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A Review of Combination Antimicrobial Therapy for *Enterococcus faecalis* Bloodstream Infections and Infective Endocarditis

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Enterococci, one of the most common causes of hospital-associated infections, are responsible for substantial morbidity and mortality. *Enterococcus faecalis*, the more common and virulent species, causes serious high-inoculum infections, namely infective endocarditis, that are associated with cardiac surgery and mortality rates that remained unchanged for the last 30 years. The best cures for these infections are observed with combination antibiotic therapy; however, optimal treatment has not been fully elucidated. It is the purpose of this review to highlight treatment options and their limitations, and provide direction for future investigative efforts to aid in the treatment of these severe infections. While ampicillin plus ceftriaxone has emerged as a preferred treatment option, mortality rates continue to be high, and from a safety standpoint, ceftriaxone, unlike other cephalosporins, promotes colonization with vancomycin resistant-enterococci due to high biliary concentrations. More research is needed to improve patient outcomes from this high-mortality disease.

Keywords. *Enterococcus faecalis*; infective endocarditis; antimicrobials.

Severe enterococcal infections, including infective endocarditis (IE), are associated with mortality rates as high as 20%–40% and have remained unchanged for the last 3 decades despite advances in antimicrobial therapy [1]. Although *Enterococcus faecalis* and *Enterococcus faecium* are the 2 most clinically relevant species, *E. faecalis* accounts for approximately 97% of all IE cases, predominantly impacting the elderly and patients with comorbidities [2]. *Enterococcus faecalis*, unlike *E. faecium,* is less frequently multidrug resistant [2]. However, lack of bactericidal activity of β-lactams [3], and ability to form biofilm at higher rates than *E. faecium* (87%–95% vs 16%–29%, respectively) [4, 5], makes treatment of *E. faecalis* infections particularly challenging and may contribute to the unchanging mortality rates. Consequently, combination antimicrobial therapy is required for deep-seated *E. faecalis* infections, and with >50% of isolates expressing aminoglycoside resistance, treatment options are becoming limited [6]. It is the purpose of this review to highlight available treatment options and their limitations and to provide direction for investigation of future novel combination therapies, including ampicillin plus non-ceftriaxone β-lactams and daptomycin combination therapy, to further aid in the treatment of *E. faecalis* IE.

METHODS

Studies were identified by conducting PubMed and Embase searches using the following keywords in 1 or more combinations with "*Enterococcus faecalis*": infective, endocarditis, bacteremia, bloodstream, infection, treatment, guideline, antibiotic, combination, synergy, resistant, biofilm, clinical, diagnosis, epidemiology, in vitro, in vivo, simulated endocardial vegetation, experimental, and β-lactamase. Manual searches of reference lists of relevant articles found from initial searches were also conducted. No limitation was placed on publication time period. Studies were selected based on authors' (M. B. and M. K. L.) judgment of relevance to topic.

ORIGIN OF COMBINATION THERAPY

For serious *E. faecalis* infections, such as IE, bactericidal agents, often as combination therapy, are preferred [2]. β-Lactam antibiotics lack bactericidal activity against enterococci when used as monotherapy, making treatment of systemic infections

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particularly challenging [3]. Although *E. faecalis* is often susceptible to ampicillin, treatment failure of 60% and lack of bactericidal activity of cell wall–active agents (ie, penicillin G, ampicillin, vancomycin) prompted efforts to identify combination therapies that would yield a bactericidal effect in severe infections [1–3]. Originally, penicillin or ampicillin was combined with gentamicin or streptomycin to facilitate intracellular uptake of aminoglycosides [3]. The recognition of in vitro bactericidal synergism between β-lactams and aminoglycosides was supported by observational clinical data and led to improvements in IE cure rates up to 75% [3]. However, rising high-level aminoglycoside resistance (HLAR), which may range to up to 63% [1, 6, 7], prompted the need for alternative therapy. Subsequently, dual β-lactam combination therapy emerged as a viable, safe treatment option for severe infections with *E. faecalis*.

