Antimicrobial Combinations

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Since the beginning of the antimicrobial era in the mid-1940's, clinicians have been interested in the use of combinations of antimicrobial agents¹⁾. Initially such combinations were utilized to expand the spectrum of the early, narrow spectrum agents. Subsequently, a variety of other reasons emerged for using antimicrobial combinations. These reasons are listed in Tab. 1. In addition to the possibility of broadened spectrum of activity, additional advantages from using antimicrobial combinations include the possibility that the combination may have a synergistic activity against the organism or organisms causing the given infection, the possibility that the use of any combination of agents may result in decreased toxicity, or the possibility that the combination may prevent or delay the emergence of resistant organisms during the treatment of the given infection. Although actual surveys have not been reported, it is my distinct impression that the majority of antimicrobial combinations employed by clinicians throughout the world are used to broaden coverage, rather than to provide the other possible benefits listed. Over the years, it has also become clear that utilization of antimicrobial agents inappropriately carries with it a significant hazard. The disadvantages resulting from the improper use of combinations of antimicrobial

agents are listed in Tab. 2. Of these disadvantages, the one which is potentially most disastrous is antimicrobial antagonism. There are numerous examples of antagonism which have been described on the basis of in vitro studies¹⁾. The general types of these interactions are listed in Tab. 3. A full discussion of these mechanisms is beyond the scope of this paper, but may be found in reference 1. Although there are numerous examples of in vitro antagonism, this antimicrobial action is actually of limited clinical significance, primarily because most of the examples listed in Tab. 3 represent situations where the bactericidal activity of one agent is converted to a bacteriostatic action by a second agent. In this setting, there is not total loss of antimicrobial activity and, as long as the patient being treated has normal host defenses, the resulting bacteriostatic activity is usually sufficient to result in cure of the infection. Nonetheless, it has been clearly demonstrated that the use of a bacteriostatic agent such as chlortetracycline in combination with penicillin (which has bactericidal activity) is likely to result in the failure of the treatment of infections such as pneumococcal meningitis which occur in a setting where local host defenses are abnormal²⁾.

There are three settings where the clinical application of antimicrobial combinations is likely to result in a positive effect based on true interaction of the agents against a given microorganism. They include the first three citations given in Tab. 1. Of these, the possibility of a synergistic effect by two or more antimicrobial agents used in com-

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Tab. 1 Ratinalle for Use of Antimicrobial Combinations

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1. Enhanced activity (Synergism)
 2. Decreased toxicity
 3. Prevent or delay emergence of resistance
 4. Broaden coverage
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Tab. 2 Disadvantages Resulting from the Improper Use of Combinations of Antimicrobial Agents

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1. Antibiotic antagonism
 2. False sense of security resulting from decreased efforts at making specific diagnosis
 3. Increased incidence of adverse drug reaction
 4. Enhancement of superinfection with organisms resistant to multiple antimicrobial agents
 5. Unnecessary expense
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Tab. 3 Mechanisms of Antimicrobial Antagonism

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1. Inhibition of bactericidal action of β -lactams by bacteriostatic agent
 2. Inhibition of bactericidal action of aminoglycosides by bacteriostatic agent
 3. Competition for same binding site
 4. Induction of resistance for one agent by another
 5. Inactivation of one or both agents in the presence of the other
 6. Unknown or unidentified
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Tab. 4 Mechanisms of Synergism Having Clinical Utility

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1. Enhanced antimicrobial uptake of one agent in the presence of another
 2. Suppression or inactivation of β -lactamase activity
 3. Sequential blockade of synthetic or metabolic pathway
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bination is most attractive. Based on in vitro studies, there are several mechanisms of antimicrobial synergism which have been clearly shown to have clinical utility. These are listed in Tab. 4.

