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Advances and updates in antibiotic combination therapy

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Abstract

Introduction: While antibiotic combination therapy remains a common clinical practice, its scientific foundation is fragile. The available evidence is fragmented, biased, and fails to capture the complexity of modern infectious disease scenarios. This perspective reinterprets the role of combination therapy through a critical lens, challenging current dogmas and proposing a pathogen-specific approach, focusing also on severe acute infections.

Areas covered: This Critical Perspective focused on selected studies from 2018 to 2025 identified through a focused PubMed search on the place in therapy and efficacy of antibiotic combinations on main gram-positive (*Streptococcus* spp., *Enterococcus* spp., and *Staphylococcus aureus*) and gram-negative (*Enterobacterales*, *Pseudomonas aeruginosa*, *Acinetobacter baumannii, Stenotrophomonas maltophilia*) pathogens.

Expert opinion: After reviewing the current available literature, in our opinion, a strong indication to use antibiotic combination therapy can be only for specific situations and clinical syndromes (such as endocarditis, toxic shock syndrome due to *S. pyogenes,* or persistent bacteremia due to *S. aureus* and few others). However, especially in severe infections due to gram negatives, clinical trial and strong data are insufficient to draw definite clinical indications. Consequently, further randomized clinical trial should be performed, and they should include new antibiotics to define the potential role of combination therapy.

Keywords: Antimicrobial resistance, Combination therapy; Gram-positive bacteria; Gram-negative bacteria; Multidrug-resistant pathogens.

Article highlights

- The efficacy of antibiotic combination therapy remains a matter of debate for clinicians and researchers.
- Clear benefits are identified only in select conditions, such as endocarditis, toxic shock syndrome, and persistent *S. aureus* bacteremia.
- Current clinical trials provide insufficient evidence to support broad use in severe and resistant Gram-negative infections.
- Additional randomized trials, including novel antibiotics, are crucial to determine the true role and synergy of combination therapy.

1. Introduction

Antibiotic combination therapy refers to the simultaneous administration of two or more antimicrobial agents to treat a single bacterial infection. The rationale behind this strategy lies in the pursuit of synergistic interactions, enhanced bacterial killing, and optimized pharmacokinetic/pharmacodynamic (PK/PD) profiles, particularly in infections involving hard-to-reach anatomical sites or high bacterial burden [1]. In theory, combination regimens may accelerate microbiological clearance, prevent resistance emergence, and provide broader empirical coverage. However, in clinical practice, these outcomes remain more aspirational than consistently demonstrable [2].

Combination therapy has historically found its strongest rationale in the empirical management of life-threatening infections, where broad-spectrum regimens are intended to maximize early efficacy and survival [3]. However, in the contest of empirical combination therapy but also when it comes to targeted therapy, the supporting evidence is inconsistent, fragmented, and often derived from small, retrospective cohorts with significant methodological limitations. One of the major challenges is the extreme heterogeneity in study designs and patient populations, which severely limits comparability and generalizability. Additionally, combination regimens are rarely standardized, making it difficult to define their true added value.

In recent years, combination therapy has also been proposed as a weapon against multidrug-resistant (MDR) bacteria [4], particularly the ESKAPE pathogens (*Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Enterobacter* spp.)—a group at the centre of the antimicrobial resistance (AMR) [5]. Nevertheless, the use of combination therapy is not without controversy. Beyond the lack of robust clinical trial data, concerns persist

regarding toxicity, antagonistic interactions, and the paradoxical risk of accelerating resistance via horizontal gene transfer [6]. Moreover, the increasing availability of novel antimicrobials is likely to reshape future treatment strategies.

This Critical Perspective aims to discuss the role of antibiotic combination therapy in the treatment of acute, severe infections caused by major Gram-positive and Gram-negative pathogens. Our goal is not only to summarize current knowledge but also to challenge assumptions, expose contradictions, and propose future directions in a field where clinical urgency often outpaces evidence.

2. Literature search

In this Critical Perspective we have focused on selected key studies from 2018 to 2025 identified through a focused PubMed search. We critically selected literature based on relevance, clinical impact, and methodological robustness including more than **60 randomized, observational, retrospective and/or prospective cohorts and in vitro studies**. Afterwards, we have structured the discussion in the following sections: (i) combination therapies for infections caused by (i) Gram-positive and (ii) Gram-negative bacteria. Each section was further divided into subsections addressing the major pathogens, summarizing the key evidence available for various infectious syndromes, mainly severe acute infections, including bloodstream infections (BSIs) and organ specific syndromes when relevant.

3. Combination therapy for Gram-positive bacteria

In the context of Gram-positive infections, combination therapy has been explored to enhance efficacy, prevent resistance, and improve clinical outcomes. Given the high prevalence of some type of infections and the available evidence, this section

concentrates on streptococci, enterococci and *Staphylococcus aureus*, which represent the most relevant pathogens in this setting. Main selected articles were summarized in **Table 1**.

3.1. *Streptococcus* species infections

Streptococcus pyogenes, commonly known as Group A beta-haemolytic *Streptococcus* (GAS), is responsible for a wide range of mild to severe infections associated with high mortality, often requiring a dual approach combining early surgical source control and targeted antimicrobial therapy [7]. For the antimicrobial treatment of necrotizing infections caused by GAS, including necrotizing soft tissue infections (NSTI) and toxic shock syndrome (TSS), current guidelines recommend prompt initiation of combination antibiotic regimens based on penicillin and an anti-toxin agent [8]. Among available options, clindamycin remains the most extensively studied anti-toxin agent. Experimental evidence supports its superiority over penicillin in high bacterial inoculum settings, through inhibition of major virulence factors such as streptolysin S, M-protein, and streptococcal pyrogenic exotoxins, and through enhanced opsonization and phagocytosis of GAS. Linezolid is emerging as a potential alternative, especially in the face of increasing clindamycin resistance and concerns about *C. difficile* infections [9]. Although clinical data are still limited, a small retrospective study found comparable outcomes between adjunctive linezolid and clindamycin in severe GAS infections [10]. Favourable clinical responses have also been reported following the addition of linezolid in patients deteriorating despite standard therapy and surgical management [11].

Non-group A beta-haemolytic streptococci (such as *Streptococcus dysgalactiae*) may also cause invasive streptococcal infections but express fewer virulence factors than GAS, and are less commonly associated with necrotizing presentations. A multicenter

retrospective study from the United States showed that adjunctive clindamycin reduced mortality in GAS infections but offered no additional benefit for non-GAS beta-hemolytic streptococci, underscoring the importance of pathogen-specific treatment decisions [12]. Non-β-haemolytic streptococci, such as *S. mitis/oralis, S. gallolyticus, S. sanguinis, S. gordonii,* and *S. mutans* are among the leading causes of infective endocarditis (IE) [13]. In cases of native or prosthetic valve IE caused by penicillin-resistant or high-minimum inhibitory concentration (MIC) strains, the 2023 ESC guidelines recommend high-dose beta-lactams (penicillin G/amoxicillin or ceftriaxone) in combination with gentamicin [14]. However, the utility of gentamicin in this setting is controversial, given its nephrotoxicity, ototoxicity, and the requirement for therapeutic drug monitoring, as well as the limited quality of supporting evidence [15]. The rationale for its use largely stems from preclinical data showing enhanced bactericidal activity in animal models, case reports, and small retrospective non-comparative cohorts. The only randomized controlled trial available in this setting, which compared 4 weeks of ceftriaxone monotherapy with a 2-week regimen of ceftriaxone plus gentamicin in a total of 51 patients, found no significant difference in clinical cure at 3 months [16]. Larger and more recent retrospective cohorts have similarly shown no clinical benefit from adding gentamicin [17].

The debate on combination therapy also extends to bone and joint infections, particularly prosthetic joint infections (PJIs). Rifampicin is frequently used in combination with anti-Gram-positive agents in this context due to its activity against biofilm, which plays a central role in PJI pathogenesis [18]. In PJIs caused by streptococci, the benefit of rifampicin remains uncertain, with only one [21] out of four key studies [19–22] showing a clear advantage over monotherapy. This large multicenter study, evaluating DAIR-treated patients, suggested that early use of

rifampicin in combination with beta-lactams may enhance efficacy against biofilm-forming pathogens and reduce early failure rates within the first 30 days after debridement [21].

Taken together, the data on streptococcal infections reflect a broader challenge in combination therapy: strong theoretical rationale and compelling preclinical evidence often contrast with weak or inconsistent clinical data.

3.2. *Enterococcus* species infections

Enterococci are Gram-positive, facultative anaerobic bacteria which colonize the gastrointestinal tract as a part of natural human intestinal microbiota, but may act as opportunistic pathogens in vulnerable hosts [23]. *Enterococcus faecalis* can cause a large variety of life-threatening invasive diseases, especially in patients with a prosthetic heart valve, transcatheter aortic valve implantation [24], structural abnormalities of the urinary tract and colorectal neoplasms [25,26]. Enterococci are of the leading causes of community-onset and nosocomial BSIs, accounting for 6% and 16% of cases, respectively [27].