DUAL β-LACTAM THERAPY

In Vitro and Experimental Animal Data

In 1995, Mainardi and colleagues were the first to report synergy between amoxicillin and cefotaxime in *E. faecalis* [8]. The results showed that the minimum inhibitory concentration (MIC) for amoxicillin decreased substantially in the presence of cefotaxime, as did the MIC of cefotaxime in the presence of amoxicillin. The proposed mechanism of synergy is that partial saturation of essential penicillin-binding proteins (PBPs) 4 and 5 by amoxicillin, coupled with complete saturation of nonessential PBPs 2 and 3 by cefotaxime leads to a bactericidal effect [8]. Taken together, the combination of cefotaxime and amoxicillin exploits the optimal inactivation of PBPs 2, 3, 4, and 5, thereby producing synergism on *E. faecalis*. Presumably, the marked impairment in cell wall synthesis is the basis for this effect.

In 1999, Gavaldà and colleagues further explored β-lactam combinations by evaluating the activity of ampicillin plus ceftriaxone (AC) against *E. faecalis* strains with HLAR [9]. They confirmed Mainardi et al's synergistic findings, and observed up to a 4-fold reduction in ampicillin MICs in the presence of ceftriaxone. Furthermore, rabbits treated with AC in HLAR *E. faecalis* endocarditis had lower bacterial vegetation counts than rabbits treated with ampicillin alone [9]. In 2003, Gavaldá et al evaluated the utility of AC vs ampicillin plus gentamicin (AG) against *E. faecalis* with or without HLAR in rabbits with catheter-induced endocarditis [10]. They determined that the 2 combinations were comparable in efficacy, and further concluded that AC may be an alternative to AG, particularly in special populations, such as patients with renal insufficiency (Table 1) [10].

Human Data

Clinical data have since evaluated the combination of AC against HLAR and non-HLAR *E. faecalis* IE [6, 11, 12]. In 2007, Gavaldà et al assessed the efficacy and safety of AC in 21 patients with HLAR, and 22 patients with non-HLAR *E. faecalis* IE in a multicenter, open-label clinical trial [6]. In this observational study of enterococcal IE, it was concluded that in addition to AC being a safe and effective treatment option for HLAR IE, it is a reasonable alternative for patents at risk for nephrotoxicity infected with non-HLAR organisms [6]. Subsequently, Fernández-Hidalgo and colleagues conducted a large, nonrandomized, multicenter, cohort study comparing the safety and efficacy of AC and AG in 246 episodes (159 subjects in AC group; 87 subjects in AG group) of IE caused by *E. faecalis* [11]. The authors concluded that the 2 combinations were equally effective as there was no difference in mortality while on antimicrobial treatment and during the 3-month follow-up, relapse, or treatment failures requiring alternate therapy. However, patients treated with AG had significantly higher rates of adverse events (ie, renal impairment) requiring therapy withdrawal [11]. These findings coincide with a retrospective study of prospectively collected data that evaluated 69 episodes of IE caused by *E. faecalis* (30 subjects in AG group; 39 subjects in AC group) [12]. Similar to Fernández-Hidalgo and colleagues, the authors did not observe a difference in in-hospital mortality or 1-year mortality between the AG and AC groups, and found that patients on AG had higher rates of treatment-induced renal failure than patients receiving AC. Interestingly, the authors captured epidemiologic data that demonstrate a significant increase in IE caused by HLAR-producing *E. faecalis* over the course of 14 years, along with an increase in AC therapy, although the small sample size limits definite conclusions (Table 1) [12].

Clinical Trials Are Limited in IE

As a result of these 2 clinical studies [6, 11], the 2015 national IE guidelines have been updated to recommend double β-lactam therapy (ie, AC) as a treatment option for HLAR infections, and a reasonable alternative to aminoglycosides for non-HLAR *E. faecalis* infections (class IIa; level of evidence B recommendation) [2]. Of note, isolates with gentamicin resistance may be susceptible to streptomycin, and vice versa, although monitoring for streptomycin concentrations is often difficult and inefficient for clinicians since it is not available within most hospitals. The guideline recognizes that the AC regimen has several limitations, notably that (1) all data were retrospectively collected without randomization; (2) treatment recommendations were center-dependent, so unmeasured confounding factors as well as treatment and indication bias impacting these results cannot be ruled out; and (3) gentamicin dosing and therapeutic drug monitoring were not consistent across all centers, and higher levels may have contributed to the observed increase in renal impairment [11, 12]. While data supporting the use of AC have limitations, it is important to note that studies recommending AG treatment are observational and have similar limitations [2, 3].

