# When are combinations of antibiotics clinically useful?


## Abstract

Antimicrobial resistance is a global crisis. Prescribing antibacterial combinations may be one way of reducing the development of resistance in target pathogens, as in the treatment of tuberculosis. Combinations may be useful for ascertaining synergy, broadening antimicrobial cover to reduce the risk of non-susceptibility, antimicrobial stewardship reasons, and immune modulation. The current research literature and/or prevailing global standards of clinical care suggest that combination therapy may be advantageous in: severe community-acquired pneumonia; severe hospital-acquired or ventilator-associated pneumonia or when there is a high risk of resistance in hospital-acquired or ventilator-associated pneumonia; multi-drug or extensively drug-resistant Gram-negative infections; and severe group A streptococcal infections. In other situations, combinations may be harmful. Overall, outside of tuberculosis, combination antibacterial therapy is likely to improve outcomes only in specific circumstances and there is little evidence to suggest that this prevents the development of bacterial resistance. Further high-quality research is essential.



**Key words: Antibiotics; Antimicrobial; Resistance; Stewardship**

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## Introduction

Antimicrobial resistance is a global health crisis. It is vital to clearly understand how to optimally prescribe antimicrobials to both treat infections effectively and minimise the further development and spread of antibiotic resistance. One approach that has been suggested is the prescribing of antimicrobial combinations, defined as prescribing two or more antimicrobial agents with antibacterial action. Potential advantages of combination therapy include synergistic action, broadening the spectrum of antimicrobial cover to reduce the risk of non-susceptibility to monotherapy, for antimicrobial stewardship reasons, and immune modulation.

Combination therapy has been recommended for the treatment of tuberculosis for decades following numerous trials (Joint Tuberculosis Committee of the British Thoracic Society, 1998). The heterogeneity in the mechanisms of action of anti- tuberculous agents is thought to prevent emergence of drug resistance. However, Brochado et al (2018) showed that combinations of mechanistically concordant antibiotics (ie antibiotics that have a similar mechanism of action, such as two cell-wall acting agents; for example, a beta-lactam plus either a glycopeptide or fosfomycin) are more likely to be synergistic against various Gram-negative bacteria in vitro. Whether these findings translate to clinical benefit remains unknown, but this finding is intriguing and somewhat counter-intuitive to how antibiotics are often, and have been, combined.

In hospitals, combinations are frequently prescribed, most commonly in high acuity or severity infections, and often to increase the spectrum of antimicrobial cover or to treat multi-drug or extensive drug resistance. However, there remains considerable debate about the value of doing so. This article reviews and discusses the evidence base for prescribing combination therapy in specific areas of acute clinical infection practice. This article will not consider anti-tuberculous, anti-viral or anti-fungal combination therapy, will not review the role of beta-lactam/beta-lactamase inhibitor combinations (although the potential for beta-lactam/beta-lactamase inhibitor combinations to be combined with other antibiotics in a novel way will be briefly discussed) or combinations such as trimethoprim-sulfamethoxazole (except as stated above), and will not discuss combinations that may have anti-biofilm activity (eg rifampicin combinations in prosthetic joint infections), although given the




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results of the recent POET and OVIVA trials prescribing oral antibiotic combinations is likely to increase for these infections (Iversen et al, 2019; Scarborough et al, 2019).

## Why do we use combination therapy in acute infections?

In the authors' own hospital, approximately one-third of all antimicrobial prescriptions are part of a combination regimen. There are several reasons why combinations are prescribed:

### To increase the spectrum of cover

Sometimes additional antimicrobials are prescribed to ensure that specific potential causal pathogens, which would not be susceptible to monotherapy, are covered. An example is the addition of a macrolide or tetracycline, usually to a beta-lactam, to cover the so-called atypical pathogens (eg *Mycoplasma* and *Legionella* species) when treating community-acquired pneumonia. Another example is the addition of metronidazole, for its anti-anaerobic action, to amoxicillin plus gentamicin in intra-abdominal infections. The broader cover offered by combination therapy reduces the potential risk of inadequate initial treatment. However, similar cover can sometimes be achieved by monotherapy, such as moxifloxacin or levofloxacin in community-acquired pneumonia and piperacillin-tazobactam in intra-abdominal infections (see below).

### To minimise the risk of non-susceptibility

Aminoglycosides are commonly added to anti-Gram-negative antibiotics to reduce the risk of non-susceptibility to monotherapy. Although this does reduce the risk of inadequate empiric antibacterial cover, the evidence that it improves clinical outcomes is less convincing, and systematic reviews suggest it may increase the risk of adverse effects (see below).