Regarding enterococcal IE, that is primarily caused by *Enterococcus faecalis* (90% of cases) [14], in clinical a prolonged (up to 6 weeks) combination regimens is needed for effective eradication [29], due the intrinsic high resistance to antibiotic-induced killing in these organisms. Standard treatment for *E. faecalis* IE includes either a synergistic dual beta-lactam regimen (ampicillin plus ceftriaxone)—which target complementary PBPs—or a combination of a beta-lactam with an aminoglycoside [28]. However, the frequent emergence of high-level aminoglycoside resistance (HLAR) and the nephrotoxicity of gentamicin have shifted practice toward ampicillin–ceftriaxone as the preferred option [30]. Therefore, this is the combination of choice for treating native valve endocarditis and

prosthetic valve endocarditis caused by HLAR *E. faecalis* [31]. However, no recommendation can be done for non-HLAR strains that could also benefit from treatment with ampicillin plus a short course of gentamicin (2 weeks) and randomized trials will be necessary for a solid recommendation [32]. Oral combinations involving amoxicillin with linezolid or fluoroquinolones are being explored as continuation therapy, but their clinical utility in IE is limited and largely investigational [33]. Alternative regimens involving daptomycin, vancomycin, or ceftaroline have been proposed, yet data remain sparse or inconclusive [34]. Ceftobiprole has shown *in vitro* activity against biofilms, and its combination with ampicillin may provide a promising, although still speculative, therapeutic option [35]. Likewise, combinations of beta-lactams with daptomycin or fosfomycin shows potential for linezolid-resistant *E. faecalis*, but require further validation [36].

E. faecium infections, often observed in immunocompromised patients, pose an even greater therapeutic challenge, due to high rates of resistance to beta-lactams and vancomycin. High-dose daptomycin (10–12 mg/kg/day), in combination with beta-lactams (ampicillin, ertapenem, ceftaroline) or fosfomycin, is currently the most rational choice for treating multidrug-resistant and vancomycin-resistant *E. faecium* IE [14]. Although guideline recommendations exist (class IIb, level C), clinical evidence supporting daptomycin combination therapy remains limited, and even less robust for linezolid [14], but daptomycin plus a beta-lactam antibiotic such as ampicillin, ceftaroline, cefepime and ceftriaxone or ertapenem has shown promise in both clinical and *in vitro* studies [37], including for a daptomycin-susceptible Vancomycin Resistant *Enterococcus faecium* (VRE).

Ceftaroline may enhance daptomycin activity by altering bacterial surface charge, thereby facilitating binding and potentiating bactericidal effects [38]. A retrospective review of

patients with VRE BSIs showed that patients receiving high-dose daptomycin plus a beta-lactam had better survival than those receiving low-dose daptomycin [39]. Alternative agents have also been combined with daptomycin, including tigecycline, and fosfomycin. The evidence for the addition of tigecycline is limited to case reports for the treatment of VRE as last-line salvage therapy, while the evidence for the addition of fosfomycin includes both *in vitro* and clinical evidence [40,41].

Linezolid, a the key antimicrobial agents and the only approved for treatment of VRE BSIs, have demonstrated *in vitro* concentration-dependent killing at higher exposures against VRE faecalis isolates with intermediate and resistant MICs (4 mg/mL and ≥8 mg/mL, respectively), showing to be superior to daptomycin in terms of mortality in earlier meta-analyses [38]. However, later meta-analyses have shown comparable mortality rates [42]. For linezolid combination therapy, only a small number of clinical cases related to VRE infection have been published, including gentamicin for persistent VRE faecium BSI and meningitis, rifampicin for meningitis, and doxycycline for a daptomycin-resistant VRE faecium BSI [38] as well as *in vitro* studies [43].

In ampicillin-resistant and vancomycin-susceptible *E. faecium* (EfARSV) uncomplicated BSIs is recommend vancomycin, with daptomycin and linezolid as potential alternatives [44]. The use of daptomycin combined with beta-lactams has been considered, mainly based on *in vitro* data with daptomycin-resistant strains; they may reduce daptomycin MIC and thus allow for the achievement of optimal PK/PD indexes using lower doses of daptomycin [45,46].

The majority of *E. faecium* strains are resistant to ampicillin, and resistance to tetracyclines (except tigecycline), fluoroquinolones, and aminoglycosides is also widespread. Daptomycin and linezolid remain cornerstones, but resistance mechanisms are

increasingly reported [38]. Moreover, vancomycin resistance, largely mediated by plasmid-encoded vanA/vanB genes, remains one of the most concerning resistance patterns in enterococci [47].

Lipoglycopeptide antibiotics showed *in vitro* activity against *E. faecium*, oritavancin against vanA and vanB VRE, whereas dalbavancin and telavancin only against vanB VRE [48].

The combination of oritavancin with fosfomycin could bring several advantages, including the ability to synergise with oritavancin, reducing MICs, to provide a hydrophilic partner drug to treat intravascular infections with a better PK/PD profile and to provide an advantage for biofilm-associated infections. Lagatolla *et al.* showed preclinical evidence to support trials combining oritavancin and fosfomycin [49]. Other authors investigated the potential of oritavancin combinations against VRE. Ceftaroline, ampicillin and ertapenem as partner drugs did not show a reliable synergism as well as ceftriaxone, daptomycin, gentamicin and linezolid as partner drugs, with no synergy detected, apart from gentamicin [38].

Among tetracyclines, tigecycline has good tissue penetration but low serum concentrations, limiting its role as monotherapy for bloodstream infections, limiting its clinical utility as a single agent for the management of VRE BSIs [38]. A 2017 meta-analysis showed higher mortality with tigecycline monotherapy compared to combination therapy [50]. Newer derivatives like eravacycline [52] and omadacycline [51] have overcome classic resistance mechanisms, but evidence in VRE BSI remains preliminary or anecdotal.

In intra-abdominal infections (cIAIs), enterococci may emerge in high-risk patients (e.g. immunocompromised, prior cephalosporins, prosthetic material), and empirical coverage is suggested in such scenarios [53].

Osteoarticular infections caused by enterococci are rare, though they are increasingly reported in PJIs. Daptomycin shows moderate bone penetration and good activity against VRE and combination with rifampicin or beta-lactams may enhance anti-biofilm activity [54].

Linezolid has higher bone penetration than daptomycin, but at a standard dose it may not be sufficient to eradicate biofilms when used alone. Synergy with rifampicin has been observed *in vitro* for *E. faecalis* biofilms [55], though clinical data are limited.

With the increasing presence of vancomycin- and ampicillin- resistant enterococci, novel therapeutic approaches are necessary due to a lack of new antimicrobial agents in the pipeline, including source control and the removal of indwelling lines and devices.

3.3 *Staphylococcus aureus*

Combining antibiotics to treat *S. aureus* is a common practice when managing biofilm-related infections and infections in which an anti-toxin agent is needed, although the dogma of the benefit of rifampicin use in the former is currently being challenged and the evidence behind the latter is of low-quality [56,57].

The last several years have seen a growing body of literature assessing the efficacy of using antibiotic combinations when treating *S. aureus* BSIs, especially in case of persistent BSIs sustained by methicillin-resistant *S. aureus* (MRSA), although its place in therapy and actual efficacy over the standard-of-care is still to be defined [58].

The first consideration when assessing the clinical efficacy of combination treatment in *S. aureus* BSIs (SAB) is the performance of standard-of-care (SOC) monotherapy to which combination treatment is compared. Indeed, the need of finding novel solutions to treat this

serious infection is prompted by the high rate of mortality of SAB, which remained fairly constant in time despite the introduction of new molecules [59]. In case of MRSA, notwithstanding the reduction in costs and increased accessibility of daptomycin, vancomycin remains the standard treatment. In case of methicillin sensitive *S. aureus* (MSSA), the standard of care did not really change in the last decades. The strategy of combining antibiotics to treat SAB has until now been translated into adding anti-staphylococcal antibiotics to SOC more than creating ad-hoc combination treatments. The second, pivotal consideration is which patients would benefit the most from combination treatment, considering the variety of clinical phenotypes related to SAB, an aspect increasingly taken into consideration [60] . In this regard, the need of addressing the efficacy of this strategy within randomized controlled trial (RCT) as opposed to cohort studies would allow to reduce the clinical selection bias related to disease severity and patient characteristics. The third consideration regards outcomes: a positive microbiological outcome (i.e. reduced bacteremia duration) is not necessarily associated with reduction in mortality, to underline the importance of taking into consideration side effects of combining antimicrobials and the baseline characteristics of the population [61].

β-lactams (with or without anti-staphylococcal activity) are the antibiotic class which has been mostly studied has adjunctive treatment to glycol/lipo-peptides in MRSA SAB, also due to the background knowledge on the seesaw effect when using vancomycin [62].

Two RCTs have contributed significantly towards this topic: CAMERA-1 (ACTRN12610000940077, Australian New Zealand Clinical Trials Registry) and CAMERA-2 (NCT02365493, ClinicalTrials.gov). The former assessed the efficacy of adjunctive flucloxacillin (7 days) in MRSA SAB treated with vancomycin (n=31 patients) versus vancomycin alone (n=29) and found an average decrease in bacteremia duration of 1 day

(p=0.06) in the combination group [63].

The CAMERA-2 study was one of the most ambitious trials assessing the efficacy of combining β-lactams (flucloxacillin/cloxacillin or cefazolin) to SOC in MRSA bacteremia. The 99% (n=348/352) of enrolled patients received vancomycin as SOC. The studied was prematurely terminated due to the high rate (23%) of acute kidney injury in the experimental arm [64]. Despite the negative results of CAMERA-2, the potential benefit of combination treatment has led to other trials evaluating the efficacy of combining anti-staphylococcal β-lactams to vancomycin, especially focusing on cefazolin (independently associated with reduced 30-day mortality, aOR 0.31, 95% CI 0.11-0.93) and new anti-staphylococcal cephalosporins (ie ceftaroline), which have a safer renal profile, resulting in inhomogeneous evidence, which is restricted to retrospective cohort studies [65–67].