As it currently stands, data providing support for optimal drug, dose, and duration for the currently available treatment

Table 1. Evolution of Dual β-Lactam Combination Therapy

Author (Year)	Subjects	Regimen	Methods	Reported Findings
Nonhuman data				
Mainardi et al (1995) [8]	50 clinical strains of *Enterococcus faecalis*	Amoxicillin plus cefotaxime	Checkerboard to test for synergy	• MIC_{50} for amoxicillin decreased from 0.5 μg/mL to 0.06 μg/mL in the presence of 4 μg/mL of cefotaxime • MIC_{50} of cefotaxime decreased from >256 μg/mL to 1 μg/mL in the presence of 0.06 μg/mL of amoxicillin
Gavaldà et al (1999) [9]	10 clinical HLAR strains of *E. faecalis*	Ampicillin plus ceftriaxone	Double disk method and time-kill studies to estimate synergy Catheter-induced endocarditis model in rabbit simulating human pharmacokinetics of ampicillin 2 g q4h alone or in combination with ceftriaxone 2g q12h	• Ampicillin MIC reduced by 1–4 dilutions in presence of 4 μg/mL of ceftriaxone • Ampicillin plus ceftriaxone had significantly lower aortic valve vegetations than ampicillin alone ($P < .001$) in rabbit experimental endocarditis model • Combination treatment synergistic against HLAR *E. faecalis* in vitro and in vivo
Gavaldá et al (2003) [10]	Endocarditis: Recovered non-HLAR *E. faecalis* in rabbit models	Ampicillin plus ceftriaxone vs ampicillin plus gentamicin	Catheter-induced endocarditis model in rabbit Treatment groups simulating human pharmacokinetics: ampicillin 2 g q4h alone; ampicillin 2 g q4h IV + gentamicin 1 mg/kg q8h IV; ampicillin 2 g q4h IV + ceftriaxone 2 g q12h IV; ampicillin 2 g q4h IV + ceftriaxone 2 g q12h IV + gentamicin 6 mg/kg q24h SC	• Bacterial counts reduced for treatment groups vs control group ($P < .05$) • All combinations were more efficacious than ampicillin alone ($P < .05$) • Treatment with ampicillin + ceftriaxone was as efficacious as ampicillin + gentamicin
Human data				
Gavaldà et al (2007) [6]	21 patients (48.8%) with HLAR *E. faecalis* and 22 patients (51.2%) with non-HLAR *E. faecalis* endocarditis	Ampicillin 2 g q4h plus ceftriaxone 2 g q12h	Observational, open-label, nonrandomized, multicenter clinical trial observing outcomes in patients receiving ampicillin plus ceftriaxone treatment	• Clinical cure rate was 67.4% (29/43 patients) • 6 (28.6%) patients in HLAR group and 8 (36.4%) in non-HLAR *E. faecalis* group died during treatment ($P > .05$) • Overall, 95.3% of patients did not report antimicrobial-related adverse effects
Fernández-Hidalgo et al (2013) [11]	246 patients with *E. faecalis* endocarditis	Ampicillin[a] 2 g q4h plus ceftriaxone 2 g q12h (n = 159) vs ampicillin[a] 2 g q4h plus gentamicin[a] 3 mg/kg/d (n = 87)	Nonrandomized, comparative multicenter cohort study comparing ampicillin plus ceftriaxone and ampicillin plus gentamicin in patients with endocarditis	• No difference in mortality during treatment: 22% vs 21% ($P = .81$) • No difference in mortality at 3-month follow-up: 8% vs 7% ($P = .72$) • Higher rates of adverse events requiring treatment withdrawal in ampicillin + gentamicin (25% vs 1%, $P < .001$) • No difference in treatment failure requiring alternate therapy (1% vs 2%, $P = .54$) • No difference in relapse (3% vs 4%, $P = .67$)
Pericas et al (2014) [12]	69 patients	Ampicillin 2 g q4h plus ceftriaxone 2 g q12h (n = 39) vs ampicillin 2 g q4h plus gentamicin 3 mg/kg/d (n = 30)	Retrospective analysis of prospectively collected data assessing antibiotic resistance, epidemiology, and comparing safety and efficacy of ampicillin plus ceftriaxone and ampicillin plus gentamicin in patients with endocarditis	• Increased rates of HLAR observed (24% in 1997–2006, 49% in 2007–2011, $P = .03$) • Ampicillin + ceftriaxone utilization increased (22% [n = 18] in 1997–2001; 31% [n = 16] in 2002–2006; 86% [n = 35] in 2007–2011; $P < .001$) • No difference in in-hospital mortality (27% vs 23%, $P = .732$) • No difference in 1-year mortality (30% vs 26%, $P = .688$) • Treatment-induced renal failure higher in ampicillin + gentamicin group (65% vs 34%, $P = .014$)

