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Combined Antibiotic Therapy

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ABSTRACT

The indications for combined antibiotic therapy are reviewed, and two major indications are discussed at length: the prevention of development of antibiotic resistance and the possibility of achieving antibiotic synergism.

Since micro-organisms vary in their behaviour in the presence of different antibiotic combinations, careful evaluation of clinical response and close laboratory control are necessary.

Antibiotics are divided into four groups and their possible combinations are described. It is emphasized that bactericidal antibiotics, e.g. penicillin and streptomycin, which act only on multiplying bacteria, may be antagonized by some bacteriostatic antibiotics, e.g. tetracycline. Clinical observations appear to confirm the usefulness of this division of the antibiotics.

SOMMAIRE

L'article passe en revue les indications d'une antibiothérapie associée et deux indications principales sont exposées en détail: la prévention de l'apparition de l'antibiorésistance et la possibilité de réaliser une synergie antibiotique.

Etant donné que les microbes ont un comportement variable vis-à-vis de différentes associations d'antibiotiques, il est nécessaire de procéder à une évaluation soigneuse des résultats cliniques et à de minutieux contrôles de laboratoire.

Les antibiotiques sont divisés en quatre groupes et leurs associations possibles examinées. On souligne que les antibiotiques bactéricides, parmi lesquels la pénicilline et la streptomycine qui agissent uniquement sur la prolifération des bactéries, peuvent être antagonisés par des antibiotiques bactériostatiques, comme la tétracycline. Les observations cliniques viennent confirmer l'utilité de cette division des antibiotiques.

BECAUSE the use of antibiotics in combination is so widely practised, no symposium on antibiotic therapy would be complete without discussing the rationale of such combinations.

Garrod,[1] in 1953, postulated five indications for combined antibiotic therapy, which have since been generally accepted:

1. A severe infection, without specific diagnosis, which requires immediate therapy. The bacteriological diagnosis or even the precise clinical diagnosis may not have been made or indeed may never be made. Although most of these infections would respond to a single antibiotic, the decision as to which drug to use is difficult and it is often necessary to prescribe a combination of different antibiotics.

2. An infection caused by a mixed bacterial flora, or multiple infections in the same patient caused by different bacteria. A variety of micro-organisms may take part in the infectious process following, for example, perforation of the colon. A similar situation may be encountered in urinary tract infections associated with indwelling catheters in which, not infrequently, three or four different bacteria are implicated. Alternatively the patient may have a urinary tract infection in addition to pneumonia, the two infective processes being caused by two different bacteria. In these cases no single drug could be effective against the variety of micro-organisms involved.

3. Prevention of toxic effects is another indication frequently mentioned as justifying combined antibiotic therapy. This is based on the assumption that if the desired antimicrobial action can be achieved only by increasing the dose of the antibiotic to a potentially toxic level, the use of two drugs with individual doses below this dangerous amount might achieve the same effect. It has been proved, however, that in any antibiotic combination both members of the pair have to be given in full therapeutic doses. The above-mentioned assumption is therefore fallacious and should not be used as a justification for combined antibiotic therapy.

4. Prevention of the development of resistance to the antibiotic.

5. The possible achievement of antibiotic synergism.

The first three of these indications are not as important as the last two.

DEVELOPMENT OF RESISTANT STRAINS

The problem presented by the appearance of resistant strains is familiar to all. It is also well known that an increase of these antibiotic-resistant varieties of organisms closely followed the introduction and extensive use of each new antibiotic.

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What is less well appreciated, however, is that not every antibiotic is equally prone to precipitate the emergence of bacterial resistance. Table I lists some of the antibiotics grouped according to the rapidity of the appearance of resistance to them. Penicillin is not listed in this table, since acquired resistance to penicillin does not seem to appear *in vivo*.

TABLE I.

Bacterial resistance develops to:		
Streptomycins Erythromycin Novobiocin	Tetracyclines Chloramphenicol	Polymyxins Bacitracin
Readily	More slowly	Rarely

The explanation usually offered to account for these differences among the antibiotics is derived from the current concept of antibiotic action. The antimicrobial drugs seem to act by interfering with the integrity of selected metabolic pathways within the bacterial cells, resulting either in inhibition of growth or lysis of the micro-organism. Different antibiotics will act by interfering with different metabolic functions of the bacteria.