An increasingly number of studies have explored the combination of daptomycin with β-lactams relying on the recognized synergistic bactericidal activity on MRSA between the two [68]. A particularly interesting combination is daptomycin plus ceftaroline. An open-labeled RCT performed in 2019 was the first (and by now the only) attempt to shed light on the efficacy of this combination: the trial compared daptomycin plus ceftaroline to SOC daptomycin (6-8 mg/kg) or vancomycin in patients with MRSA BSIs. The trial enrolled 40 patients but was early terminated due to the difference in mortality between the experimental arm (0%) and the SOC arms (26%) [69]. Consequently, the best available evidence on the efficacy of this treatment strategy relies on case-series and retrospective cohort studies, the largest one (n=24 daptomycin-ceftaroline combination vs n=113 SOC) dating back to 2020 and showing promising results in terms of 30-day mortality (-80% in a subgroup of patients with endovascular source of infection) and BSIs duration [70]. Another combination explored in clinical practice is daptomycin plus fosfomycin, which

showed promising results in the BACSARM study (2020, NCT01898338). The trial randomized 155 patients to either combination or daptomycin monotherapy; receiving combination treatment was significantly associated with lower 6-week microbiological failure (0 vs 9 patients), lower complicated BSIs (16.2% vs 32.1%; p = .022) but higher rate of side effects (17.6% vs 4.9%) and no significant increase in treatment success [71].

Although most of the effort towards finding new treatment solutions focuses on MRSA, studies assessing combination treatments for MSSA BSIs have been performed and their need is increasingly being recognized. The combination of cloxacillin plus fosfomycin vs cloxacillin monotherapy was assessed in a RCT which enrolled 214 participants randomized 1:1 but was stopped for futility due to the finding that combination treatment did not reach statistical significance in terms of treatment success at day 7 and mortality [72].

Another combination assessed for MSSA BSIs was SOC (cefazolin or cloxacillin) plus daptomycin for 5 days, which did not result in shorter bacteremia or reduced 90-day mortality when compared to SOC monotherapy in a RCT on 104 participants (modified-intention to treat population) [73].

Despite these negative results, the efforts to find possible companion drugs for MSSA SAB treatment are ongoing: the Adjunctive Treatment Domain of the Staphylococcus aureus Network Adaptive Platform (SNAP, NCT05137119) has published the protocol of a RCT that will assess the efficacy of adjunctive clindamycin (and possibly other drugs) to SOC in SAB episodes sustained by both MRSA and MSSA [57].

An open question regards the utility and efficacy of combination treatment when using new anti-staphylococcal drugs that are either approved for SAB (i.e. ceftobiprole), that are

currently used off-label for BSIs (i.e. ceftaroline, dalbavancin, oritavancin) or that have been recently approved for skin and soft tissue infections/community acquired pneumonia (delafloxacin, omadacycline). In these cases, apart from ceftaroline, whose use as an adjunctive treatment has been mentioned in the previous sections, the evidence is either missing or it is still limited to the pre-clinical phase. For ceftobiprole, a study assessing its synergy with FDA-approved drug library identified anti-staphylococcal β-lactams to be the most synergistic compounds against MRSA, particularly cloxacillin, while no or minor synergy was found with daptomycin or vancomycin [74]. Several studies have accessed the *in vitro* synergy of dalbavancin with other anti-staphylococcal compounds, with oxacillin and ceftaroline showing potent synergy, as well as linezolid, without antagonistic effect [75]. For omadacycline evidence is more limited, although a study reported a synergistic activity between omadacycline and rifampin in a biofilm *in vitro* model [76].

The intrinsic heterogeneity of SAB is among the common limitations identified in all trials. Indeed, clinical trials for *S. aureus* BSIs often use a "one size fits all" approach, treating all patients the same regardless of risk. This includes patients from diverse infection sources, making it difficult to identify the best treatment, especially for high-risk endovascular patients. Retrospective analyses are biased, as combination therapy is often given to the highest risk patients outside trial settings. The low percentage of endovascular cases in studies limits their applicability. There is a need to stratify patients based on clinical features and consider new approaches for high-risk groups. However, challenges remain in determining how to do this effectively [58]. Recently, increasing effort is being made on this point by trying to identify clinical sub-phenotypes of *S. aureus* infection associated to worse outcomes (NCT06574399, [60]).

The last unanswered point regards duration of combination treatment: indeed, a balance

must be found between providing the maximum potential benefit of the enhanced treatment while limiting side effects and applying antimicrobial stewardship considerations: in this regard, starting with treatment combination within 24/48 hours in selected, high-risk cases and rapidly de-escalating to monotherapy could provide this balance, although rapidly identifying high-risk patients and markers to guide treatment de-escalation are still lacking [58].

4. Combination therapy for Gram-negative bacteria

Gram-negative bacteria (GNB) pose a major health challenge, especially due to rising antimicrobial resistance worldwide [77]. Treatment options for multidrug-resistant Gram-negative bacteria (MDR-GNB) infections are limited, and mortality is high [78]. Combination therapy have been proposed as a promising strategy, particularly for non-fermenting (NF-GNB) and for empiric treatment, mainly due to the higher mortality reported in severe infection when appropriate therapy is delayed [78]. However, the evidence remains scarce, with studies showing mixed results depending on the pathogen, antibiotic regimen, and patient population [79]. A recent systematic review (134 studies, >11,000 patients, 1945-2018) assessed 92 combination therapies for carbapenem-resistant GNB severe infections, but no clear recommendations could be drawn, due to suboptimal data reporting, heterogeneity, and lack of standardized antibiotic regimens [80]. Given these discrepancies, both IDSA [81] and ESCMID [82] guidelines offer recommendations based on low-certainty evidence (**Table 2**). This section analyzes key studies (2018-2025) of combination therapy for GNB, and main selected articles were summarized in **Table 3**. For the purpose of this Perspective, we excluded as combination therapy novel β-lactams/β-lactamase inhibitors (BL/BLI) regimens, which are conceptually

distinct from true combination—defined as the simultaneous use of at least two active antibiotics.

4.1 Main treatment options for GNB treatment

Before the introduction of novel BL/BLI, combination therapy was chosen for severe MDR-GNB infections, despite its known limited efficacy and high toxicity (such as carbapenems with colistin or aminoglycosides). Nowadays, the treatment landscape has evolved with safer and highly effective agents, transforming monotherapy in the preferred strategy [81,82]. Among past combination therapies, polymyxin-based regimens (such as colistin combined with carbapenems), were explored due to their *in vitro* synergy [83], but two randomized trials (AIDA [84] and OVERCOME [85]) failed to demonstrate clinical benefit in real life. Fosfomycin, remains a potential companion drug due to its broad spectrum, unique mechanism of action, excellent tissue penetration and low antagonism *in vitro* [86]. In a cohort of 363 GNB-BSI, IV-fosfomycin improved 14-day mortality and microbiological eradication, but increased adverse events without affecting 30-day mortality [87]. A review performed in 2024, highlighted fosfomycin's role in combination therapy for MDR-GNB, because of its efficacy in PK/PD studies and the improved stability when associated with PBP-3-targeting β-lactams, even if further research is needed to refine dosing, enhance bacterial killing, and limit resistance development [88]. Regarding new BL/BLI, a meta-analysis on ceftazidime/avibactam (CAZ/AVI) with or without another agent for carbapenem-resistant GNB found similar mortality (RR=1.18, 95% CI 0.88–1.58; p=0.259) and microbiological cure rates (RR=1.04, 95% CI 0.85–1.28; p=0.705) of combination therapy compared to monotherapy [89]. Another meta-analysis confirmed this result (30-days mortality: RR 0.91; 95% CI, 0.71-1.18), and reported a borderline higher microbiological eradication rate (RR 1.15; 95% CI 1.00-1.32) [90]. In addition, a

retrospective study of 303 carbapenem-resistant *Enterobacterales* (CRE)-infected patients assessing combination of CAZ/AVI and an aminoglycoside, reported a protective trend but was more commonly used in critically ill patients, introducing a possible bias [91]. Even cefiderocol's role in combination therapy remains uncertain, but a large Italian multicenter study (n=200) reported combination use in ~50% of cases, particularly for carbapenem-resistant *A. baumannii* (OR 2.56, p=0.047) [92]. In terms of treatment outcome, in another study 30-day mortality difference was not demonstrated between monotherapy (n=70) and combination therapy (n=72) (HR 1.08, p=0.78) in patient with GNB infections [93]. Among recently approved antibiotics, eravacycline was tested *in vitro* against 60 carbapenem-resistant strains showing polymyxin B as the most active combination against *E. coli* (35% synergy), followed by eravacycline-amikacin and eravacycline-imipenem (15%). Against *K. pneumoniae*, eravacycline-polymyxin B showed 30% synergy, followed by eravacycline-amikacin (25%), while for *A. baumannii*, eravacycline-ceftazidime and eravacycline-imipenem exhibited 70% and 50% synergy, respectively [94].