### For antimicrobial stewardship reasons

Some combination regimens are considered less likely to cause *Clostridium difficile* infection or other adverse events than alternative monotherapy. Fluoroquinolones and cephalosporins have been associated with a higher risk of *C. difficile* infection; combinations considered to be of lower risk are often preferred by antimicrobial stewardship teams (Dingle et al, 2017). However, the evidence base for some preferred combinations, whether prescribed for stewardship or other reasons (see above), being more favourable from antimicrobial stewardship perspectives vs monotherapy providing equivalent cover is often questionable. Further evidence on the risk/benefit ratio of monotherapy vs combination therapy for antimicrobial stewardship purposes is required.

### Synergy

Combinations are sometimes prescribed to ascertain synergy, therefore accelerating pathogen clearance, at least theoretically or based on in-vitro or in-vivo animal data (Pletz et al, 2017). Whether this translates to true clinical benefits remains controversial. Synergy is the interaction of two or more agents to produce a combined effect greater than the sum of the individual agents. Synergistic combinations improve outcomes in animal models, but high-quality clinical evidence is scarce. In-vitro studies demonstrated synergy of various combinations against enterococci, an important cause of infective endocarditis (Kollef, 2000).

Brochado et al (2018) showed that antibacterial combinations that targeted similar mechanistic processes were more likely to be synergistic, but this was not a universal paradigm. For example, amikacin and tobramycin-based beta-lactam combinations, which are mechanistically different, were often synergistic; interestingly, more so than gentamicin-based regimens, which is the agent commonly used in the UK. Of 18 combinations tested against various Gram-negative bacteria using amikacin (plus amoxicillin, cefotaxime or aztreonam), 12 resulted in synergy vs two synergisms and two antagonisms with gentamicin.

### Immunomodulatory effects

Some antibiotics are thought to have immunomodulatory properties; in the treatment of severe group A streptococcal infections, clindamycin may improve outcomes by having an

anti-toxin effect, although human data to strongly suggest outcomes are actually improved in clinical practice are limited (see below).

### Other theoretical benefits

Theoretically, it is possible that combinations could reduce drug-related adverse effects if lower doses of each drug could be prescribed, while maintaining clinical efficacy; the clinical viability of this approach is unknown, but might mitigate the negative impacts of combination therapy, using standard dosing, on the human microbiome.

By considering the characteristics of antibiotics, it may be possible to overcome some bacterial resistance mechanisms by prescribing combinations, including when more than one mechanism is present. A good example is the emergence of ceftazidime-avibactam plus aztreonam as a combination for extensive drug-resistant Gram-negative infections. This combination has several theoretical advantages:

1. Aztreonam is stable against metallo-beta-lactamases, so the combination could overcome a wider range of beta-lactamases
2. The action of two beta-lactams and a beta-lactamase inhibitor at different penicillin-binding proteins may be synergistic (ceftazidime-avibactam acts mainly at penicillin-binding proteins 1 [ceftazidime], 2 [avibactam] and 3 [ceftazidime] whereas aztreonam acts at penicillin-binding protein 3 in *Escherichia coli*)
3. The 'protection' of aztreonam by avibactam and/or the 'protection' of ceftazidime-avibactam by aztreonam (by acting as a beta-lactamase 'suicide' inhibitor).

As antibiotics with unique mechanisms emerge, such as cefiderocol, which is a beta-lactam but also a siderophore (by binding to free iron, it uses bacterial iron transport mechanisms as a 'trojan horse' to enter the periplasmic space and then act as a traditional beta-lactam), this approach might be useful in clinical practice, although further research is required.

## When should we use combination therapy?

### Severe community-acquired pneumonia

In keeping with National Institute of Health and Care Excellence (2014) guidance, many hospital guidelines in the UK recommend the use of a macrolide (some use doxycycline) in addition to a beta-lactam for moderate or severe community-acquired pneumonia in order to cover the so-called atypical pathogens.

In a systematic review of multiple studies of different designs, a macrolide plus a beta-lactam was found to be superior to beta-lactam therapy alone for mortality, but only in severe community-acquired pneumonia (Horita et al, 2016). This was mainly driven by the results of observational studies. Another systematic review of five randomised controlled trials ($n$=2011), only one of which was a combination vs monotherapy study, found that in hospitalised patients with community-acquired pneumonia there was a statistically significant reduction in clinical failure when patients were treated with atypical cover, but mortality and other outcomes were not improved (Eljaaly et al, 2017). A systematic review comparing different combination regimens found no difference as to whether the atypical cover provided was by a macrolide or fluoroquinolone antibiotic (Liu et al, 2019).