The metabolism of bacteria is a highly complex process, since a monocellular organism has to carry out a multitude of biochemical processes. Mutations within the population occur frequently with the production of strains that are able to produce the same essential metabolic end-product by using different biochemical pathways. If this new cell possesses an altered metabolism which is not interfered with by the antibiotic in question, a resistant strain has emerged. Further administration of the antibiotic will result in the eventual disappearance of all the sensitive micro-organisms, at the same time permitting the new resistant mutant to multiply and dominate the infective process.

For some strains and for some antibiotics the appearance of resistant populations is a step-by-step process, each new population being slightly more resistant than the previous one. In other instances this is an all-or-none phenomenon, the newly emerged resistant clone being totally resistant to very high concentrations of antibiotic.

The emergence of antibiotic-resistant bacterial populations, however, does not depend solely on the characteristics of the antibiotic. It is also dependent, to a very high degree, on the nature and mutation characteristics of the bacterial species. Some organisms, particularly those which are highly adapted to a parasitic existence in the human body, do not possess the versatility of metabolic channels which can be used to bypass the block caused by the antibiotic. Others, most notably *Mycobacterium tuberculosis*, have a high rate of mutation and are notorious for the development of resistant strains.

These considerations may be illustrated by means of a concrete example, such as a staphylococcal infection that is treated with erythromycin only. Even after a relatively short period of exposure to the drug, resistant mutants may appear,[2] which are able to bypass the metabolic pathway blocked by the antibiotic. If this infection had been treated with a combination of antibiotics, such as erythromycin and chloramphenicol, the only mutants able to survive the combined assault of the two drugs would be those able to bypass both the pathway inhibited by erythromycin and the pathway blocked by chloramphenicol. Since the rate of mutation in staphylococci is estimated as one cell per 10^6 to 10^9 cells, the emergence of a mutant able to bypass both the pathways blocked by erythromycin and chloramphenicol would be infinitely less likely, e.g. one cell per 10^{12} to 10^{18} cells.

This is the theoretical background to the use of a combination of antibiotics in treating infections caused by bacteria which have a high mutation rate. Indeed before the discovery of penicillinase-resistant semisynthetic penicillins, a combination of erythromycin and chloramphenicol was frequently mentioned as the regimen of choice for penicillin-resistant staphylococcal infections. At that time it was suggested that in the treatment of staphylococcal infections certain antibiotics, such as erythromycin and novobiocin, should never be used alone but always in combination. Barber *et al.*[3] were able to show that if these drugs were used in combination in the treatment of such infections, the appearance of multiple antibiotic-resistant staphylococcal strains was significantly reduced.

Mycobacterium tuberculosis is the other important bacterial organism with a high rate of mutation which gives rise to strains resistant to streptomycin and the other antituberculous agents. The use of a two-drug or three-drug regimen is therefore mandatory in the therapy of tuberculosis of any kind. To prevent the emergence of resistant mutants, all of the drugs used have to be given in full therapeutic doses. Reduction of the dose, even in the dose of one of the potentially toxic drugs, may allow the selection of a mutant with low-grade resistance against this antibiotic and the defeat of the main purpose of the combined therapy.

SYNERGISM

The last but probably the most far-reaching indication for combined antibiotic therapy is the possible synergistic effect which may be obtained. Before embarking on a discussion of this possibility, the concepts of synergism and antagonism as applied to antibiotics must be defined.

The action of two drugs on bacteria is said to be additive when the effect is the sum of the action of each individual antibiotic when given separately. It is synergistic when the effect exceeds the sum of the actions of the individual com-

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ponents. Finally, it is antagonistic when the combined effect is less than that of the more potent member of the drug pair, when given alone.

These effects are observed clinically and can be demonstrated in the laboratory. The laboratory methods, described by Garrod,[1] are very demanding but frequently necessary for the intelligent direction of such cases. The procedures involved are much more elaborate and time-consuming than anything previously undertaken in a routine clinical bacteriology laboratory. It is not enough to determine the possible effect of drug pairing on simple bacteriostasis; it is necessary as well to demonstrate synergism or antagonism with regard to the bactericidal effect. By varying the relative concentrations of antibiotics in *in vitro* combinations, a series of effects may be shown, ranging from synergism through indifference to antagonism.[4] For this reason the laboratory tests have to be carefully standardized and evaluated.