Perhaps the best example of the clinical application of synergistic antimicrobial combinations may be found in the treatment of enterococcal endocarditis³⁾. Enterococci are relatively resistant to

numerous antimicrobial agents. Indeed, unlike streptococci, enterococci are inhibited but not effectively killed by cell wall-active agents such as penicillin and ampicillin. Studies in the early chemotherapeutic era clearly demonstrated high relapse rates when patients with enterococcal endocarditis were treated with penicillin alone³⁾. Combinations of penicillin plus streptomycin (or other aminoglycosides) have subsequently been shown to produce a synergistic killing activity both in vitro and in vivo against enterococci, and this has led to the recommendation of combination therapy utilizing penicillin, ampicillin, or vancomycin with streptomycin or gentamicin for serious enterococcal infections such as endocarditis, meningitis, and possibly bacteremia³⁾. The mechanism of the synergistic action of cell wall-active agents and aminoglycosides has been clearly elucidated and has been shown to be the result of the enhanced uptake of the aminoglycosides in the presence of the cell wall-active agent⁴⁾. Similar mechanisms of synergism have been shown to occur when cell wall-active agents plus aminoglycosides have been utilized against a variety of other organisms including streptococci, staphylococci, *Pseudomonas aeruginosa*, and numerous other organisms¹⁾.

Returning to the *Enterococcus*, another important aspect of antimicrobial interaction is demonstrated by those enterococci against which combination therapy is not synergistic. It has been known for many years that enterococci with high-level resistance to aminoglycosides are not killed synergistically by combinations of cell wall-active agents and the aminoglycosides to which the organisms exhibit high-level resistance^{5, 6)}. During the past twenty years, enterococci have acquired numerous mechanisms of high-level resistance, including alterations in ribosomes, production of chromosomally- or plasmid-mediated inactivating enzymes, or changes in permeability³⁾. Recent wide-spread dissemination of enterococci with high-level genta-

micin resistance has provided convincing evidence of the importance of synergistic therapy in curing enterococcal endocarditis. Indeed, patients who acquire endocarditis (or meningitis) due to enterococci with high-level resistance to aminoglycosides, often fail to respond or relapse after therapy with cell wall-active agents alone; and, in some cases, patients with infections due to such organisms have been cured only by surgical removal of the infected tissue³⁾.

Combinations of cell wall-active agents and aminoglycosides have also been employed effectively in the treatment of other infections due to gram-positive organisms. The use of penicillins plus aminoglycosides allows the physician to shorten the course of therapy of endocarditis due to viridans streptococci from four weeks (with penicillin, ampicillin, or a cephalosporin alone) to two weeks⁷⁾. In the case of endocarditis due to *S. aureus*, it has not been possible to show a definitive clinical advantage of combination therapy over single drug therapy, although combination therapy has been utilized in short course (two-week) treatment of right-sided *S. aureus* endocarditis in drug addicts⁸⁾.

Combinations of anti-pseudomonal penicillins plus aminoglycosides have been frequently utilized in the treatment of serious infections due to *Pseudomonas aeruginosa*. While the benefit of such combination therapy appears to be well documented, the exact mechanism is not clear. Early studies demonstrated that synergistic antimicrobial interaction was important in the cure of serious *Pseudomonas* infections⁹⁾. However, more recent studies, while clearly confirming the value of combination therapy for serious *Pseudomonas* infections, have suggested that a synergistic interaction is not required for successful outcome. Thus, the benefit from combination therapy may be due, not only to a synergistic interaction, but also to prevention of the emergence of resistant organisms during therapy or some other, as yet undefined, benefit¹⁰⁾. It

has also been suggested that the addition of rifampin to antimicrobial regimens directed against *Pseudomonas aeruginosa* may be of benefit. However, while there is anecdotal evidence supporting such therapy, a recent evaluation failed to show a significant effect on mortality rates in patients with serious *Pseudomonas* bacteremia treated with rifampin plus piperacillin/tobramycin compared with patients receiving piperacillin/tobramycin alone¹¹⁾. This occurred despite the fact that patients receiving the triple drug combination seemed to have fewer episodes of break-through bacteremia or relapse¹¹⁾. Thus, definitive resolution of this question will require further clinical study.