Overall, the evidence suggests antimicrobial regimens that include atypical respiratory pathogen cover should be prescribed for patients with severe community-acquired pneumonia, which may well be a combination regimen if monotherapy with a respiratory fluoroquinolone or other appropriate monotherapy is considered undesirable from an antimicrobial stewardship perspective.

### Severe cases of healthcare-associated pneumonia

This category includes cases of healthcare-associated pneumonia with septic shock, a high risk of multidrug resistance or previous colonisation, previous antibiotic use, or recent prolonged hospital stay. Guidelines from the European Respiratory Society recommend initial combination therapy in those with hospital-acquired pneumonia or ventilator-associated pneumonia at high risk of a poor outcome (as defined above; Torres et al, 2017). This is in keeping with a meta-analysis of combination vs monotherapy in patients with severe bacterial infections that showed a survival advantage with combination

therapy when analyses were stratified by mortality risk and shock (odds ratio 0.49; 95% confidence interval 0.35–0.70), but not in less severe infections (Kumar et al, 2010). To what extent non-susceptibility was important is unclear. When prescribed, combination therapy for hospital-acquired or ventilator-associated pneumonia should be targeted at the highest risk patients (as defined above).

## Resistant Gram-negative infections

Combination therapy is often used for severe Gram-negative infections. Fitzpatrick et al (2016) performed a prospective observational study involving 679 patients with confirmed Gram-negative bacteraemia (611 with complete data) from 10 acute English hospitals. One-third of patients received combination therapy, mostly with an aminoglycoside. Overall, 17% of patients received a regimen that was not active in vitro against the causative organism. Resistance was high for co-amoxiclav, the most commonly prescribed agent (prescribed for 32% of patients), followed by piperacillin/tazobactam (prescribed for 30% of patients). When prescribed in combination with an aminoglycoside, in vitro non-susceptibility decreased from 27% to 2% for co-amoxiclav and from 15% to 6% for piperacillin-tazobactam. The presence of non-susceptibility did not affect mortality at 7 or 30 days.

The current global antimicrobial resistance crisis in Gram-negative infections, however, has resulted in the widespread prescribing of clinically untested combination antibacterial regimens, which have become the standard of care for severe multi-drug resistant and extensive drug resistant Gram-negative infections, often using colistin-based regimens. The clinical evidence base, which is predominantly observational, perhaps suggests improved outcomes in high severity infections with the combination therapy approach (Gutiérrez-Gutiérrez et al, 2017). However, in a trial of predominantly severe *Acinetobacter baumannii* infections, colistin combination therapy was no better than colistin monotherapy, in keeping with a systematic review (Paul et al, 2018; Vardakas et al, 2018).

Emerging evidence also suggests that newly licenced broad-spectrum anti-Gram-negative agents, whether combined or not, may be better than colistin-based regimens (McKinnell et al, 2017; van Duin et al, 2018). Whether using these agents in combination protects them from the development of resistance in the target pathogen is unclear, but many doctors continue to use such agents in combination, particularly in high severity infections. Until higher quality evidence emerges, this is arguably reasonable practice, but only in severe multi-drug or extensive drug-resistant Gram-negative infections. Whether the addition of a second agent, such as an aminoglycoside to co-amoxiclav, is more favourable from an antimicrobial stewardship perspective vs equivalent spectrum monotherapy requires further investigation.

## Severe group A streptococcal infections

Combinations of antibiotics may also be used for the immunomodulatory properties of one or more of the agents prescribed to attenuate inflammation or prevent toxin production. A relatively common example of this in clinical practice is the addition of clindamycin, usually to beta-lactam therapy, for the treatment of severe group A streptococcus infections. Although group A streptococcus more commonly causes infections such as tonsillitis and scarlet fever, it can also cause life-threatening invasive infections such as necrotising fasciitis, bacteraemia and streptococcal toxic shock syndrome. The incidence of scarlet fever in the UK has reached the highest level in the last 50 years with 1 in every 500 children under the age of 10 years affected (Lamagni et al, 2018); this increases the incidence of invasive infections in the general population.

Despite group A streptococcus always being susceptible to penicillin, mortality associated with invasive infections is high. In-vitro and in-vivo animal studies found that clindamycin reduced virulence factors and improved outcomes, regardless of whether the group A streptococcus was susceptible in vitro to clindamycin or not (Andreoni et al, 2017). An observational study in humans showed that survival of patients with toxic shock syndrome was improved with use of clindamycin (Linnér et al, 2014). Although high-quality clinical evidence to support combination therapy with clindamycin is lacking, the high mortality of invasive group A streptococcus infections means that the current risk:benefit ratio favours combination therapy, in keeping with the global standard of clinical practice.