TABLE II.

Primarily bactericidal antibiotics
Penicillin
Streptomycins
Polymyxins
Vancomycin
Primarily bacteriostatic antibiotics
Tetracyclines
Chloramphenicol
Erythromycin
Novobiocin

Nevertheless it is possible with certain drug pairs to demonstrate a rather consistent pattern of behaviour, and it was on the basis of such observations that Jawetz and Gunnison[5] in 1952 formulated their basic law of combined antibiotic action. Having divided the antibiotics into two large groups, those with primarily a bactericidal action and those with a bacteriostatic effect, as shown in Table II, Jawetz and Gunnison postulated that:

(a) A bacteriostatic antibiotic combined with another bacteriostatic antibiotic may bring about an additive effect.

(b) A bactericidal antibiotic in combination with another bactericidal antibiotic may be synergistic.

(c) A bacteriostatic antibiotic added to a bactericidal antibiotic may bring about antagonism.

The explanation for these effects lies in the mechanism of action of these antibiotics. Some bactericidal compounds, such as penicillin, act only on actively multiplying cells, whereas bacteriostatic antibiotics interfere with the metabolism of resting bacteria and prevent their multiplication. If a bacteriostatic agent which acts on resting bacteria by preventing the multiplication of micro-organisms is combined with a bactericidal antibiotic which acts only on actively multiplying bacteria, because of the inhibiting action of the bacteriostatic agent no multiplying bacteria would be present for the bactericidal drug to act upon. The result would be an antagonistic effect. On the other hand, if two bactericidal drugs such as penicillin and streptomycin are combined, both will act in the same phase of bacterial growth but on different metabolic pathways, bringing about a possible synergistic effect. Bacteriostatic drugs given together tend to be, at best, only additive, since their action consists solely in the inhibition of bacterial multiplication.

With increasing knowledge relative to the site of antibacterial action of different antibiotics and in the face of many conflicting clinical and laboratory observations, it was soon apparent that the basic law formulated by Jawetz and Gunnison needed revision. Such a revision was attempted by Manten and Wisse[6] in 1961, and this was further amended by Garrod and Waterworth[7] in 1962. On the basis of their experiments and clinical observations, Garrod and Waterworth proposed a division of antibiotics into four groups. The bactericidal antibiotics were subclassified as:

(a) Those acting only on multiplying bacteria (penicillin, vancomycin and the streptomycin group); these will be antagonized by some bacteriostatic compounds such as the tetracycline group, chloramphenicol and the erythromycin group.

(b) Those acting on resting bacteria as well (polymyxin group and bacitracin); these will not be antagonized by bacteriostatic compounds.

The bacteriostatic antibiotics were subclassified as:

(a) Those active within a short period of exposure to resting bacteria (chloramphenicol, and the tetracycline and erythromycin groups); these will antagonize bactericidal antibiotics not active against resting bacteria.

(b) Those active only after a relatively long exposure to resting bacteria (sulfonamides and cycloserine); these will not antagonize bactericidal antibiotics.

In addition it should be recognized that antibiotics within the same group do not antagonize each other. Indeed penicillin and streptomycin frequently act synergistically. The different penicillin preparations, such as the original benzylpenicillin and the semisynthetic penicillins, do not antagonize each other and can be used in combined therapy. The combination of benzylpenicillin and one of the semisynthetic, penicillinase-resistant penicillins is suggested for the initial treatment of staphylococcal infections until laboratory tests are available.

It should be emphasized that none of the foregoing considerations can be applied to every bacterial strain in every infectious process. Many infections present individual problems with respect to the choice of combined drug therapy, and even when the proposed combination fits into the above-

noted scheme, clinical or laboratory confirmation may be necessary, depending on the micro-organism involved and the clinical state of the patient to be treated. Unfortunately, as mentioned, the laboratory tests involved are extremely time-consuming and elaborate, and very few laboratories carry them out. It should be noted that the commercially available "fixed" combinations of antibiotics are seldom suited for combined therapy, since these preparations do not take into account the varied conditions encountered in clinical practice.