Abbreviations: HLAR, high-level aminoglycoside resistance; IV, intravenous; MIC_{50}, minimum inhibitory concentration (50 corresponds to median); q4h, every 4 hours; q8h, every 8 hours; q12h, every 12 hours; SC, subcutaneous.

[a]Renal dose-adjusted as needed.

options remain controversial. A recent study investigated optimal gentamicin treatment duration in 84 patients with non-HLAR *E. faecalis* IE by comparing 2 groups: patients admitted prior to the Danish 2007 guideline modification vs patients admitted after guideline modification that recommended reducing gentamicin treatment duration from 4–6 weeks to 2 weeks [13]. Forty-one patients received gentamicin for a median of 28 days (interquartile range [IQR], 18–42 days), and 43 patients received a median of 14 days (IQR, 7–15 days). There was no difference between groups for the primary outcome of 1-year event-free survival (27 [66%] vs 29 [69%], $P = .75$) measured from the end of treatment. No differences in complications, relapse, in-hospital mortality, baseline renal function, or 14-day renal function were observed between groups. However, patients receiving 14-day treatment with gentamicin therapy experienced a significantly lower reduction in renal function at discharge compared to those receiving the full course, as measured by estimated glomerular filtration rate (median, –11 mL/minute vs –1 mL/minute, $P = .009$) [13]. They concluded that patients may be adequately treated with 2 weeks of gentamicin, thereby avoiding renal impairment that is associated with long duration of aminoglycoside therapy [13]. However, this study was limited by a small sample size and insufficient power, thereby leaving the optimal duration of therapy unclear.

Interestingly, other studies demonstrate that toxicity resulting in gentamicin discontinuation occurred after approximately 2 weeks of treatment [11, 12]. Although Fernández-Hidalgo did not directly evaluate a shorter gentamicin treatment duration, the authors describe outcomes of gentamicin treatment failure due to adverse events, namely renal dysfunction. For the 25% of patients who failed AG therapy, the median duration of therapy with gentamicin was 14 days (IQR, 12–20 days) [11]. Furthermore, 10 patients did not receive combination therapy after stopping gentamicin and completed their treatment course with ampicillin monotherapy [11]. Pericas et al reported that 43% of patients in the AG group had to discontinue treatment due to toxicity; 13 patients were switched to AC therapy after a median of 18 days (range, 5–30 days; IQR, 15–24.5 days) [12]. Overall these data indicate that gentamicin toxicity is associated with longer treatment durations, and a 2-week treatment course may be reasonable.