### *Pseudomonas* infections in cystic fibrosis and resistant *Pseudomonas* infections

Combination therapy is commonly prescribed for severe *Pseudomonas* spp. infections. Traugott et al (2011) suggested various advantages of this approach: to improve the probability of adequate therapy given potential resistance, ascertain synergy as demonstrated in vitro, and to minimise the development of resistance (commonly develops in *Pseudomonas* spp.). Combination therapy is supported by a small cohort study of 136 patients with extensive drug resistance pseudomonal pneumonia, which showed significantly higher 28 day survival (90% vs 51% vs 0%; $P<0.001$) with combination therapy compared to active monotherapy or inactive therapy respectively (Khawcharoenporn et al, 2018). In contrast, a 2018 meta-analysis of combination vs monotherapy in *Ps. aeruginosa* bacteraemia included 17 studies ($n=2504$) and showed no significant difference in mortality (Tang et al, 2018).

Combination antimicrobial therapy is generally considered a global standard of care for *Pseudomonas* spp.-associated respiratory exacerbations in patients with cystic fibrosis. Despite this, the clinical evidence base for such practice remains weak as demonstrated by the systematic review by Elphick and Scott (2016) that compared monotherapy vs combination anti-pseudomonal therapy; eight trials and 356 patients were included. As a result of heterogeneity, a full meta-analysis was not performed. There were no significant differences in lung function or bacteriological outcomes. In a group of patients that have a lot to lose by evolving resistance, it appears reasonable to continue the combination therapy approach, but more research is required.

## When should combination therapy be avoided?

### Non-severe community-acquired pneumonia

The evidence discussed above suggests that combination therapy with atypical pathogen cover is not required for patients hospitalised with mild community-acquired pneumonia (CURB65=0 or 1). Moderately severe community-acquired pneumonia (CURB65=2), with an expected mortality of approximately 10%, is more challenging. In the authors' hospital, oral doxycycline, which covers common bacterial respiratory pathogens including atypical bacteria, is suggested in local guidelines when patients are physiologically stable and able to take oral therapy. Intravenous benzylpenicillin plus intravenous clarithromycin is suggested for a patient who the responsible clinician thinks requires intravenous therapy or who, for example, is vomiting. This or similar approaches are a reasonable compromise between the antimicrobial stewardship concerns of broad-spectrum combination therapy and the risk of undertreating patients.

### Less severe cases of healthcare-associated pneumonia

This category applies to cases of healthcare-associated pneumonia without septic shock, a high risk of multidrug resistance or previous colonisation, previous antibiotic use, or recent prolonged hospital stay. As discussed above, the evidence suggests a survival benefit when combination therapy is prescribed for the highest risk patients with hospital-acquired or ventilator-associated pneumonia. It is worth noting that in the above-mentioned meta-analysis by Kumar et al (2010), combination therapy was associated with a statistically significantly increase in mortality in patients deemed lower risk (odds ratio 1.53; 95% confidence interval 1.16–2.03). The guidelines from the European Respiratory Society therefore recommend monotherapy in low-risk patients with hospital-acquired or ventilator-associated pneumonia (Torres et al, 2017). This is supported by a meta-analysis that showed no statistically significant difference between monotherapy or combination therapy in the empirical treatment of ventilator-associated pneumonia, although most of the included studies excluded high severity patients and those with septic shock (Aarts et al, 2008).

### Susceptible Gram-negative infections

As already discussed, there may be benefit in using combination therapy for multi-drug resistant or extensive drug resistant Gram-negative infections, particularly if of high

severity, but the need for this is much more debatable in infections caused by more susceptible Gram-negatives or of less severity. This is in keeping with the systematic review of Paul et al (2014) that included 7863 patients from 69 trials, performed during an era of less Gram-negative resistance, and compared beta-lactam monotherapy vs combination therapy with an aminoglycoside for sepsis. Subgroup analyses for Gram-negative infections revealed no statistically significant difference in clinical failure or mortality between monotherapy and combination arms. Likewise, there was no difference in the development of bacterial resistance and, across both Gram-positive and Gram-negative infections, monotherapy was statistically significantly less likely to cause bacterial superinfections (risk ratio 0.75; 95% confidence interval 0.57–0.99), possibly a surrogate marker for the greater negative impact of combination therapy on the human microbiome. The risk of nephrotoxicity with monotherapy vs combination was also significantly lower (risk ratio 0.30; 95% confidence interval 0.23–0.39). These results suggest that combination therapy with an aminoglycoside offers no advantages over monotherapy for susceptible Gram-negative infections and, importantly, may cause harm via superinfection or nephrotoxicity.