A second type of antimicrobial synergism which clearly has clinical utility is that which occurs when β -lactamase production is suppressed or inhibited by an agent given in combination with a β -lactam antibiotic which can be hydrolyzed by β -lactamase. Although it is possible in vitro to prevent or suppress production of β -lactamase by the addition of an agent such as erythromycin or chloramphenicol which inhibits protein synthesis, clinical application of β -lactamase-chloramphenicol and β -lactamase-erythromycin combinations has not been practical because the positive interaction is absolutely concentration dependent¹²⁾. If the concentration of chloramphenicol or erythromycin exceeds that necessary to inhibit β -lactamase production, it inhibits general protein synthesis and may result in antimicrobial antagonism¹²⁾. The discovery and deployment of effective β -lactamase inhibitors such as clavulanic acid, sulbactam, and tazobactam have made it unnecessary to utilize agents which inhibit β -lactamase production. Combinations of these β -lactamase inhibitors with a wide variety of β -lactams has resulted in a marked broadening of the effective spectrum of activity of many widely-used β -lactam agents^{1,12)}. However, since β -lactamase inhibitors are usually administered in fixed combination with β -lactam antimicro-

bial agents, it is somewhat questionable whether the clinical deployment of β -lactamase inhibitors should be considered as examples of true synergism by antimicrobial combinations, or simply as examples of the utilization of broad-spectrum β -lactams with activity against β -lactamase-producing organisms. For purposes of subsequent discussion, I will arbitrarily consider them as broad-spectrum agents alone.

Combinations of agents which act on common biochemical or biosynthetic pathways may also result in vitro synergism. A prime example of this is the combination of trimethoprim with a sulfonamide. Such combinations are often additive or synergistic because they block sequential steps in the synthesis of folic acid by bacteria¹³. Since many bacteria are unable to utilize pre-formed folic acid, they must synthesize it from para-amino benzoic acid, providing the opportunity to inhibit folate synthesis with agents such as sulfonamides and trimethoprim.

A variety of agents which inhibit bacterial cell wall synthesis have been discovered. Cell wall synthesis by bacteria takes place in several steps, both in the cytoplasm and outside of the bacterial cell membrane. This means that it is possible to utilize agents in combination which affect sequential steps in cell wall synthesis. Combinations of agents which inhibit the first step in cell wall synthesis such as cycloserine or fosfomycin plus agents which inhibit later steps (β -lactams) often result in an additive or synergistic effect in vitro¹³. The same is true for combinations of vancomycin with β -lactam agents against certain organisms¹³. Thus far, such combinations have not been widely utilized in antimicrobial chemotherapy. However, recent studies examining the potential utility of fosfomycin or vancomycin in combination with various β -lactam antibiotics against methicillin-resistant strains of *Staphylococcus aureus* show considerable promise¹³.

Another potential use of antimicrobial combinations based on interactions against a given microbe is the suppression of resistance which could theoretically occur when combinations are utilized¹³. The best example of this application of combination therapy may be found in the treatment of tuberculosis. When an agent such as streptomycin is utilized alone against strains of *M. tuberculosis*, organisms with low levels of resistance ($\text{MIC} > 1$ mcg/ml) arise with a frequency of 10^{-9} , and organisms with high-level resistance ($\text{MIC} > 100$ mcg/ml) with a frequency of 5×10^{-10} . Although such mutation rates are relatively low, they are high enough to allow frequent emergence of resistance during treatment of cavitary disease. The use of combinations of agents effectively diminishes the likelihood of mutational resistance to a level that makes it unlikely to occur during therapy if patients are treated with full courses of effective agents¹³.

Rifampin is a drug which has activity against a broad variety of organisms in addition to *M. tuberculosis*. However, mutational resistance to this drug also occurs with high frequency when it is used alone¹³. If it is to be utilized in the treatment of non-tuberculous infections such as those caused by *S. aureus*, *S. epidermidis*, or *Pseudomonas aeruginosa*, it is necessary to give it in combination with one or more agents to prevent emergence of resistance¹³. Recent studies in the United States have shown that combinations of vancomycin plus rifampin are highly effective in the treatment of prosthetic valve endocarditis due to methicillin-resistant strains of *S. epidermidis*¹⁴. However, when only these two agents are utilized, a significant number of organisms still develops resistance to rifampin, and, for that reason, current recommendations of optimal therapy for *S. epidermidis* prosthetic valve endocarditis include vancomycin plus rifampin for 6 weeks, with gentamicin for the initial two weeks to prevent emergence of rifampin

resistance⁷⁾.