4.2 Carbapenem-resistant *Enterobacterales*

In 2017, the INCREMENT retrospective cohort-study, emphasized the impact of appropriate therapy in patients with BSI due to CRE, showing nearly doubled mortality in those receiving inappropriate therapy, and protection of combination therapy only in patients with high-mortality score. Tigecycline, colistin, and aminoglycosides were commonly used in combination [95]. A more recent study in China found that inappropriate empiric therapy in GNB infections (including NF-GNB) led to 48% mortality, compared to 16% for appropriate one, with protective combination therapy only in patients with sepsis or septic shock [96]. Despite combination strategy did not improve clinical outcomes, a 2021 Dutch cohort study of 626 patients with GNB BSI showed that

combination therapy (e.g. adding short-course aminoglycosides in high-risk patients) can reduce the risk of inappropriate empirical therapy (eight-fold lower in the study) [97]. Among *Enterobacterales,* KPC-producing *Klebsiella pneumoniae* (KPC-Kp) poses a global health threat. CAZ/AVI shows 97% susceptibility, with *in vitro* synergistic effects when combined with amikacin (90% of isolates), partial synergy with colistin (43%), and indifference with tigecycline (67%) [98]. CAZ/AVI plus amikacin or tigecycline enhances antibacterial activity, with aminoglycosides boosting CAZ/AVI efficacy and reducing the resistance development by disrupting protein synthesis and membrane permeability [98]. A 2022 retrospective study showed no difference in 30-day survival between patients with KPC-Kp BSI who received CAZ/AVI alone or in combination. However, the combination with fosfomycin was associated with fewer recurrence of non-bacteraemic KPC-Kp infections, particularly urinary ones [99]. In another retrospective multicenter study of patients with carbapenem-resistant *K. pneumoniae* BSI, CAZ/AVI was administrated in combination therapy in 52.5% (mainly with tigecycline [40.5%] and fosfomycin [31%]), without showing lower mortality (HR 0.71; 95% CI 0.21–2.39, p= 0.672) [100]. A 2023 retrospective study analyzed 11 patients with a KPC-Kp variant (CAZ/AVI-resistant and meropenem-susceptible), treated with meropenem alone or combined with amikacin or fosfomycin, achieving clinical cure. However, 27% developed a CAZ/AVI-susceptible and meropenem-resistant strain. Fosfomycin retained 80% susceptibility, with full synergy with meropenem in 40% of cases. All patients had ICU stays and prior CAZ/AVI exposure, with selection of KPC variants (2–8% of KPC-Kp strains) [101]. Given its higher resistance barrier to *KPC Ω-loop* mutations, meropenem/vaborbactam and imipenem/cilastatin/relebactam could be safer choices for severe infections [102]. Finally, for carbapenemases producing *Enterobacterales* (CPE) like NDMs, VIMs, IMPs, ceftazidime/avibactam in combination with aztreonam is a guidelines' approved

combination therapy because of its efficacy against metallo-beta lactamases (MBL) [81]. However, a single drug combination of aztreonam and avibactam is going to be commercialized [103].

4.3 *Pseudomonas aeruginosa*

β-lactams combination therapy is often chosen as empiric therapy in critically ill patients with risk factors for difficult-to-treat (DTR)-*P. aeruginosa* [104]; however, due to paucity of clinical trials and inconsistent observational studies its definitive role remains controverse. In case of septic shock presentation, a recent multicenter retrospective Italian study reported a lower 30-days all-cause mortality of *P. aeruginosa* BSI (25% vs. 56.8%, *p*=0.007) comparing empirical combination therapy (mainly β-lactams and aminoglycosides) with monotherapy (improved survival in multivariate analysis: aHR 0.38; 95% CI 0.15–0.95; p=0.039). However, in definitive therapy, no survival benefit was observed (HR 0.48; 95% CI 0.17–1.31; p=0.152), supporting de-escalation to a single active agent once susceptibility is confirmed [105]. Conversely, in another study evaluating *P. aeruginosa* BSI with septic shock (7.5% [6/80] and 13.1% [14/107] combination and monotherapy, respectively), a survival benefit was observed in the combination regimen (β-lactams and aminoglycosides, 76%) compared to β-lactams monotherapy, even after age, neutropenia, Pitt score, and inadequate treatment adjustment (HR 0.30, 95% CI 0.13–0.71, p=0.006) [106]. Another retrospective study including different *P. aeruginosa* infections, did not observe better survival rates, neither in patients with hypotension (p=0.876) [107]. Specifically addressing carbapenem-resistant *P. aeruginosa,* a retrospective cohort study reported a potential benefit of combination therapy, especially for patients with high SOFA score and Charlson comorbidity index, but mortality rates did not differ between groups [108]. As far as regards new BL/BLI, ceftolozane/tazobactam

(CEF/TAZ) is the preferred regimen for DTR-*P. aeruginosa*, but clinical trials comparing monotherapy with combination therapy are lacking. Current available evidence comes from observational studies that did not show lower mortality with combination therapy; a retrospective cohort study found 66.7% cure rates at day 7 for CEF/TAZ alone vs 60% with CEF/TAZ plus colistin or aminoglycoside, without differences in resistance development [109]. Remarkably, in an observational study of DTR-*P. aeruginosa* infections treated with CAZ/AVI, combination therapy was associated with a lower clinical cure rate at 14 days compared to monotherapy (aOR: 0.02; 95% CI: 0.01-0.38; P = 0.009) [110]. Moreover, in a study evaluating combination treatment in GNB-pneumonia (mainly administrated in NF-GNB, 49.2% vs. 34.4%, p=0.005; and used in 106 *P. aeruginosa* cases), no difference in all-cause mortality at day 28 was observed (32.9% vs. 28.5%, p=0.36) [111]. Similarly, a post-hoc analysis of the RCT iDIAPASON trial evaluated monotherapy (n=94) versus combination therapy (n=75) in *P. aeruginosa*-VAP, showing no clinical benefits in terms of in-hospital mortality (18.1% vs. 26.7%, p= 0.1801), recurrence VAP rates (p=0.3190) or subsequent acquisition of MDR bacteria (p=0.7372) [112].

Due to these conflicting results, both IDSA [81] and ESCMID guidelines [82] do not recommend routine combination therapy for DTR *P. aeruginosa,* that can be considered only in selected cases (e.g lack of availability/activity of any β-lactam agent).

4.4 *Acinetobacter baumannii*

For carbapenem-resistant *Acinetobacter baumannii* (CRAB), the role of combination therapy has been particularly debated, especially due to the lack of demonstrated efficacy of a single agent used in monotherapy [81]. The combination therapy has been proposed based on synergistic interactions and enhanced bactericidal activity *in vitro* between polymyxins and other antibiotics, including carbapenem [83], and rifampicin [113];

however its clinical utility of remains controversial. Despite new antibiotic treatment options, polymyxins are still considered for CRAB infections treatment, but there are uncertainties regarding dosage, PK/PD issues, toxicity and their effective role in combination therapy. Two studies performed in 2019 and 2020, comparing combination therapy of colistin with meropenem in CRAB BSI revealed different outcomes: one observed a trend toward lower mortality and higher clinical success in monotherapy, especially in patients with a Pitt score ≥4 [114], the other did not found differences in effectiveness and nephrotoxicity [115]. Regarding colistin-rifampicin association for CRAB pneumonia the most recent RCT (2019) showed no clinical or microbiological benefit [116]. Colistin-ampicillin/sulbactam [117] was also tested in an RCT, showing no survival benefit but reduced clinical failure [117]. In a prospective multicenter study evaluating CRAB-pneumonia, fosfomycin-containing regimens were associated with higher 30-day survival (HR 0.04, CI 95% 0.01–0.13, p<0.001) [118] while evidence from direct treatment comparisons suggest that patients who received combination therapy with fosfomycin for severe infections, had similar or improved outcomes compared with monotherapy and other combinations [87,88]. Regarding the effectiveness of cefiderocol in CRAB infections, an Italian study including 38 patients (N=29 monotherapy, n=11 combination, including ampicillin/sulbactam in 45.4% cases), did not show differences in 30-days mortality (48.3% vs 45.5%, p=0.87), clinical failure (27.6% vs 45.5%, p=0.06) and microbiological failure at the end of treatment (13.8% vs 0%, p=0.19) [119]. Finally, sulbactam/durlobactam, a bactericidal BL/BLI combination, represent a promising option for severe CRAB infections [120].

In conclusion, there is very low evidence supporting combination therapy for CRAB, leading to divergent international guidelines' recommendations. The IDSA guidelines recommend combination therapy with at least two agents until clinical improvement is

reached, due to limited clinical data on single agents effectiveness [81]. In contrast, ESCMID suggest combination only for severe, high-risk infections, with a conditional recommendation and very low-certainty [82]. Potential combination drugs, alongside high-dose ampicillin-sulbactam, include tetracycline derivatives (especially minocycline), polymyxin B, aminoglycosides, or cefiderocol [81,82].