## *Staphylococcus aureus* bacteraemia

Combination antimicrobial therapy, particularly using rifampicin, most commonly with flucloxacillin, has been a relatively common practice in the UK when treating *Staphylococcus aureus* bacteraemia. A large multicentre randomised controlled trial in NHS hospitals in the UK found no overall benefit compared to standard antibiotic therapy with respect to primary or secondary outcomes, including mortality, and concluded that rifampicin should not be routinely prescribed in this context. Moreover, a statistically significant greater proportion of patients who received rifampicin had antibiotic or trial drug-modifying adverse effects (17% vs 10%) and drug interactions (6% vs 2%) (Thwaites et al, 2018). A post-hoc analysis suggests that to reduce the risk of recurrence (but not mortality), the addition of rifampicin may benefit higher risk patients (according to a score based on body mass index, immunosuppression, renal disease, diabetes and liver disease), although further confirmatory work is required (Szubert et al, 2019).

## Cellulitis

In the treatment of limb cellulitis, it has been common practice in the UK to prescribe penicillin plus flucloxacillin or, particularly in more severe cases which have been admitted to hospital, to add clindamycin to flucloxacillin. As discussed above, in severe group A streptococcus infections this has become an accepted standard of care, albeit one based on relatively low-quality clinical evidence. In cellulitis, which is often caused by *S. aureus* or group A streptococcus (both are covered by adequate dosing of flucloxacillin monotherapy), evidence suggests that combination therapy is either not beneficial or harmful.

A small randomised control trial assessed the effect of adding benzylpenicillin to flucloxacillin on clinical response in 81 patients with lower limb cellulitis. There was no difference in the mean number of doses required to achieve clinical response or other outcomes (Leman and Mukherjee, 2005). Another randomised control trial assessing the impact of cephalexin plus trimethoprim-sulfamethoxazole compared to cephalexin alone on cure rate of uncomplicated cellulitis in North America found no benefit in clinical resolution (Moran et al, 2017). A double-blind randomised control trial of 410 patients attending emergency departments and general practices in the UK did not show any benefit of the addition of clindamycin to flucloxacillin in the treatment of limb cellulitis. Importantly, more than double the proportion of patients receiving combination therapy experienced diarrhoea (21.5% vs 9.3%) (Brindle et al, 2017).

Whether the addition of clindamycin is beneficial in uncomplicated skin or soft tissue infections specifically caused by group A streptococcus requires further investigation, although it is unlikely such research will be performed. In uncomplicated cellulitis, and by extrapolation probably other uncomplicated skin and soft tissue infections most likely to be caused by *S. aureus* or streptococci, therefore, combination therapy should be avoided.

## Key points

- Antibiotic resistance is a global health concern, but for acute bacterial infections the clinical evidence base that combination antimicrobial therapy reduces the development of resistance in target pathogens is weak.
- Combination antimicrobial therapy can reduce the risk of non-susceptibility to monotherapy and may improve clinical outcomes in severe community-, hospital- and ventilator-associated pneumonia, severe multi- and extensively-drug resistant Gram-negative infections, and severe group A streptococcal infections.
- In *Staphylococcus aureus* bacteraemia and for other more susceptible, non-severe acute bacterial infections, combination therapy may lead to patient harm and, in the main, should be avoided.
- An individualised approach should be adopted with consideration of clinical outcomes, adverse effects, drug–drug interactions, and antimicrobial stewardship and human microbiome risks.
- Combination antimicrobial therapy should only be prescribed for patients who are truly likely to benefit and avoided when the risk–benefit analysis suggests the probability of harm and/or lack of clinical benefit is greater.

## Conclusions

Antibacterial combination therapy may be beneficial in specific clinical circumstances, although the clinical evidence base is often observational or relatively poor quality. In general, combination therapy has more commonly been shown to be beneficial in severe or multi-drug resistant or extensive drug resistant infections. Combination therapy has been shown to be non-beneficial with or without harm in non-severe pneumonia, susceptible Gram-negative infections (nephrotoxicity and superinfections with aminoglycoside combinations), *S. aureus* bacteraemia and uncomplicated limb cellulitis (diarrhoea with clindamycin).

Given that combination antimicrobial therapy may cause more adverse effects, drug–drug interactions and damage to the human microbiome without necessarily improving clinical outcomes compared to equivalent monotherapy cover, healthcare professionals thinking of prescribing a combination of antimicrobials should always appraise the need for such therapy and whether equivalent clinical outcomes, including antimicrobial stewardship considerations, could be as or more safely ascertained with monotherapy.

### Conflicts of interest

The authors have no conflicts of interest to declare.


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