While it is theoretically possible to decrease toxicity of antimicrobial agents by using several agents in combination (provided that both are given in decreased dosages), in actual fact this rarely occurs. Most clinicians utilize agents in full dosage when employing them for combination therapy, and, for that reason, the possibility of decreasing toxicity with antimicrobial combination is largely an illusion.

Having examined a number of clinical settings where combination therapy is useful, I would now like to examine the issue of combination therapy versus monotherapy with the newer broad-spectrum antimicrobials. The discovery and clinical use of antimicrobial agents with remarkably broad spectra of activity and clinical efficacy over the past fifteen years make it reasonable to consider the possibility that these new agents could replace combinations of antimicrobials in certain clinical settings. The major issues to be considered are listed in Tab. 5.

Although no agent exists which is effective against all known microorganisms, the newer carbapenems such as imipenem and meropenem, the new β -lactamase inhibitor/ β -lactam combinations, and other new antimicrobial agents have remarkably broad spectra of activity. This means that it is possible to utilize them in many clinical settings where combinations were previously utilized to provide coverage of the multiple organisms present in infections such as intraabdominal infections, pelvic infections, diabetic foot infections, and the like.

The issue of the emergence of resistance during monotherapy is a valid one. Recently Milatovic et

al. examined the emergence of resistance during treatment of infections with a variety of antimicrobial agents¹⁵⁾. They found that in patients receiving monotherapy with aminoglycosides, fluoroquinolones, or β -lactams, resistant organisms were cultured in between 4.7 and 13.4% of cases, and, in approximately half of these situations, the development of resistance led to therapeutic failure. The organism which stood out as most likely to develop emergence of resistance during therapy was, not surprisingly, *Pseudomonas aeruginosa*¹⁵⁾. Although there are data which suggest that the use of combinations may prevent emergence of resistance in clinical infections¹⁵⁾, it is also clear that combinations do not prevent the emergence of resistance in all cases, especially when dealing with serious *Pseudomonas* infections¹⁶⁾. Moreover, a number of studies suggest (but do not prove) that organisms which develop mutational resistance during therapy may be less virulent or more susceptible to host defenses than their susceptible counterparts¹⁷⁾.

The issue of the importance of synergism has been addressed in a number of recent studies. An interesting paper by Martino and colleagues, and studies by other investigators as well, suggest that high serum bactericidal activity is likely to be more important than a synergistic effect in a variety of infections¹⁸⁾. Since many of the new antimicrobial agents (especially the broad-spectrum cephalosporins and carbapenems) produce remarkably high serum bactericidal titers against a broad range of infecting organisms, it may not be necessary to have a synergistic effect in the majority of serious infections as long as one can obtain reasonable serum bactericidal activity against the infecting organism.

The issue of toxicity is essentially a moot point. As noted earlier, it is highly unlikely that combination therapy will result in less toxicity than treatment with a single drug. Thus, monotherapy is inherently less likely to result in adverse effects

Tab. 5 Monotherapy vs Combinations of Antimicrobials—Major Issues

1. Breadth of coverage
2. Emergence of resistance
3. Synergism (bactericidal activity)
4. Toxicity
5. Clinical efficacy

than combination therapy.