4.5 *Stenotrophomonas maltophilia*

Stenotrophomonas maltophilia infections are primarily treated with trimethoprim/sulfamethoxazole (TMP-SMX). Data comparing monotherapy and combination therapy for *S. maltophilia* are conflicting and limited to observational studies with small sample size, patient heterogeneity, and varying treatment combination. A multicenter study on *S. maltophilia* HAP did not find correlation between mortality and combination therapy (used in 59.4% of cases) [121]. Another study comparing monotherapy with TMP/SMX (n=214) and combination therapy (n=38, mainly including as the primary agent TMP/SMX) showed no difference in clinical response after 7 days (39.7% vs. 47.4%, p=0.38), but higher 30-day mortality in the combination one (p=0.03) [122]. A recent multicenter study (307 cases of *S. maltophilia* pneumonia) showed no reduction in 30-day mortality with combination therapy (n=171, mainly TMP/SMX and fluoroquinolone) versus monotherapy (n=136) [123]. Combination treatment with cefiderocol and other agents (minocycline, TMP-SMX, and fluoroquinolones) was explored based on *in vitro* data showing increased efficacy on MDR-*S. maltophilia* [124]. Its use in clinical practice has been evaluated in a multicenter cohort comparing monotherapy (n=330) and combination therapy (n=77) in *S. maltophilia* infections (72% pneumonia). The study showed no significant difference in clinical cure (55% vs 65%, p=0.108; OR, 0.66; 95% CI, 0.38–1.13) and in-hospital mortality (52% vs 49%; p=0.732; OR, 1.09; 95%

CI, 0.66–1.79). However, patients who received monotherapy had a lower risk of 30-day mortality (adjusted OR, 0.45; 95% CI, 0.22– 0.90) and acute kidney injury (9% vs 18%; p = 0.027; OR, 0.47; 95% CI, 0.23–0.93) [125].

Despite these limited and conflicting data, IDSA guidelines suggest combination therapy with at least two active agents (e.g., cefiderocol, minocycline, TMP-SMX, or levofloxacin) until clinical improvement, due to insufficient data for supporting single agent use. Alternatively, a combination of CAZ/AVI and aztreonam can be considered, though clinical data supporting this combination are limited [81].

5. Conclusions

In conclusion, while antibiotic combination therapy remains a common approach in the management of severe infections, robust evidence supports its routine use only in selected clinical scenarios and pathogens. The heterogeneity of data, lack of standardized regimens, and frequent reliance on retrospective analyses hinder broad generalizability. Novel antibiotics have further reshaped the therapeutic landscape, challenging the added value of combinations. Future efforts should prioritize randomized, pathogen- and syndrome-specific trials to clarify when combination therapy truly offers clinical benefit—beyond theoretical synergy. A more nuanced, evidence-driven approach is urgently needed to optimize patient outcomes and antimicrobial stewardship.

6. Expert opinion

Antibiotic therapy is a cornerstone of modern medicine, playing a critical role in treating bacterial infections. While monotherapy is often an effective standard of care, combination antibiotic therapy is frequently employed. The common drivers leading to this approach

include the need to enhance efficacy, prevent resistance, broaden spectrum coverage, and achieve synergistic effects.

By reviewing the evidence present in the literature on antibiotic combination treatment among the main Gram-positive and Gram-negative bacteria, we found some generalizable advantages: (i) achieving synergistic effects enhancing efficacy (synergy): some antibiotic combinations work synergistically, leading to greater bacterial killing than either drug alone (e.g., β-lactam + aminoglycoside); (ii) broadening spectrum of coverage: helps treat polymicrobial infections or cases where the causative pathogen is unknown; (iii) preventing and overcoming antibiotic resistance **by targeting multiple essential pathways simultaneously**: using multiple antibiotics can reduce the likelihood of resistance emergence, especially in difficult-to-treat bacteria (e.g., *Pseudomonas aeruginosa* or *Enterobacteriaceae*); (iv) treatment of severe infections: recommended in life-threatening infections like sepsis and endocarditis, where rapid bacterial clearance is crucial; (v) overcoming intrinsic resistance mechanisms: some bacteria possess resistance mechanisms that can be bypassed with a second antibiotic (e.g., β-lactamase inhibitors combined with β-lactams); (vi) potential cost savings when infections are rapidly and appropriately treated reducing the duration therapy and the hospitalization time.

On the other end, drawbacks of combination treatment are also commonly identified within studies and include: (i) increased risk of toxicity: some combinations can lead to nephrotoxicity or ototoxicity; (ii) higher cost: more expensive than monotherapy due to multiple drugs being used; (iii) increased risk of superinfection: broad-spectrum combinations can disrupt normal flora, leading to infections by resistant organisms such as *Clostridioides difficile*; (iv) selection for multidrug resistance (MDR) – inappropriate use of combination therapy can drive resistance; (v) antagonistic interactions: some antibiotic

combinations may reduce efficacy rather than enhance it; (vi) pharmacokinetic/pharmacodynamic challenges: different antibiotics may have different half-lives, dosing schedules, or interactions that complicate treatment (**Figure 1**).

As described in this Critical Perspective, combination antibiotic therapy is widely used in various clinical scenarios, including severe gram-negative infections and in serious gram-positive infections i.e. severe streptococcal infections, enterococcal endocarditis and in SAB. However, the evidence remains scarce; the data derived from mostly retrospective or prospective cohort studies showing mixed results depending on the pathogen, antibiotics and patient population without final clear recommendations.

One of the major step forward to cover the role of the combination antibiotic therapy is the development of risk-based approaches to determine which patient populations might benefit most from this approach. Instead of a one-size-fits-all strategy, this framework considers variables such as severity of illness, immune status, prior colonization with resistant organisms, and the likelihood of polymicrobial infection. For example, critically ill patients with septic shock, immunocompromised hosts, or those with suspected MDR infections may warrant early empirical combination therapy, while more stable patients may not benefit and could even be harmed by increased toxicity or disruption of the microbiome.

Looking ahead, future decision models are expected to be increasingly integrated with rapid microbiological diagnostics and immunological profiling. Rapid molecular testing can now identify resistance genes and specific pathogens within hours, allowing for earlier de-escalation or escalation of therapy. When coupled with immunological stratification—such as host transcriptomics or biomarker profiling—clinicians could tailor antimicrobial strategies not only to the pathogen, but also to the host's immune trajectory. This

personalized approach could optimize the timing, intensity, and duration of combination therapy, while minimizing unnecessary exposure.

However, current clinical guidelines remain largely driven by retrospective cohort studies, which often suffer from confounding and selection bias. These studies may not reflect the complexity of real-world decision-making and frequently lack granularity on host-pathogen interactions. As a result, guidelines may overgeneralize recommendations, failing to account for individual patient characteristics or dynamic clinical scenarios.

To overcome these limitations, there is a pressing need for prospective, randomized clinical trials that stratify patients not only by pathogen species or resistance patterns, but also by clinical phenotypes and host factors. For instance, trials could investigate the benefit of combination therapy in patients with high inflammatory states versus immunoparalysis, or in those with different organ dysfunction profiles. This stratification would enable more nuanced conclusions and better guide clinical practice.

In summary, the field of antibiotic combination therapy is moving toward more individualized, data-driven approaches. Integrating risk-based decision-making, rapid diagnostics, and immunological insights—while moving beyond retrospective data toward rigorously designed prospective studies—will be essential to optimize outcomes and stewardship in both Gram-positive and Gram-negative infections.

In these last years, the phenomenon of phage–antibiotic synergy (PAS) has many benefits including more effective elimination of bacteria than the separate use of the agents [126]. Phage therapy is an emerging therapeutic approach for treating bacterial infections that do not respond to traditional antibiotics. The potential combination of phage

therapy to systemic antibiotics to treat a patient with recurrent infections might be solving approach for clinical management [127]. PAS combination therapy should be a promising therapeutic alternative, which has gained renewed attention as a potential solution to the escalating crisis of antibiotic resistance [128]. Until these novel options enter the clinical arena, it will be up to physicians to make the most efficient use of currently available drugs against these MDR organisms [129].

Combination antibiotic therapy plays a crucial role in managing infections due to Gram-positive and Gram-negative infections. However, its use should be guided by evidence-based practices to minimize toxicity and resistance risks. As bacterial resistance continues to evolve, combination therapy will remain an essential tool in combating difficult-to-treat infections [130-132]

Over the next years, major efforts are expected to be made in every step of severe bacterial infection management, due to the most studies available are old and retrospective. Further RCT are urgently required to optimize clinical outcomes and to establish clear indications for combination therapy, particularly in critically ill patients.

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Table 1- ~~Main recent studies (from 2018 to 2025) addressing combination treatment strategies for Gram-positive pathogens~~

Study	Type of Study	Combination regimen	Type of infection/pathogen	Results	Conclusions on benefit of CT
Streptococcus spp.					
Eschriuela-Vidal *et al.*, 2023 [17]	Retrospective multicentre study	Monotherapy (n=415, cephalosporin in 331 cases) vs. β-lactams + aminoglycoside (n=499)	IE due to viridans and gallolyticus group streptococci with intermediate susceptibility to penicillin	In-hospital mortality was 11.9%, and 190 (20.9%) patients developed acute kidney injury. **Monotherapy was not associated with in-hospital mortality** (OR: 1.01; 95% CI 0.26–3.96; p=0.982)	**Findings support the use of cephalosporin monotherapy in order to avoid nephrotoxicity without adversely affecting patient outcomes**
Babiker *et al*., 2021 [12]	Retrospective multicentre cohort study	β-lactams + clindamycin vs. β-lactams alone	Invasive infection caused by GAS or by NABS	**GAS cohort**: **lower in-hospital mortality in CT** (18 [6·5%] of 277 patients) than monotherapy (55 [11·0%] of 500 patients; aOR 0·44 [95% CI 0·23–0·81]). **NABS cohort**: **higher in-hospital mortality in CT** (ten [9·8%] of 102) than monotherapy (nine [4·6%] of 193), but this difference was not significant (aOR 2·60 [0·94–7·52])	**Addition of clindamycin to BLA therapy reduced mortality in patients with GAS infections, whereas this benefit was not observed in infections caused NABS**
Heil *et al*., 2021 [10]	Retrospective single center cohort study	Empiric therapy + clindamycin vs. empiric therapy + linezolid	GAS isolated from blood and/or tissue cultures	**No difference in reduction of SOFA score** over the first 72 hours in patients receiving clindamycin vs. linezolid. In the entire cohort (n=26, clindamycin; n=29, linezolid), **no difference in inpatient mortality** (2% vs 1%) or any secondary outcomes.	**There was no difference in reduction of critical illness among patients treated with adjunctive clindamycin vs linezolid.**
Enterococcus spp.					
Antonello *et al.*, 2024 [43] **23/11/2025 05:16:00**	Systematic review *in vitro* studies	Linezolid synergistic properties *in vitro*	*Enterococcus* spp.	*Enterococcus spp*. isolates (n=206). The most frequent interaction was indifferent effect (247/343, 72%). The highest	**Overall limited synergistic in vitro properties of linezolid with other**