Clinical observations seem to confirm the validity of this modification of the original theory of combined antibiotic action advanced by Jawetz and Gunnison. The surprising fact is, however, that very few clear-cut examples of consistent synergistic or antagonistic effects have been demonstrated in clinical practice. Penicillin and streptomycin seem to act synergistically in infections caused by *Streptococcus fecalis* and this action is utilized in the treatment of bacterial endocarditis caused by this organism. The combination of penicillin and tetracycline was shown to be antagonistic in experimental studies of pneumococcal infections in animals,[8] and one published clinical study supports this finding.[9]

SUMMARY

Owing to the emergence of resistant mutants, some antibiotics should be given in combination in the treatment of certain infections.

The combination of penicillin preparations with those of the tetracycline group should be avoided, owing to the possibility of antagonism between these antibiotics. Antagonism may also occur between penicillin and chloramphenicol.

Antagonism will not occur between members of the same antibiotic group. Benzylpenicillin may be given with the new semisynthetic penicillin preparations.

There is much variability in the behaviour of any combination of antibiotics, even against strains of the same bacterium. Every infection presents an individual problem and close clinical observation and/or laboratory control is essential. The use of commercial combinations of antibiotics should be avoided.

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PAGES OUT OF THE PAST: FROM THE JOURNAL OF FIFTY YEARS AGO

THE PAGAN'S OATH ON SECRECY

No declaration of the principles of medical behaviour ever yet placed before the profession is better than that said to have been composed by Hippocrates. That Hippocrates wrote it has been doubted, but the oath is always known as Hippocratic. The oath of Hippocrates is an admirable rule of conduct for the medical man.

Doubtless a much more elaborate and comprehensive declaration could be drawn up, but it is questionable whether it would be an improvement on the pagan's. It is the tenor or spirit of this declaration that is important. To one detail in it I should like to draw attention—the passage which mentions professional secrecy. The translation by the late Professor Young of Glasgow is as follows:

"Whatever I shall see or hear even when not called in for medical attendance, whatever I shall come to know in the ordinary intercourse of life, which it would be improper for me to repeat, I shall keep silence regarding it. I shall hold it secret. May I, keeping this oath in its entirety, enjoy my life and art in happiness, and have credit among all men for all time. May the opposite befall me if I break it."

This injunction to treat as confidential what the patient may reveal to us has been scrupulously observed by many generations of medical men. But I have reason to believe that this wise provision is not so carefully observed here as it should be. The profession will pardon my being outspoken in this matter. I have had to listen to quite a number of complaints from patients and their friends as to the way in which their cases have been discussed in assemblies of laymen, in clubs and in general society. Now no one will maintain that this is as it should be, indeed it is diametrically opposite to what should be. While I think the suggestion I once heard that there should be a chair of Medical Ethics at Dalhousie University perfectly absurd, even if funds were available for such a purpose, yet I do believe that the young men, for whose training we are responsible, should have such examples of propriety in this respect put before them that the last thing they would dream of would be to betray any patient's confidences. The form of Latin oath which is taken by the graduates in medicine at Dalhousie University is evidently based on the Hippocratic. As it is possible that owing to its being in Latin, its full import has not been appreciated by some who have subscribed to it, I give it in the translation kindly made for me by Professor Howard Murray:

"I, who am now on the point of having bestowed upon me the title of Doctor in the Profession of Medicine, do in the presence of Holy God, the Searcher of Hearts, promise that I will continue in the performance of every duty pertaining to a grateful heart towards Dalhousie University up to the latest breath of my life. Then, further, that I will practise the Profession of Medicine carefully, virtuously and honestly, and, as far as shall lie within my power, will give faithful attention to all things which may contribute towards the restoration of the sick. And, finally, with regard to matters seen or heard in the practice of the healing art about which secrecy ought to be maintained, that I will not divulge these without serious cause. As I promise these things may the Deity vouchsafe to me His favour and assistance."

I am quite aware that under certain circumstances, moral or medico-legal, certain professional secrets may have to be revealed at the proper time and to the proper person, but this sort of thing is quite other than discussing cases in lay society as one discusses the war or the weather. Nor are the laity blameless in this matter: if they do not wish their cases discussed in general society, they ought to be very careful not to request information to which they have no claim. "Oh, Doctor So-and-So, what is wrong with Mr., Mrs., or Miss So-and-So?" is an exceedingly reprehensible form of question. You might just as well call on his banker and ask the amount of Mr. So-and-So's bank-balance.—D. F. Harris, *Canad. Med. Ass. J.*, 5: 877, 1915.