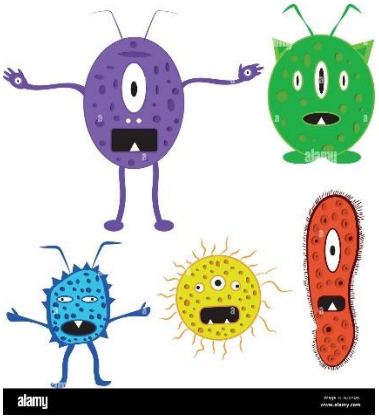
Double Coverage of Gram Negative Organisms

When a patient is admitted to the hospital with a suspected infection, it is common to initiate two broad spectrum antibiotics with coverage of the most commonly associated bacteria as empiric therapy. This is in part due to evidence suggesting that inappropriate antimicrobial treatment can be reduced with empiric administration of combination therapy, leading to overall better outcomes. Once cultures result, antimicrobial coverage should be narrowed and antibiotics de-escalated to a single agent based on sensitivity data. However, in more recent years, there has been debate as to whether or not to treat gram negative bacteria with two antibiotics that ideally have different mechanisms of action in order to target bacteria in multiple ways or enhance the efficacy of one another. This is especially true with multi-drug resistant bacteria and bacteria more commonly acquired in the hospital setting such as *Serratia*, *Klebsiella*, *Pseudomonas*, *Enterobacter*, and *Acinetobacter*. Combination therapy has been increasingly utilized for invasive infections caused by gram negative bacteria, especially in patients with neutropenia, ventilator-associated pneumonia, and the severely ill. The utilization of empiric combination therapy ensures adequate coverage of potentially resistant organisms, but there is little evidence to support continued combination therapy once an organism is isolated and susceptibility is known.

. Synergy between two antimicrobials is defined as a greater-than-2-log increase in bactericidal activity *in vitro* compared with that of each agent alone.[(1)] In some instances, when a gram negative infection is suspected, the empiric use of a *B*-lactam plus an aminoglycoside has been utilized. The rationale for this combination is based on data suggesting that aminoglycoside monotherapy is associated with worse outcomes as well as the potential synergistic effects of these two classes of antibiotics. *B*-lactam antibiotics work by opening the cell wall and may help facilitate the entry of aminoglycosides in order to exert their action and target ribosomal RNA of bacteria.[(2)] In 2010, Martinez et al examined the 30-day mortality due to gram negative bacteremia among patients treated with a *B*-lactam alone or combination therapy with an aminoglycoside. In this retrospective study, an overall association between combination therapy and survival was not found; however, subgroup analysis revealed that combination therapy was an independent protective factor in episodes presenting as shock or neutropenia. In addition, in this study combination therapy improved the appropriateness of empiric therapy in those with extended-spectrum beta-lactamase (ESBL) or AmpC producing *Enterobacteriaceae* and *P. aeruginosa*.[(3)]



In 2004, Paul et al conducted a meta-analysis of studies that showed combination therapy provided no advantage over monotherapy in patients with gram negative infections, including *Pseudomonas* bacteremia.[(4)] Additionally, another meta-analysis reviewing gram negative bacteremia specifically found no mortality benefit with combination therapy in comparison to monotherapy. However, in this meta-analysis, mortality benefits were reported in patients with

P. aeruginosa bacteremia. This finding was based on only five studies with the largest study utilizing an aminoglycoside as monotherapy.[5]

While the synergism between *B*-lactams and aminoglycosides has been shown *in vitro*, clinical evidence to support the use of combination therapy for gram negative organisms is limited and conflicting. When a pathogen is susceptible to one agent, there does not appear to be a synergistic benefit in clinical outcomes with the addition of a second agent.[1]When considering combination therapy, it is important to weigh the limited benefits with the risks of increased adverse effects.

Another reason combination therapy has been appealing is the belief that it can help prevent or delay the emergence of resistance to antimicrobial therapy. The increasing prevalence of multi-drug resistant bacteria is a major health problem that can lead to considerable mortality and morbidity. There are three categories for the mechanism of action of antibiotic combinations: inhibition of targets in different pathways, inhibition of different targets in same pathway, or inhibition of same target in different ways.[6] Through the use of combination therapy, it is postulated that bacteria are unable to develop multiple resistance mutations at once, as utilized in the management of HIV and tuberculosis.[7] Clinical trials show conflicting data regarding the benefit of combination therapy on reduced resistance, with some studies demonstrating an increase in the development of superinfections with the use of combination therapy.[1]

Strong evidence supporting the use of combination therapy for gram negative infections is lacking. This is demonstrated in the most recent 2019 American Thoracic Society / Infectious Diseases Society of America guidelines for community acquired pneumonia in adults, in which combination therapy for pneumonia including patients with *Pseudomonas* risk factors in not recommended. The use of additional unnecessary, antimicrobials can increase costs, the risk of adverse effects, and potentially resistance without true proven benefit.

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