

and that antimicrobial effectiveness is often decreased by this type of therapy. Thus, the use of penicillin-sulfonamide combinations is not recommended in the treatment of "mixed" bacterial infections. (3)

Enhancement of antibacterial activity

Another reason commonly given for the use of drug combinations is that some types of infections are more effectively treated by two or more drugs given in concert. Tuberculosis, subacute bacterial endocarditis due to Group D streptococci, and probably some strains of *Streptococcus viridans* are cited as examples of such infections. Some data have also suggested treatment of some forms of brucellosis and some infections due to *Proteus mirabilis* by combinations of drugs. Combinations of penicillin and sulfonamide, however, are not the agents of choice in any of these infections.

Careful laboratory studies have demonstrated that the use of the combination of penicillin and a sulfonamide can have three possible effects: enhancement of antibacterial activity beyond the additive effects of the two drugs (synergism); activity equal to the additive effect of the two drugs (addition); or activity less than the sum of the separate activities (antagonism). (4) It is not generally possible to predict which of these effects will be encountered in a given case. Fixed sulfonamide-penicillin combinations should not be used, since the antagonistic effect is an ever present possibility.

Treatment of infections before etiology is known or in case it is impossible to determine etiology

At times it is necessary to treat patients with severe infections before the etiology has been determined. There are indeed valid indications for the use of drug combinations in such cases; however, in all cases the drugs used should be given at least initially by the parenteral route. This requirement in itself would preclude the use of oral sulfonamide-penicillin mixtures. Furthermore, the use of other drug mixtures has been shown to be much more effective than the sulfonamide-penicillin combinations. (1)

Many of the same factors affect the use of sulfonamide-penicillin combinations in cases in which it is difficult or impossible to determine the etiology of an infection. A possible exception is the use of penicillin-sulfonamide combinations in the treatment of acute otitis media. Group A streptococci, pneumococci and *Haemophilus influenzae* are the common bacterial causes of acute otitis media. It should be noted, however, that *H. influenzae* very rarely causes otitis media after the age of three or four years, and multiple antibacterial agents are thus not indicated for the treatment of this entity in older children or adults. Because *H. influenzae*, Group A streptococci and pneumococci cause otitis media during the first few years of life, it has been common practice to use sulfonamide-penicillin combinations in this early age group. Data to support this regimen are minimal, and, indeed a recent in vitro study indicates that sulfonamides in the commonly used triple formulation inhibited only 20 percent of typable and 40 percent of the nontypable strains of *H. influenzae* at concentrations within the usual therapeutic range. (5) The results of treatment of otitis media with penicillin alone appear to be about as good as those with penicillin in combination with the sulfonamides. (6) It should also be noted that other drugs, such as the tetracyclines and ampicillin, have been shown to be effective against *H. influenzae* when given alone.

Exposure of patients to multiple drugs

The sulfonamides and penicillin are potentially dangerous drugs. (1) Reactions are common, and the reactions can be severe and even fatal. The use of both drugs simultaneously therefore increases the risk to the patient, and the combination is to be avoided for this reason. Another troublesome aspect of this problem is that it is difficult to detect the drug causing an untoward reaction when multiple drugs are used.

Use of fixed drug mixtures

The question of the control of drug dosage should always be considered when fixed drug combinations are used. In this situation, the physician never finds it possible to increase or lower the dose of one component of the mixture without at the same time affecting the dose of the other. In such circumstances the tendency is either to raise the dose of one drug to a desired level, and thus inadvertently to give an overdose of the other, or to lower the dose of one