CONCERN FOR DEVELOPMENT OF RESISTANCE

Enterococcal resistance to β-lactams is primarily acquired by overproduction of PBP5, and by amino acid substitutions that result in altered binding site and reduced β-lactam interaction with PBP5 [14]. Additionally, rare isolates of *E. faecalis* produce β-lactamase enzymes, which in theory could compromise β-lactam therapy against enterococcal endocarditis and further limit the available treatment options [3, 15]. Although the impact of enterococcal β-lactamase in low-inoculum infections is difficult to detect, the impact in high-inoculum infections, such as endocarditis, has not been fully elucidated. Data suggest that although most β-lactamase enzymes are inducible, enterococcal β-lactamase is produced constitutively, and at substantially lower amounts [3, 15]. Furthermore, the enzyme remains membrane bound, making detection of phenotypic resistance difficult unless high inocula are used [3, 15].

CEFTRIAXONE SAFETY AND ADVERSE EVENT CONCERNS

Currently, AC combination therapy is the only tested option for the treatment of IE and bacteremia due to HLAR *E. faecalis* with supportive clinical data. While seemingly safe as compared to AG, safety risk associated with ceftriaxone use should not be negated. In addition to being an independent risk factor for *Clostridium difficile* infections [16] numerous clinical and observational studies implicate ceftriaxone as a major risk factor for occurrence of vancomycin-resistant *E. faecium* (VRE) infection, including bacteremia [17, 18]. This is in addition to a wealth of animal studies that have linked ceftriaxone use to promotion of gastrointestinal (GI) colonization by VRE [19, 20]. It is suggested that the high biliary excretion of ceftriaxone, with levels that exceed GI concentrations of 5000 μg/mL, promote overgrowth of ampicillin- and vancomycin-resistant *E. faecium*, whose MIC for ceftriaxone typically exceeds 10 000 μg/mL [20]. This ability of ceftriaxone to "select" for drug-resistant enterococci not only poses a risk to individual patients, but also threatens public health by contributing to developing of resistance in multiple organisms in the hospital environment. Consequently, studies investigating alternative treatment options, particularly novel β-lactam combinations, are crucial to expand the therapeutic armamentarium against these organisms.

OTHER COMBINATION THERAPIES AND FUTURE RESEARCH POTENTIAL

Novel Dual β-Lactam Combinations

Unlike ceftriaxone, other cephalosporin antibiotics, such as cefepime [19] and ceftaroline [21], do not appear to promote VRE colonization. When cefepime, cefotetan, ceftriaxone, and ceftazidime were studied in the GI tract of mice, it was noted that cefepime was the least likely of the 4 to cause VRE colonization (no difference in colonization compared to 0.9% sodium chloride), while ceftriaxone and cefotetan reached the highest levels of colonization [19]. This is presumably a result of minimal biliary excretion of cefepime and ceftaroline, and lack of antianaerobic effect of cefepime. The combination of ampicillin plus ceftaroline demonstrated efficacy similar to AC in several in vitro pharmacodynamics studies [22, 23]. A recent in vitro study evaluated high-inoculum *E. faecalis* against ampicillin in combination with ceftaroline, cefepime, and ceftriaxone in an in vitro pharmacodynamic model simulating human concentration-time profiles [22]. The data indicated that AC activity was similar to ampicillin plus ceftaroline and ampicillin plus cefepime. Although

ceftaroline and cefepime are not associated with VRE colonization, their utilization necessitates careful evaluation for safety and development of resistance. Dual β-lactam therapy warrants further investigation, not only for efficacy, but also for the development of resistance and optimal dosing.

Daptomycin Plus β-Lactam Therapy

Daptomycin, a lipopeptide antibiotic with activity against gram-positive bacteria, is of interest in treating enterococcal infections due to its activity against *E. faecalis* and *E. faecium*, including VRE. Recent data have indicated that the combination of daptomycin with β-lactam antibiotics has synergistic effects [24, 25]. Daptomycin activity can be potentiated due to β-lactam–mediated shifts in surface charge of enterococci, causing increased uptake of the drug. While daptomycin combination therapy is more often observed in patients with resistant strains of *E. faecium,* case reports of successful utilization of daptomycin combination therapy in patients with severe *E. faecalis* infections have been published [24, 26].

