ANTIMICROBIAL AGENTS

Summary of a Round Table Discussion

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Antimicrobial agents have had an especially great impact in pediatrics. Although many diseases have been conquered easily with proper antimicrobial therapy, there still remain difficulties and failures. Dr. Lepper opened the session with a discussion of some of the failures of antimicrobial therapy.

HYPERACUTE INFECTIONS

Hyperacute infections, i.e., infections which are often fatal within 24 hours from the onset of symptoms, and resistant strains of organisms, account for the vast majority of failures in the use of antibiotics. A few cases cannot be classified into either category and remain as unexplained failures.

The magnitude of the problem of hyperacute infections can be judged by the fact that in a contagious disease hospital about a third of the fatalities from nontuberculous, bacterial infectious diseases occur within the first 24 hours from the onset of symptoms. Meningitis due to meningococcus or pneumococcus, or meningococcemia, are most commonly encountered in this group. In Dr. Lepper's experience, those patients who will die within 24 hours from onset of symptoms can be predicted early from clinical observations, and they command "heroic therapy."

A lively discussion of the use of adrenal corticosteroids as part of "heroic therapy" in hyperacute infections ensued. Dr. Riley pointed out that they are useful agents but have serious side effects and definite hazards. They are known to decrease the resistance of the host to infection. (The effect of cortisone on streptococcal infections in the rabbit was cited: 58 out of 66 rabbits pretreated with cortisone died; 5 of 60 control animals died.) Instances of empyema developing during treatment of pneumococcal pneumonia with both antibiotics and ACTH were described. The discussants agreed that at no time should adrenal corticosteroids be used in the treatment of infectious processes without simultaneous administration of adequate amounts of appropriate antibiotics.

Dr. Lepper reviewed some of the salient facts in connection with the use of cortisone and allied substances in the treatment of overwhelming infections, including meningococcemia and the Waterhouse-Friderichsen syndrome. In the period before cortisone was readily available, it was used in half of all such patients who died (death rate, 5%). With the liberal use of cortisone between 1952 and 1954, there was no demonstrable change in the death rate from overwhelming infections. Then, because of the danger of superimposed infection, the use of cortisone was restricted—again without a change in the death rate. For the patients treated with cortisone, the death rates in these three periods were: 100, 81 and 100%, respectively.

In an effort to elucidate more subtle differences which might occur from the use of cortisone, Dr. Lepper conducted controlled studies with four types of meningitis: Hemophilus influenza, meningococcal, pneumococcal, and tuberculous. In 57 pa-
tients with H. influenzae meningitis, 28 received cortisone, 29 did not. The only difference noted was a significantly greater incidence of subdural effusions in those patients who received cortisone. From this it was concluded that cortisone is not indicated as an adjunct in the treatment of H. influenzae meningitis. Of 56 patients with meningococcal meningitis, half received cortisone (7 patients with Waterhouse-Friderichsen syndrome were excluded from this group) and half did not. No significant difference could be detected in the two groups. In the patients with Waterhouse-Friderichsen syndrome, all received steroids; the mortality rate was comparable to that given in the literature. Dr. Lepper noted that none of these patients had evidence of adrenal insufficiency after recovery. In the group with pneumococcal meningitis, 14 patients received steroids, 14 did not. There was one death in each group; the value of steroids was not established for this disease. Similarly in tuberculous meningitis, it was difficult to establish definite value for the use of the steroids.

The requirement of large numbers of cases of any given disease to demonstrate small differences was stressed. A current study in five centers, using double-blind technique, may prove helpful. The group was cautioned against generalizing from one infection to another, or from one form of tuberculous infection to another. They were urged to avoid the routine use of adrenal steroids in serious infections; to select the patients who are to receive steroids carefully; and to avoid the rationalizations of “maybe I can get away with it” and “it doesn’t seem to do any harm.”

**QUESTION:** Has the use of adrenal steroids in acute laryngotracheobronchitis lowered the incidence of tracheotomy?

**DR. LEPPER:** To my knowledge, there is no study available with sufficient numbers of patients upon which to base an opinion.