The final question concerning monotherapy is "Does it work?". To answer that question I would like to examine briefly three areas where combinations have been traditionally employed: 1) the treatment of intraabdominal infections (where the infections are caused by mixed bowel flora); 2) initial therapy of community-acquired infections (where the infecting agent is not initially known), and 3) treatment of infections in neutropenic patients (where combinations are often employed to produce broad coverage and synergistic activity). A large number of recent publications suggests that the new broad-spectrum cephalosporins, the new β -lactamase-inhibitor- β -lactam combinations, and the new carbapenems are as effective as combination therapy for serious intraabdominal infections. In many cases, this is likely to be true, but one must examine the published data very carefully. For example, a number of the published studies suggest that various third generation cephalosporins are as effective as the combination of clindamycin and an aminoglycoside in the treatment of serious intraabdominal infections. On close examination it is clear that, while many of these studies have shown no significant difference in outcome for patients treated with third generation cephalosporins versus combination therapy, it is also clear that the patients selected for these studies do not have severe infections in many cases. More important is the fact that many of these studies report only small numbers of cases, and thus cannot exclude the possibility that there is a real statistical difference between the two study groups (beta error). Studies which include large enough numbers of seriously ill patients, moreover, clearly show that there are differences among the third generation cephalosporins in their activity in patients with serious intraabdominal infections and that coverage of anaerobes is important in this regard. The recent study by Lau and colleagues from Hong Kong showed that

moxolactam (which has good activity against anaerobes) was more effective than cefotaxime or cefoperazone in the therapy of complicated appendicitis¹⁹⁾. A number of other studies make exactly the same point: anaerobic coverage is important for successful outcome in the treatment of intraabdominal infections^{20, 21)}. It is not surprising, therefore, that monotherapy with moxolactam or imipenem should be demonstrated to be as effective as combination therapy with clindamycin plus an aminoglycoside for serious intraabdominal infections^{19, 22)}. Moreover, recent studies also suggest that fixed combinations of broad-spectrum β -lactams such as ampicillin, ticarcillin, or piperacillin with β -lactamase inhibitors such as clavulanic acid, sulbactam or tazobactam, are also highly effective in the treatment of intraabdominal infection. Studies during the past decade have also shown that broad-spectrum agents such as moxolactam, cefotaxime, or imipenem are as effective as combination therapy for the treatment of community-acquired non-life threatening infections²³⁾. It should be noted, however, that these agents were studied in settings where infections due to methicillin-resistant *S. aureus* and multiply-resistant *Pseudomonas aeruginosa* (which would not be effectively covered by the agents utilized) were not prevalent.

Perhaps the most difficult task for monotherapy is in the treatment of infections in neutropenic patients. Recently a series of studies have suggested that monotherapy with ceftazidime is as effective as combination therapy for infections in neutropenic hosts²⁴⁾. While ceftazidime was as effective as the comparative agents under the conditions of the clinical study, it should be noted that many of the patients treated with ceftazidime required modification of their therapy because of the presence of infecting organisms which were resistant to ceftazidime. Indeed, in many centers, emergence of staphylococci and other gram-positive organisms resistant to ceftazidime, or the emergence of

organisms such as *Enterobacter* during monotherapy with ceftazidime has severely limited the potential utility of this agent for monotherapy in neutropenic patients²⁵⁾. Not surprisingly, imipenem has recently been shown to be highly effective as monotherapy for the treatment of febrile neutropenic patients^{26, 27)}. While the studies which document the effectiveness of imipenem are likely valid, it should be noted that this agent may not be effective against many strains of methicillin-resistant staphylococci and that emergence of resistance to this agent when utilized as monotherapy for *Pseudomonas* infections may occur in a significant number of patients¹⁵⁾. Thus, not all clinicians are willing to abandon combination therapy for infections in seriously ill neutropenic patients. The dangers of using a drug which does not produce adequate coverage for all potential infecting organisms as a monotherapeutic agent in seriously ill neutropenic patients is clearly demonstrated by the recent failure of ciprofloxacin as a monotherapeutic agent in this setting²⁸⁾.

From the above it can be clearly seen that the new broad-spectrum agents can be effectively used as monotherapeutic agents in certain selected settings where previously combination therapy was indicated. Their broad spectrum of coverage makes them particularly attractive for the treatment of infections due to mixed flora, or in settings where the infecting organism has not been initially identified. However, it is also clear that there are a number of settings where combination therapy remains an important option, despite the availability of potent new antimicrobial agents. Moreover, clinical acumen remains the key element in the successful deployment of antimicrobial agents. Neither combination therapy, nor monotherapy with a potent new agent is a substitute for good clinical judgment.

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