combined therapy with a CWA plus the aminoglycoside. The authors found an overall cure rate of 81% (75 of 93 cases), even though patients received substantially shorter courses of aminoglycoside therapy than had previously been suggested by expert guidelines. It is of note that these outcome figures compared favorably with most historical control studies of enterococcal IE [2, 5]. They concluded that reducing the aminoglycoside component to ~2 weeks would maintain clinical efficacy while reducing potential toxicities in this high-risk patient population with enterococcal IE.

As noted above, in vitro and experimental IE data have suggested the potential efficacy of double–β-lactam combinations of third-generation cephalosporins and ampicillin for enterococcal IE [10–12]. Gavalda et al. [42] explored the clinical efficacy of such combinations for the treatment of IE due to *E. faecalis.* In an open, prospective, multicenter study, 18 cases of definite IE were evaluated. Of these 18 cases, 13 were caused by HLRAg isolates. The combination of ampicillin plus ceftriaxone showed in vitro bactericidal synergy against 7 HLRAg strains tested, with either an additive or indifferent effect observed in the remaining strains; it is of note that no evidence of clinical or microbiologic relapse was observed during the 3-month follow-up period. All 16 assessable patients were cured by 1 month of double–β-lactam therapy. Two patients died, but there was no evidence of active infection noted at autopsy. The authors concluded that the combination of 2 β-lactam antibiotics was a safe and effective alternative for the treatment of enterococcal IE [42]. It should be underscored that a high-dose ceftriaxone regimen (4 g/day) was used to assure high and sustainable drug levels; 2 patients experienced substantial, albeit reversible, neutropenia and were withdrawn from the study. It should be emphasized that these data have been published in abstract form only, and we anxiously await full publication of these data.

SUMMARY

There are few proven synergistic approaches for the treatment of IE that have been globally demonstrated via in vitro models, experimental IE models, and human clinical trials, except treatment of IE caused by enterococci. Novel approaches, such as short-course aminoglycoside therapy and double–β-lactam combination therapy, appear to be very promising for treatment of enterococcal IE. It appears that short-course CWA-aminoglycoside combinations are highly effective against VGS IE, which makes affected patients amenable to outpatient therapeutic strategies in uncomplicated cases. Although synergistic combination therapy with CWA-aminoglycoside regimens remains widely used by clinicians for *S. aureus* IE, there remains very little definitive existing human data that demonstrate the clinical benefit of such an approach.

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