**QUESTION:** Is there more likelihood of recurrent laryngotracheobronchitis when cortisone is used?

**DR. LEPPER:** This has not been demonstrated. I do not believe cortisone is indicated routinely in the treatment of this disease.

**QUESTION:** What is the mechanism of action of steroids in infections?

**DR. LEPPER:** The fundamental action is not known, but they suppress the inflammatory response which is one mechanism of defense. With long-term use of steroids, there will usually be a decrease in the patient’s antibody titer.

**QUESTION:** With the decrease in antibody titer, will there be an increase in the rate of recurrence of infections?

**DR. LEPPER:** In our series, there was no statistically significant difference in the recurrence rate; however, cortisone was not used for long enough periods of time to demonstrate reduced antibody titers.

**QUESTION:** What dosages of steroids were used?

**DR. LEPPER:** Hydrocortisone, 2.5 mg/kg intravenously, for 5 days. Decreasing doses were then used for 3 days, and ACTH was given intramuscularly for 2 days prior to cessation of all steroid therapy.

**QUESTION:** The New England Journal of Medicine (258:639, March 27, 1958) recently reported a series of patients with meningococcemia treated with steroids and concluded that there was no good reason for their use in this disease. What is your comment on this report?

**DR. LEPPER:** I am inclined to agree with the authors; however, considerable pressure will be brought to bear to use the steroids in this disease because of its high fatality rate. I believe at present that criticism will be greater if it is not used than if it is. The present literature does not contain satisfactory evidence for not using steroids in meningococcemia.

**RESISTANT ORGANISMS**

The second factor responsible for failures in antibiotic therapy, strains of organisms resistant to available agents, was discussed primarily by Dr. Harris Riley. Some organisms are naturally resistant and some,
while predominantly sensitive, may develop resistance. The premature or young infant, the extremely old patient, or some underly ing serious disease predisposing to infection, share, in common, characteristics of the host which favor infections by resistant strains of organisms. Some antimicrobial agents eradicate sensitive strains, allowing resistant ones to grow; thus treatment itself may produce resistant strains. Dr. Lepper illustrated this with a brief discussion of the staphylo coccus: The per cent of all staphylococci resistant to erythromycin rose rapidly soon after it became widely used, while the per cent resistant to penicillin slowly decreased. However, when erythromycin was used less abundantly, there was a rapid decline in the per cent of resistant strains at first, and then the per cent resistant, just as with penicillin, has declined much more slowly. The “back-mutation” rate varies with different antibiotics but it would probably take many years for staphylococci to become sensitive to most antibiotics once again if their use were discontinued.

Considerable variation in the degree of resistance of staphylococci will be found in different hospitals and in different communities. In Oklahoma City, for example, most of the strains are still sensitive to erythromycin. It seems clearly related to the use of particular antibiotics—those communities and hospitals in which erythromycin enjoys popular use will have predominantly strains of staphylococci resistant to erythromycin.

SUPERIMPOSED INFECTIONS

What appears to be a second infection arising in association with antibiotic treatment is sometimes in reality a mixed infection in which two organisms were present initially, but only one was recognized in pre-treatment cultures; the other is free to grow. True superimposed infections may come about as the result of autogenous spread; for example, infection in the kidney may be cured but a new, resistant organism may spread from the gastrointestinal tract, where antibiotic treatment favors the growth of resistant organisms. Or, superimposed infection may occur from exogenous spread, such as may be produced by improper catheterization during the diagnosis of urinary tract disease. A genuine superimposed infection was not noted by Dr. Lepper in a series of nine patients with indwelling catheters when multiple cultures were obtained before treatment was started. Thus, in these nine patients, all had mixed infections which could be misinterpreted as superimposed infections. He concludes that probably infections of the genito-urinary tract have a mixture of organisms at the onset of therapy more often than is commonly appreciated. Thus, it is essential to treat the patient, not the bacteria, for the patient may well tolerate one organism better than another which may emerge as the result of therapy.

**QUESTION:** How much reliance do you place on laboratory determination of sensitivity of various organisms to different antibiotics?