Sierra-Hoffman et al report using daptomycin (6 mg/kg every 48 hours) in combination with ampicillin (1 g every 6 hours) for the treatment of mitral valve IE in an 89-year-old woman with stage 4 chronic kidney disease [26]. The patient was not a surgical candidate, and received 6 weeks of treatment. Subsequent surveillance blood cultures 2 weeks after cessation of therapy remained negative, and the patient remained alive without signs or symptoms of IE at her 1-year follow up [26]. Although this case report used a 6 mg/kg/day dose, several in vitro, in vivo, and clinical outcome studies suggest that higher doses (10–12 mg/kg/day) are associated with better patient outcomes, particularly in severe infections [27–29]. This suggests that synergistic combinations may be daptomycin dose-sparing. Further studies exploring dosing for synergistic combinations of daptomycin and β-lactams are warranted.

Daptomycin (8 mg/kg/day) plus ceftaroline was successfully used in a case report of a 63-year-old man with recurrent aortic valve endocarditis caused by HLAR *E. faecalis* [24]. Therapy was initiated after patient failed 6 weeks of AC therapy as evidenced by recurrent signs and symptoms of IE, and doubling in vegetation size from 5 mm to 10 mm. This combination was selected due to unpublished observations of synergy against several bacteremia-causing enterococci [24]. A 4-fold reduction in daptomycin MIC, as well as increased daptomycin binding to the enterococcal cell membrane in the presence of ceftaroline, was observed [24]. Smith and colleagues evaluated several β-lactams in combination with daptomycin [25]. Similar to Sakoulas et al, the authors found that ceftaroline demonstrated the greatest daptomycin MIC reduction (average, 19.1 ± 17.6-fold [baseline daptomycin MIC / daptomycin combination MIC]), followed by (in decreasing order) cefepime, ceftriaxone, ampicillin, ertapenem, cefazolin, and cefotaxime [25]. Time-kill studies demonstrated synergy with daptomycin in combination with ceftaroline, ampicillin, ertapenem, ceftriaxone, and cefepime. Inconsistent synergy was noted with daptomycin and cefotaxime. No synergy was observed with daptomycin in combination with cefazolin, possibly due to differences between PBP binding profiles of β-lactam antibiotics [25].

Fosfomycin Combinations

Fosfomycin demonstrated synergy in combination with daptomycin in in vitro studies [30]. However, a follow-up in vivo aortic valve endocarditis study in rats infected with an HLAR, β-lactamase–producing strain of *E. faecalis* demonstrated no difference between the number of valves sterilized by daptomycin alone vs daptomycin plus fosfomycin when administered as a continuous infusion through the left internal jugular vein [31]. More recent in vitro data demonstrated synergy with fosfomycin in combination with ceftriaxone [32], rifampin, tigecycline, and teicoplanin (unavailable in the United States), and antagonism with ampicillin [33]. Teicoplanin is particularly interesting for further investigation as previous in vitro data demonstrate advantage over vancomycin against *E. faecalis* [34]. Despite in vitro synergy, current fosfomycin use is limited to uncomplicated urinary tract infections and should not be used to treat severe infections due to limited systemic absorption when administered orally [35]. Intravenous formulations of fosfomycin are currently unavailable in the United States, but may have future utility. A recent study of in vitro and in vivo (guinea pig model) use of intraperitoneal fosfomycin demonstrated promising activity against both planktonic and biofilm-forming *E. faecalis* when fosfomycin was used in combination with gentamicin and daptomycin [36], demonstrating a need for further investigation.

Miscellaneous Combinations

Several other in vitro and in vivo studies have been conducted evaluating combination therapy [37–40]. Synergistic combinations and their respective study designs are summarized in Table 2. Of particular interest, Arias et al evaluated a β-lactamase stable cephalosporin, ceftobiprole (currently unavailable in the United States), and observed efficacy against bla^{+} and VanB-resistant strains of *E. faecalis* in addition to synergy when used in combination with aminoglycosides [37]. Overall, ceftobiprole demonstrates high affinity for enterococcal PBPs, and requires further exploration in human subjects.