				synergism rates: linezolid in combination with rifampin (10/49, 20.4% of interactions) and fosfomycin (16/84, 19.0%, of interactions). Antagonistic effect accounted for 7/343 (2.0%) of total interactions.	**antibiotics**
Giuliano *et al.,* 2023 [27]	Retrospective study	Ampicillin in combination with ceftobiprole (n=22)	*E. faecalis* invasive infections	Clinical success rate: 81% Microbiological cure: 86% Well- tolerated antimicrobial regimen	**Reasonable option for the treatment of severe invasive infections**
Tseng *et al.,* 2023 [41]	Observational study	Total n=224: daptomycin monotherapy (n=176) vs. daptomycin + fosfomycin (n=48)	VRE BSI	**Higher in-hospital mortality in monotherapy:** 77.3% vs. CT 47.9% (p<0.001). Multivariable logistic regression analysis predicted lower mortality with fosfomycin CT (aOR: 0.35; 95% CI 0.17–0.73; p=0.005)	**The combination of high-dose daptomycin with fosfomycin improved the survival rate of patients with VRE BSI compared to daptomycin alone**
Maurille *et al.,* 2023 [55]	Retrospective cohort study	Total n=36: amoxicillin (n=15), rifampicin (n=10), linezolid (n=9) and/or FLQ (n=11)	Prosthetic joint- or osteosynthesis-infections caused by enterococci from 2013 to 2020	Clinical success at 1 year was 67% (18/27). The only variable statistically associated with a decreased risk of clinical failure was a duration of antibiotic therapy of 12 weeks (p=0.04).	**A better outcome was not demonstrated for patients with combination therapy and rifampicin use**
Mirna *et al.,* 2022 [30]	A meta-analysis of comparative trials	Ampicillin + ceftriaxone (AC) vs. ampicillin + gentamicin (AG)	*E.faecalis* IE	**Treatment with AC was non-inferior to AG**: no significant differences in-hospital mortality, 3-month mortality, relapses or treatment failure. **AC was associated with a lower prevalence of nephrotoxicity**	**Treatment with AC non-inferior to treatment with AG**

				(OR 0.45 [0.26-0.77], p=0.0182) **and drug withdrawal** due to **AEs** (OR 0.11 [0.03-0.46], p=0.0160)	
Chuang *et al.,* 2022 [41]	Prospective observational multicentre study	Daptomycin+ fosfomycin (n=106)	VRE BSI	Overall 28-day mortality: 40.6% Independent of Charlson comorbidity index and Pitt bacteraemia score, fosfomycin MIC ≥128 mg/L [aOR = 3.05; 95% CI = 1.01–9.19; p=0.047] and daptomycin dose (aOR: 0.64; 95% CI 0.43–0.97;p=0.04) predicted mortality	**Higher daptomycin dose and susceptibility to fosfomycin were independently associated with lower mortality in patients with VRE BSI**
Lagatolla *et al.,* 2022 [49]	*In vitro* and *in vivo* study	vanA (n=5) and vanB (n=5) clinical isolates of E. *faecium* using oritavancin + fosfomycin both *in vitro* (checkerboard, time killing) and *in vivo* (Galleria mellonella)	VRE BSI	Synergistic effect in 80% of isolates and an additive effect in the remaining isolates. The CT restored fosfomycin susceptibility in 85% of fosfomycin-resistant isolates. CT of oritavancin and fosfomycin provided a CFU/mL reduction > 2 $\log_{10}$ and prevented the bacterial regrowth seen after 8–24 h. The CT in a biofilm assay showed a strong synergistic effect in one isolate and an additive effect in the other. *In vivo* a higher survival rate of the larvae treated with CT	**Preclinical evidence to support trials combining oritavancin and 44fosfomycin for VRE BSI in humans, even when biofilm is involved.**
Iversen *et al*., 2019 [33]	Randomized, noninferiority, multicenter trial **Partial Oral Treatment of Endocarditis (POET)**	To continue IV treatment (n=199 patients) or to switch to OAT oral antibiotic treatment (n=201). OAT for E. faecalis n=51: Amoxicillin + moxifloxacin (n=24), amoxicillin + linezolid (n=13), amoxicillin + rifampicin (n=6) , moxifloxacin + linezolid (n=5), amoxicillin + ciprofloxacin (n=2), amoxicillin	*E. faecalis* ampicillin susceptible (MIC ≤ 4 mg/L) IE (left side of the heart on native or prosthetic valves)	The primary composite outcome: all-cause mortality: IV treatment 2/13 (15%), oral 1/7 (14%) Relapse of positive blood culture: IV treatment 3/5 (60%), oral treatment 3/5 (60%)	**Changing to oral antibiotic was noninferior to continued IV antibiotic treatment**

		(n=1)			
Pericàs *et al.*, 2018 [29]	Retrospective from a prospectively collected cohort	Ampicillin + gentamicin (AG) (n=32; n=9 for 4weeks) vs. ampicillin + ceftriaxone (AC) (n=46, n=14 for 4weeks)	*E.faecalis* IE	**No significant differences** in 1-year mortality according to the type of treatment (31% and 24% in AG and AC, respectively;p= 0.646) or duration (26% and 27% at 4 and 6 weeks, respectively; p=0.863). **Relapses were more frequent among survivors treated for 4 weeks than for 6 weeks:** (3/18 [17%] at 4 weeks and 1/41 [2%] at 6 weeks; p=0.045)	**Similar clinical outcome and efficacy and safety** A 4-week course of antibiotic treatment might not be suitable
Chuang *et al.*, 2018 [39]	Prospective observational cohort study (2010–2015)	Daptomycin (DAP) (n=114) vs. DAP + β-lactams (BLA) (n=87)	VRE BSI	**No differences in mortality** between the DAP and DAP + BLA groups on univariable analysis (10/27 vs. 34/87, p=0.85) **Subgroup analysis DAP MICs ≤2 mg/L: DAP + BLA lower mortality** (aHR, 0.23; 95% [CI], 0.06–0.93;p=0.04). **High-dose (≥9 mg/kg) DAP + BLA had a better survival** than those receiving low-dose DAP alone (aHR = 5.16), low-dose DAP + BLA (aHR = 5.39), and high-dose DAP alone (aHR = 19.01) (p<0.05 for all comparisons).	**Benefit use of high-dose DAP + BLA for treatment of VRE-BSI**
Staphylococcus aureus					
CAMERA-1 (ACTRN12610000940077) [63]	Randomized controlled trial	Vancomycin ± flucloxacillin	MRSA BSI	**Lower BSI duration in CT**: 3.0 days (CT) vs. 4.0 days (monotherapy) (p=0.06). **No significant difference in mortality.**	**No significant impact on mortality; potential for bacteremia duration reduction**
CAMERA-2 (NCT02365493) [64]	Randomized controlled trial	Vancomycin ± flucloxacillin/cloxacillin/cefazolin	MRSA BSI	99% (n=348/352) received vancomycin. Trial stopped early due to acute kidney failure in 23% of combination group vs. 6% in control (p<0.001). **No significant**	**Increased nephrotoxicity without mortality benefit**

				reduction in mortality.	
Daptomycin + Ceftaroline RCT (NCT02660346) [69]	Open-label randomized controlled trial	Daptomycin ± ceftaroline	MRSA BSI	Mortality: 0% (combination) vs. 26% (SOC) (p=0.02). Trial early termianted	**Suggests benefit, but underpowered study; further trials needed**
BACSARM (NCT01898338) [71]	Randomized controlled trial	Daptomycin ± fosfomycin	MRSA BSI	Microbiological failure: 0% (CT) vs. 9 patients (monotherapy). **Lower rates of complicated bacteremia in CT:** 16.2% (CT) vs. 32.1% (monotherapy) (p=0.022). Side effects: 17.6% (CT) vs. 4.9% (monotherapy)	**Promising microbiological benefit but higher side effects**
MSSA Combination Study [72]	Randomized controlled trial	Cloxacillin ± fosfomycin	MSSA BSI	214 patients enrolled. Trial stopped early due to futility. **No significant difference in treatment success** at day 7 (p>0.05).	**No clear benefits over monotherapy**
MSSA Combination Study (Cefazolin/Cloxacillin + Daptomycin) [73]	Randomized controlled trial	Cefazolin/cloxacillin ± daptomycin	MSSA BSI	**No significant difference in bacteremia duration** (p=0.3) **or 90-day mortality** (p=0.6).	**No clear advantage of combination therapy**
SNAP (NCT05137119) [57]	Adaptive platform trial	Standard-of-care ± clindamycin	MRSA and MSSA BSI	Ongoing study	**Potential to clarify the role of combination therapy in *S. aureus* bacteremia**
Ceftobiprole Synergy Study [74]	Pre-clinical study	Ceftobiprole ± beta-lactams	MRSA	Cloxacillin as the most synergistic compound. No or minor synergy with daptomycin/vancomycin.	**Beta-lactams may enhance ceftobiprole efficacy**
Dalbavancin Synergy Study [75]	Pre-clinical study	Dalbavancin ± anti-staphylococcal antibiotics	*S. aureus*	Synergy observed with oxacillin, ceftaroline, and linezolid. No antagonistic effect with linezolid.	**Potential combination options for further study**
Omadacycline Biofilm Study [76]	Pre-clinical study	Omadacycline ± rifampin	*S. aureus* biofilm model	Synergistic activity observed between omadacycline and rifampin in biofilm model.	**Possible use in biofilm-related infections**