**DR. LEPPER:** There are many variables in the determination of resistance and sensitivity. The present disc method is highly variable but efforts are being made to standardize it. However, it will always be only an approximation. Species identification is more important than testing for sensitivity or resistance. Occasionally, an antibiotic will be effective despite the laboratory statement of “resistant.” Bacteriology may be able to tell you what to use, but never when to use it. Clinical judgment remains the important factor in the proper selection of antibiotic therapy.

NEW ANTIMICROBIAL AGENTS

**Amphotericin (Fungizone®—Squibb)**

Amphotericin, a member of the nystatin family, is the first real breakthrough in the treatment of systemic mycotic infections, according to Dr. Lepper. It has limited usefulness because of the necessity for intravenous administration; this could prove to be an advantage by delaying the emergence of resistant organisms so frequently seen when an antibiotic is abundantly used.
However, there is no documentation of the development or spread of strains resistant to amphotericin as yet. Amphotericin is useful in cutaneous and systemic candidiasis, histoplasmosis and cryptococcosis when given intravenously, and will eradicate Candida albicans from the stool when given orally. The dosage recommended for intravenous use is 0.25 mg/kg/24 hours, increasing to 1 to 1.5 mg/kg/24 hours as dictated by the severity of the infection. It is usually possible to administer it for only 1 month to 6 weeks because of the technical problem of administration. The most recent preparations have not seemed to produce renal complications as were noted with the earlier, presumably less pure, forms.

**Kanamycin (Kantrex®—Bristol)**

Dr. Riley pointed out that kanamycin is similar in its properties and action to neomycin and streptomycin. It has the same general range of effectiveness against gram-negative rods; and it has some anti-staphylococcal activity which is particularly important in those strains resistant to other antibiotics. In general, it is not effective against pseudomonas, pertussis, tularemia, streptococcus; effectiveness is equivocal in typhoid fever and salmonella infections.

The preparation is available for intramuscular injection. Pain is noted at the site of injection, and abscesses have been noted to develop. The dosage suggested is 25 mg/kg/day for less serious infections; 50 mg/kg/day in 2 doses is the usual quantity administered. For severe infections, 100 mg/kg/day for the first day or two days of treatment may be given, then decreasing to the lower quantities subsequently.

Toxicity may be noted in the form of deafness, as with streptomycin, and renal complications: casts, albumin and elevation of the blood urea nitrogen. Toxic effects will probably not occur if the dose of 50 mg/kg/day for 10 days is not exceeded. Abnormalities in the urine disappear completely upon discontinuation of the drug.

Dr. Riley described good results in serious staphylococcal infections resistant to other antibiotics. However, complete cross-resistance is noted with neomycin; i.e., organisms resistant to neomycin will also be resistant to kanamycin. In Dr. Riley’s opinion, kanamycin has a greater margin of safety than neomycin and it should probably replace neomycin. The use of a topical preparation of kanamycin will considerably enhance the emergence of resistant strains, as has been the case with neomycin, and is to be decried. Kanamycin and neomycin may be used in preoperative preparation of the gastrointestinal tract; there is virtually no absorption of the drugs when taken orally, but this is not recommended because of the development of resistant strains.

**Question:** Is there an aerosol form?

**Dr. Riley:** Yes. It has been used in bronchiectasis and cystic fibrosis of the pancreas with results similar to those obtained with neomycin.

**Question:** Is kanamycin effective orally in E. coli enteritis and is it preferable to neomycin?

**Dr. Riley:** I have had no experience with oral administration in diarrhea due to pathogenic E. coli, but parenteral administration has been effective in several cases. Because of fewer toxic effects it is preferred to parenteral neomycin.

**Ristocetin (Spontin®—Abbott)**

Ristocetin is available for intravenous use only and is effective against staphylococci and enterococci. There is no good evidence that adequate blood levels are obtained from its use intramuscularly. It is somewhat more toxic than another new antibiotic, vancomycin. Ristocetin has produced thrombocytopenia and leukopenia in 5% of patients treated, as well as deafness with prolonged administration. In Dr. Lepper’s experience, no strains of staphylococci have been found to develop resistance to this drug. However, experience with the use of this agent is still limited.