CONCLUSIONS

Although aminoglycoside-containing regimens have been the standard of enterococcal IE treatment, the rise in resistance and availability of less nephrotoxic agents have led to novel treatment options [2]. Double β-lactam therapies have emerged as a novel strategy in the treatment of serious high-inoculum enterococcal infections due to their favorable side effect profiles and tolerability during long-term use. Currently, AC is the only combination β-lactam therapy supported by clinical data for

Table 2. Combination Regimens Against *Enterococcus faecalis* for Future Animal and Human Studies

Synergistic Combination[a]	Study Design	Result	Author (Year)
Human data			
Daptomycin + ampicillin	Patient case report of infective endocarditis	Successful treatment up to follow-up	Sierra-Hoffman et al (2012) [26]
Daptomycin + ceftaroline	Patient case report of infective endocarditis	Successful treatment	Sakoulas et al (2013) [24]
In vitro and in vivo data			
Ampicillin + ceftaroline	Two-compartment simulated endocardial vegetation model	Synergy for dual β-lactam combinations	Werth and Shireman (2017) [23]
Ampicillin + cefepime; ampicillin + ceftaroline	In vitro high-inoculum *Enterococcus faecalis* endocarditis model	Synergy for dual β-lactam combinations	Luther et al (2016) [22]
Ampicillin + ceftaroline	In vitro time-kill experiments	Synergy for dual β-lactam combinations	Werth (2015) [41]
Daptomycin + ceftaroline; daptomycin + ampicillin; daptomycin + ertapenem; daptomycin + ceftriaxone; daptomycin + cefepime	Combination minimum inhibitory concentrations and in vitro time-kill experiments	Synergy demonstrated between daptomycin and β-lactam combinations	Smith et al (2015) [25]
Daptomycin + gentamicin	Stationary-phase in vitro pharmacodynamics model with simulated endocardial vegetation and *Galleria mellonella* survival assays	Synergy demonstrated between daptomycin and gentamicin	Luther et al (2014) [39]
Fosfomycin[b] + rifampin; fosfomycin[b] + tigecycline; fosfomycin[b] + teicoplanin[c]	In vitro time-kill experiments and biofilm assays	Synergy demonstrated between various fosfomycin combinations against planktonic and biofilm-forming bacteria	Tang et al (2013) [33]
Tigecycline + daptomycin; tigecycline + rifampin	In vitro time-kill experiments and in vivo mouse models	Synergy demonstrated with tigecycline combinations of daptomycin and rifampin	Silvestri et al (2012) [40]
Fosfomycin[b] + daptomycin; fosfomycin[b] + gentamicin	In vitro time-kill experiments and foreign-body infection model in guinea pigs	Synergy demonstrated between various fosfomycin combinations against planktonic and biofilm-forming isolates	Oliva et al (2014) [36]
Fosfomycin[b] + ceftriaxone	In vitro assays evaluating fractional inhibitory concentration	Synergy demonstrated with fosfomycin and ceftriaxone	Farina et al (2011) [32]
Ciprofloxacin + rifampin; linezolid + rifampin	In vitro biofilm eradication determined via Calgary Biofilm Device method	Ciprofloxacin and linezolid with rifampin demonstrated antibiofilm activity	Holmberg et al (2012) [38]
Ceftobiprole[c] + gentamicin or streptomycin	In vitro time-kill synergism experiments	Demonstrated synergy between ceftobiprole and aminoglycosides	Arias et al (2007) [37]

[a]Only combinations demonstrating synergy within study included in list.

[b]Currently only dosage form available in the United States is oral with minimal systemic absorption, thereby limited to the treatment of urinary tract infections until intravenous formulations become available.

[c]Unavailable in the United States.

the treatment of IE and bacteremia due to HLAR enterococci. However, AC combination is not without risk (ie, resistance, VRE colonization). Therefore, there is a critical need to investigate novel drug combinations and explore dosing strategies that optimize dose and overall exposure needed to improve efficacy and suppress the emergence of resistance.

Notes

Disclaimer. The views expressed are those of the authors and do not necessarily reflect the position or policy of the US Department of Veterans Affairs.

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