Abbreviations: **aHR:** adjusted hazard ratio; **aOR:** adjusted odds ratio; **BSI:** blood-stream infections; **CT**: combination therapy, **FLQ**: fluoroquinolones; **GAS:** Group A beta-haemolytic streptococci; **IE:** infective endocarditis**; IV:** intravenous**; MRSA:** methicillin-resistant *S. aureus*; **MSSA:** Methicillin-sensitive *S.*

aureus; **NABS**: Non-group A beta-hemolytic streptococci; **OAT**: oral antibiotic treatment; **OR:** odds ratio; **PS**: propensity score; **RCT**: randomized clinical trial; **SOFA**: Sequential Organ Failure Assessment; **VRE**: vancomycin-resistant enterococci

Table 2 - ~~Comparison of current main international guidelines recommendations on combination therapy strategies for Gram negative pathogens~~

Pathogen	IDSA	ESCMID
Carbapenem-resistant Enterobacterales	◊ MEM/VAB, CAZ/AVI and IMI/REL are preferred treatment options for KPC-producing CRE; ◊ CAZ/AVI in combination with aztreonam or cefiderocol as monotherapy are preferred options for MBL-producing *Enterobacterales;* ◊ CAZ/AVI is the preferred treatment for OXA-48 producing *Enterobacterales*; ◊ CT is not suggested for infection caused by CRE	◊ CRE infections susceptible to CAZ/AVI, MEM/VAB or cefiderocol, CT is not recommended; ◊ Severe infections caused by CRE producing MBL, CAZ/AVI in combination with aztreonam; ◊ Severe infections susceptible in vitro only to polymixins, AMG, tigecycline or fosfomycin, treatment with more the one active drug *in vitro* is recommended; ◊ Carbapenem-based combination therapy is not recommended unless MIC is <8 ml/L and BLBLI are not available;
DTR-*Pseudomonas aeruginosa*	◊ CT is not suggested if susceptibility to ceftolozane/tazobactam, ceftazidime/avibactam, imipenem-cilastatin/relebactam, or cefiderocol has been confirmed	◊ Insufficient data to recommend CT with new BL/BLI or cefiderocol; ◊ When treating severe infections treated with AMG, fosfomycin or polymyxins: CT of 2 *in vitro*-active agents; ◊ Monotherapy for non-severe infections;
Carbapenem-resistant *Acinetobacter baumannii*	◊ CT with at least 2 agents, whenever possible, is suggested, at least until clinical improvement is observed, because of the limited clinical data supporting any single antibiotic agent.	◊ Not recommended polymyxin-meropenem CT and polymyxin-rifampin CT; ◊ For severe and high-risk CRAB infections, suggested CT including 2 *in vitro*-active agents (polymyxin, AMG, tigecycline, sulbactam combinations); ◊ For patients with CRAB infections with a meropenem MIC <8 mg/L, consider carbapenem CT, using high-dose extended-infusion carbapenem dosing
MDR-*Stenotrophomonas maltophilia*	◊ Recommended: 1. CT of 2 of the following agents: cefiderocol, minocycline, TMP-SMX, or levofloxacin or 2. CT of ceftazidime-avibactam and aztreonam.	NA

Abbreviations: **AMG**: aminoglycosides; **BL/BLI*:*** β-lactam/β-lactamase inhibitors; **CAZ/AVI**: ceftazidime/avibactam; **CRAB**: carbapenem-resistant *Acinetobacter baumannii*; **CRE**: carbapenem-resistant *Enterobacterales;* **CT**: combination therapy; **DRT:** difficult-to-treat; **IMI/REL:** imipenem-cilastatin/relebactam**; MEM/VAB;** meropenem/vaborbactam**; MBL:** metallo-beta-lactamases**; MDR:** multi-drug resistant; **NA:** not applicable.

Table 3- ~~Main recent studies (from 2018 to 2025) addressing combination treatment strategies for Gram-negative pathogens~~

Study	Type of Study	Combination regimen	Type of infection/ pathogen	Results	Conclusions: on benefit of CT,
Multiple GNB involved					
OVERCOME trial, 2023 [85]	RCT	Colistin and placebo (n=213) vs. colistin and meropenem (n=210)	BSI and/or Pneumonia; CRAB: 165 vs. 164 CRE: 34 vs. 35 CRPA: 23 vs. 20	**No difference in 28d mortality:** 43 vs. 37%;p=0.17; **No difference in clinical failure**: 65 vs. 58%; difference, 6.8 percentage points; 95% CI, 23.1 to 16.6); **No difference in microbiologic cure**: 65 vs. 60%; difference, 4.8 percentage points; 95% CI, 25.6 to 15.2).	**No benefit**
AIDA trial, 2018 [84]	RCT	Colistin (n=198) vs. colistin and meropenem (n=208)	BSI, VAP, HAP or UTI; CRAB: 151 vs. 161 CRE: 34 vs. 39 CRPA: 13 vs. 8	**No difference in clinical success** 14d after randomization: RR for failure with CT of 0.93; risk difference: –5.73% (–13.89 to 2.43); **No difference in 28d all-cause mortality**: (86/198 [43%] vs. 94/208 [45%]); **No survival benefit observed** (log rank p=0.66).	**No benefit**
Barbier *et al*., 2024 [111]	Prospective observational study	Monotherapy vs CT (β-lactams 95.1% as pivotal drugs)	Pneumonia; GNB (CT more frequently in NF-GNB, 49.2% vs. 34.4%, p=0.005)	**No difference in 28d all-cause mortality:** 28.5% vs. 32.9% (p=0.36). Cumulative survival overtime did not significantly differ (IPTW HR 1.07; 95% CI, 0.74–1.55; p=0.71); CT exerted no independent effect on outcome, in IPTW analysis (aOR 1.14; 95% CI, 0.73–1.77; p=0.56).	**No benefit**
Belati *et al*., 2024 [87]	Retrospective observational study	363 patients (CT with IV fosfomycin, n=98)	GNB BSI;	**No reduction in crude mortality for fosfomycin-CT** (21% vs 29%, P = 0.147). On multivariable Cox-regression, **fosfomycin-CT resulted in protection for mortality** (aHR 0.51, 95% CI 0.28–0.92), but not other combo-therapies (HR 0.69, 95% CI 0.44–1.16). fosfomycin-CT benefit in severe infections (SOFA > 6, PITT ≥ 4) and if IV-fosfomycin was initiated ≤24 hours.	**Uncertain benefit on mortality, possible benefit in severe infections**
Piccica *et al*., 2023 [93]	Retrospective observational study	Cefiderocol monotherapy (n=70) and CT (=72)	BSI, Pneumonia, IAI, UTI, ABSSSI; *A. baumannii* (63%), *P. aeruginosa* (19%), *K. pneumoniae* (16%).	**No difference in 30-days mortality:** 33% vs. 40%, p=0.39, even when adjusted with IPTW-adjusted Cox regression (HR 1.08, 95% CI 0.61–1.92, p=0.78); **No difference in microbiological cure**: 45.8% vs 52.3%. p=0.68.	**No benefit**
Deelen *et al*., 2021 [97]	Prospective cohort study	626 β-lactams therapy (CT with AMG, n=156)	BSI, Pneumonia, IAI, UTI, ABSSSI; GNB	**No difference in 30-days mortality:** 13.6% in CT with AMG vs 17.3%; aOR 1.57 (0.84-2.93)	**No benefit**
Enterobacterales					
Bulman *et al.,* 2024 [91]	Retrospective cohort study	303 patients treated with CAZ/AVI (CT, n=77)	BSI, Pneumonia, UTI and others; CRE	**CT with an AMG prior to initiation of CAZ/AVI was independently associated with 30-day mortality:** aOR 4.512, 95% CI 1.797–11.327	**No benefit**
Giacobbe *et*	Prospective	426 patients (CT, n=83)	*K. pneumoniae* BSI	**No difference in 30d mortality (**HR 0.53; 95% CI 0.12–	**No benefit**