**Vancomycin (Lilly)**

Vancomycin will soon be available com-
mercially, also only in a form for intravenous use. It appears to be effective against all staphylococci. Because of the high incidence of venous thrombosis and phlebitis, it should be reserved for the more serious staphylococcal or enterococcal infections such as subacute bacterial endocarditis. Hearing impairment may be encountered with prolonged use. Improved refining is expected to decrease the incidence of toxic manifestations. Vancomycin has had insufficient use to make valid comparisons with rifistocetin as to relative effectiveness but at present is believed to be a safer agent.

Sulfamethoxypyridazine (Kynex®—Lederle)

This drug may be compared in its activity and usefulness to other preparations of sulfonamides. No organisms resistant to sulfonamides will be sensitive to sulfamethoxypyridazine. However, it differs in the rate of excretion and therefore high, prolonged concentrations in the blood may be obtained with single doses. The drug must be used correctly to avoid undesirable complications. The dosage recommended is as follows: 40 to 50 mg/kg/day is given orally in one or two doses for the first 3 or 4 days of therapy; thereafter, the dose is decreased to 25 or 30 mg/kg/day for the remainder of the course. The prolonged levels—as long as a week after the last dose, some of the drug may be detected in the blood—make the treatment of toxic manifestations a problem. Toxicity would be expected to be comparable to that observed with other preparations of sulfonamides.

Dr. Lepper cautioned that the use of sulfamethoxypyridazine in the prophylaxis of rheumatic fever has not received sufficient study to recommend a change from the present penicillin regimen. Studies using 30 mg/kg once a week are being made; some of the drug has been detected in the blood at the end of the week at this dosage in 80% of patients.

The chief advantage of this drug over other preparations of sulfonamides lies in the fewer number of daily doses required.

COMBINATIONS OF ANTIBIOTICS

A number of attributes, desirable and undesirable, have been ascribed to combinations of antibiotics, two or more agents used either separately but simultaneously, or in fixed proportions. Dr. Lepper discussed the pros and cons in a frank and helpful manner.

It has been held that combinations of antibiotics delay the development of resistant organisms. This has been clearly demonstrated in the treatment of cavitary tuberculosis with streptomycin and isoniazid. It has not yet been conclusively shown that this is true for staphylococcal infections using combinations of novobiocin, erythromycin and chloramphenicol (any two of the three). Dr. Lepper reported 22 cases of staphylococcal septicemia successfully treated in this manner without the development of resistant strains.

The use of two agents favors the overgrowth of doubly resistant organisms in the normal flora of the respiratory, urinary and gastrointestinal tracts and increases the incidence of doubly resistant organisms in the environment.

The case for increased effectiveness of combinations of antibiotics is less well substantiated. Combinations of bacteriostatic and bactericidal agents are potentially antagonistic, but this is probably a limited phenomenon in vivo. To demonstrate true antagonism, it is necessary to give the bactericidal agent in less than adequate dose and the bacteriostatic agent first. However, it remains more desirable to use two bactericidal or two bacteriostatic agents if combinations are to be used.

Synergy, i.e., enhanced activity beyond a simple additive effect, is often claimed for two particular agents but is probably by and large a myth. In the treatment of serious and difficult infections, some additional antibacterial activity may be obtained with two or more drugs, but only if each drug
is given in the maximum tolerated dose.

Commercially-available combinations of antibiotics have the major disadvantage of fixed proportions, making it impossible to alter the dose of one agent without altering the dose of the other. Combiotic® is a classic example: it contains a relatively excessive amount of streptomycin, especially for adults with infections for which a combination of penicillin and streptomycin may be indicated. The indiscriminant use of this combination of agents has severely jeopardized the effectiveness of streptomycin because of the continued favoring of spread of resistant organisms. Dr. Lepper stated that, in his opinion, there is no rationale whatsoever for the use of some combinations with fixed ratios in single-dose forms, such as tetracycline and oleandomycin (Signemycin®). Dr. Riley suggested that, when two antimicrobial agents are to be used simultaneously, it is preferable to give adequate amounts of each drug rather than to rely on a fixed, commercially-prepared combination of the two drugs.