***al.*, 2023** [130]	observational study			2.37, p=0.531); Appropriate CAZ/AVI-based CT was not associated with reduced mortality compared to CAZ/AVI monotherapy (HR 0.71; 95% CI 0.21–2.39, p=0.672).	
Pseudomonas aeruginosa					
Vena *et al.*, 2024 [105]	Retrospective observational study	1. Empirical monotherapy (n=74) vs. CT (n=24) (mainly carbapenem or piperacillin /tazobactam+AMG) 2. Definitive monotherapy (n=46) vs. CT (n=25)	*P. aeruginosa* BSI with septic shock	**1. Lower 30-day all-cause mortality rate in empirical combination therapy:** 56.8% vs. 25%, p=0.007; In a multivariate Cox regression analysis receiving an empirical CT was the only variable associated with improved survival (aHR 0.38; 95% CI 0.15–0.95; p=0.039). **2. No differences regarding the definitive therapy (monotherapy vs. combination)** in the univariate analysis (HR 0.48; 95% CI 0.17–1.31; P = 0.152).	**Only as empirical therapy (not in definitive)**
Chen *et al.*, 2024 [108]	Retrospective cohort study	Monotherapy (n=93) vs. CT (n=186)	BSI, Pneumonia, UTI and others; CRPA	**Higher clinical success for CT** (60.2% vs. 73.1%, p=0.028), **no differences in complete clinical success** (36.2% vs. 42.0%, p=0.931) **and 28d mortality** (15.1% vs 18.8%, p=0.436); monotherapy showed to be a risk factor for clinical failure in patients with SOFA ≥2 or a Charlson comorbidity index ≥6 (OR 0.469, 95% CI: 0.231-0.953; and OR 0.467, 95% CI: 0.222-0.980).	**Uncertain benefit**
Foucrier *et al.*, 2023 [112]	Post-hoc analysis of an RCT trial (iDIAPASON)	Definitive monotherapy (n=94) vs. CT (n=75)	VAP; *P.aeruginosa;*	**No difference in in-hospital mortality:** 18.1% vs. 26.7% (p= 0.1801); No difference in recurrence rate of VAP (p=0.3190), or the acquisition of MDR bacteria during the ICU stay (p=0.7372).	**No benefit**
Corbella *et al.*, 2022 [110]	Retrospective cohort study	CAZ/AVI monotherapy (n=32) vs. CT (n=29)	BSI, Pneumonia, UTI; DRT-PA	**Less clinical cure rates at d14 in combination therapy**, maintained in the final model as a factor negatively associated with clinical cure (aOR 0.02; 95% CI: 0.01–0.38; p=0.009).	**No benefit**
Babich *et al.*, 2021 [107]	Retrospective observational study	Monotherapy (n=843) vs CT (n=276; 58.7% with an AMG)	BSI, Pneumonia, UTI and others; *P. aeruginosa*	**No difference in 30d-mortality:** 17.1% vs. 16.3%, p=0.765 (even in the group presenting with hypotension, p=0.876), **in clinical failure at d7:** 43.3% vs 38%, p=0.168 **and microbiological failure:** 67.2% vs. 64.1%, p=0.348.	**No benefit**
Díaz-Cañestro *et al.*, 2018 [109]	Prospective observational study	CEF/TAZ monotherapy (n=21) and CT with colistin or AMG (n=37)	BSI, Pneumonia, IAI, UTI, osteoarticular; DRT-PA	**No difference in clinical and microbiological cure at d7**: 66.7% vs 60%, without adjustment.	**No benefit**
Tschudin-Sutter *et al.*,	Retrospective cohort study	β-lactams monotherapy (n=107) vs. CT (n=80,	BSI; *P. aeruginosa*;	**Lower mortality in CT** (HR 0.26, 95% CI 0.11–0.60, p=0.002), and after adjusting for age, neutropenia at	**Overall benefit**

2018 [106]		76% β-lactams and AMG)		diagnosis, PITT bacteremia score, and inadequate empirical treatment (HR 0.30, 95% CI, 0.13–0.71, p=0.006)	
Acinetobacter baumannii					
Park *et al.*, 2019 [116]	RCT	Colistin (n=5) vs. colistin and rifampin (n=4)	Pneumonia; CRAB	**Higher microbiological response at d14, although not statistically significant**: 40% vs. 100%, p= 0.196; **No differences in clinical response at d14**: 80% vs 66.7% (p>0.999)	**Uncertain benefit**
Makris *et al.*, 2018 [117]	RCT	Colistin (n=19) vs. colistin and high-dose ampicillin/ sulbactam (n=20)	VAP; CRAB	**No difference in 28d-mortality**: 63% vs. 50%; **Better early cure rate in CT:** 15.8% vs. 70%, p=0.001; CT was independently associated with favorable clinical response (OR 43.6, 95% CI, 3.594–530.9), in multiple regression analysis.	**Uncertain benefit**
Calò *et al.*, 2023 [119]	Retrospetive/ Prospective observational study	38 patients (monotherapy =29, CT=11)	BSI, Pneumonia, IAI, UTI, ABSSSI and others; CRAB	**No differences between the two groups in 30-days mortality** (48.3% vs 45.5%, p=0.87), **clinical failure** (27.6% vs 45.5%, p=0.06) **and microbiological failure at EOT** (13.8% vs 0%, p=0.19)	**No benefit**
Katip *et al.*, 2020 [115]	Restrospective cohort study	Colistin (n=193) vs. colistin and meropenem (n=1 31)	BSI; CRAB	**No difference in morality at the EOT** (aOR 0.93, 95% CI, 0.51-1.71, p=0.935), **clinical response** (aOR 1.05, 95% CI 0.62-1.74, p=0.860), **microbiological response** (aOR 1.28, 95% CI 0.74-2.20, p=0.371) and **nephrotoxicity** (aOR 0.84, 95% CI 0.52-1.36, p=0.492)	**No benefit**
Park *et al.*, 2019 [114]	Retrospective cohort study	Colistin (n=40) vs. colistin and meropenem (n=31)	BSI; CRAB	**Trend lower 14-days overall mortality in CT** (47.5% vs 25.8%) **and higher clinical success** (40% vs. 61.3%) especially in patients with higher Pitt bacteriemia score of ≥4 (66.7% vs 27.8%). Logistic regression analysis showed that Pitt score, pneumonia, and CT (OR 0.15, 95% CI, 0.03–0.65, p=0.011) were significantly associated with mortality.	**Overall benefit**
Stenotrophomonas maltophilia					
Almangour *et al.*, 2024 [125]	Retrospective cohort study	Monotherapy (n=330) vs. CT (n=77)	Mainly pneumonia, (72%); *S. maltophilia*	**No difference in clinical cure (**55% vs 65%, p=0.108; OR 0.66; 95% CI, 0.38–1.13) and **in-hospital mortality (**52% vs 49%; p=0.732; OR 1.09; 95% CI, 0.66–1.79); **Monotherapy had a lower risk of 30-day mortality** (adjusted OR 0.45; 95% CI, 0.22– 0.90) **and acute kidney injury** (9% vs 18%; p=0.027; OR, 0.47; 95% CI, 0.23–0.93).	**No benefit**
Chen *et al.*, 2023 [123]	Retrospective observational	Monotherapy (n=136), CT (n=171) with	HAP; *S. maltophilia*	**No differences in 30d mortality risk**: OR 1.124, 95% CI 0.707–1.786, p= 0.622, in a PS weighting analysis;	**Possible benefit in immunocompromised**

	study	different agents		CT was associated with a decreased risk of death in immunocompromised patients (OR 0.404, 95% CI .170–0.962, p=0.041), and individuals with APACHE II scores ≥15 (OR 0.494, 95% CI 0.256–0.951, p=0.035).	**patients**
Guerci *et al.*, 2019 [121]	Retrospective observational study	282 patients (59.4% treated with CT)	HAP; *S. maltophilia*	**CT was not associated with the primary endpoint (time to in-hospital death):** HR = 1.27, 95%CI, 0.88-1.83], p=0.20	**No benefit**
Shah *et al.*, 2019 [122]	Retrospective cohort study	Monotherapy (n=214) vs CT (n=38) with different agents	Pneumonia; *S. maltophilia*	**No differences in clinical response after 7d:** 39.7% vs. 47.4%; p=0.38, even after controlling for immune status, APACHE II score and polymicrobial pneumonia (aOR 1.51, 95% CI 0.63–3.65). **30d all-cause mortality was greater with CT** (22.9% vs. 39.5% p=0.03);No differences in 30d microbiological cure (p=0.44), recurrence (p=0.53), infection-related mortality (p=0.19) and isolation of a non-susceptible isolate during or after therapy (p=1.00 each).	**No benefit**

Abbreviations: **ABSSSI**: acute bacterial skin and skin structure infections; **AMG**: aminoglycosides; **aOR:** adjusted odd ratio; **BSI:** blood-stream infections; **CAZ/AVI:** ceftazidime/avibactam**; CEF/TAZ:** ceftolozane/tazobactam; **CRAB**: carbapenem-resistant Acinetobacter baumannii; **CRE:** carbapenem-resistant Enterobacterales: **CRPA**: carbapenem-resistant Pseudomonas aeruginosa; **CT**: combination therapy, **d**: days; **DRT-PA:** difficult-to-treat Pseudomonas aeruginosa**; EOT:** end of treatment; **GNB**: Gram-negative bacteria; **HAP:** hospital-acquired pneumonia; **HR:** Hazard ratio; **IAI:** intra-abdominal infections; **IPTW:** inverse probability of treatment weighting; **NF-GNB**: Non-fermenting Gram-negative bacteria; **VAP**: ventilator-associated pneumonia; **PS**: propensity score; **RCT**: randomized clinical trial; **RR**: relative risk; **UTI**: urinary tract infections

Table and figure legends

Table 1- Main recent studies (from 2018 to 2025) addressing combination treatment strategies for Gram-positive pathogens

Table 2- Comparison of current main international guidelines recommendations on combination therapy strategies for Gram negative pathogens

Table 3- Main recent studies (from 2018 to 2025) addressing combination treatment strategies for Gram-negative pathogens

Figure 1- Advantages and challenges of antibiotic combination therapy

Figure 1.