The use of two or more antibiotics is indicated in tuberculosis (isoniazid and streptomycin), brucellosis (tetracycline and streptomycin), and subacute bacterial endocarditis (penicillin and streptomycin). Dr. Lepper does not employ two or more antibiotics in the treatment of meningitis (chloramphenicol or tetracycline for gram-negative rods, penicillin for gram-positive organisms, any of these agents for meningococci).

The use of two or more antibiotics simultaneously is not indicated for routine treatment of most infectious processes or for systemic prophylaxis. Nor is it indicated in the treatment of stable though incurable situations such as cystic fibrosis of the pancreas when the patient is doing moderately well.

**QUESTION:** Would you comment on the relation between blood levels and therapeutic effect?

**DR. LEPPER:** The answer will depend upon whether one holds that “peaks and valleys” in the concentration of antibiotic in the blood are more desirable than a continuous concentration. I am a “continuous level” man. Concentrations of antibiotics beyond the level required to kill the bacteria have not been shown to be of any advantage unless there is a particular problem of penetration into the tissues.

**QUESTION:** What do you use in treating pharyngitis and otitis media when bacteriologic studies are not available?

**DR. LEPPER:** Our studies show that penicillin will be effective in all but about 2-4% of cases; therapy will have to be changed in that per cent because of resistant staphylococci or H. influenzae. Tetracycline and erythromycin will each be effective in all but about 3%, the staphylococci again being the reason one will have to change to another agent. Resistant staphylococci are somewhat more frequent with these drugs than with penicillin. The sulfonamides have not been as effective, in my experience, against the streptococci as have antibiotics. Sulfonamides will keep streptococci away in rheumatic fever prophylaxis but they are not as good at getting rid of them once infections starts.

**DR. RILEY:** I am reluctant to use penicillin alone in the treatment of acute suppurative otitis because of the high incidence of H. influenzae as the causative organism.

**QUESTION:** What do you recommend for prophylaxis of rheumatic fever?

**DR. LEPPER:** I believe the American Heart Association’s recommendation of oral penicillin, 250,000 units twice daily, is at present the preferred method.

**DR. RILEY:** The use of benzathine penicillin intramuscularly at monthly intervals was much more economical, was quite effective, and the only disadvantage was the discomfort associated with the injection.

**QUESTION:** Are there significant differences among the oral penicillin preparations?

**DR. LEPPER:** Oral penicillin V is better than penicillin G; potassium penicillin V provides a higher 1-hour concentration in the blood than other forms, but somewhat lower concentration at 3 hours. Therefore,
it has no advantage and perhaps is somewhat inferior. May I caution the group not to rely upon oral penicillin in the treatment of acute illness. The danger of vomiting is always present and also 5 to 10% of patients will not obtain adequate concentrations in the blood with the doses usually employed. And there is no way of knowing which of your patients will be in that group.

**Question:** How long do you continue antibiotic therapy in the usual infections?

**Dr. Riley:** If the antibiotic is indicated at all, it must be continued at least 4 days after a satisfactory clinical response has been obtained, as judged by subsidence of the inflammatory process, and general well-being of the child, not just by the return of the temperature to normal.

**Questions:** How do you manage outbreaks of staphylococcal infections in a newborn nursery?

**Dr. Lepper:** Antibiotics should be used only as a stop-gap and must not replace proper epidemiologic study and appropriate control measures. I recommend the use of erythromycin in all affected patients until the epidemiology, and sensitivity of the organisms, can be determined. Then appropriate changes in therapy may be made as indicated.

**Dr. Riley:** I think scrupulous asepsis and education of all personnel associated with the infants are of the greatest importance.

**Question:** Do you use continuous or intermittent antibiotic therapy in the milder cases of cystic fibrosis of the pancreas?

**Dr. Lepper:** In limited experience, I have noted no difference in the clinical course with either regimen. Empirically I would prefer intermittent therapy.

**Dr. Riley:** We are using in most of the patients with cystic fibrosis of the pancreas continuous antibiotic therapy, but use a schedule of rotation of agents.

**Question:** What is your opinion of the use of gamma-globulin to potentiate the effectiveness of antibiotics?

**Dr. Lepper:** I have not had experience with it but I do know the clinical reports are not statistically valid.
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*Pediatrics* 1959;23;1192

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