• Antimicrobial Therapy of Acute Infections* •

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Today, most of the bacterial and rickettsial infections, formerly responsible for high morbidity and mortality in our population, can be successfully treated with antimicrobial agents. These dramatic results are largely achieved by the use of six antimicrobial agents; penicillin, streptomycin, the sulfonamide drugs, aureomycin, chloramphenicol, and terramycin. A consideration of the therapy of acute infectious disease may, therefore, be conveniently presented as a discussion of the use of these agents. The newest of the six agents are the broad spectrum antibiotics, aureomycin, chloramphenicol, and terramycin. This name has been applied to them because of the breadth of their spectrums of antimicrobial activity. They are active against some of the large particle viruses, the rickettsiae, Gram-negative bacilli, Gram-positive cocci, Gram-positive bacilli, and even in some of the protozoal infections.

In addition to their broad spectrums, they possess other valuable properties which enhance their effectiveness, i. e., activity after oral administration, and elimination in high concentration in the urine. Moreover, the emergence of resistant organisms has not been a problem in therapy.

As with many oral medications, gastrointestinal intolerance has occurred in a minority of cases. Nausea and vomiting and diarrhea have been the principal causes of difficulty. No successful means of counteracting these side effects has yet been evolved aside from the discontinuance of therapy when the symptoms become severe. Chloramphenicol, in our experience, has been the best tolerated of the three agents.

The therapy for many of the acute infections which are encountered today is described in table 1. The choice of agents is indicated in the order of preference. When the activity of the agent is not known, it is shown by the letter "U". In a few instances, combinations of agents are the choice of therapy and these are appropriately indicated.

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There has been a tendency in recent years to minimize the importance of pneumococcal pneumonia. This has largely resulted from the development and widespread use of specific antimicrobial therapy in its treatment. It should not be forgotten that pneumococcal pneumonia is still a common cause of serious illness and, as an example, in the past 3 years in the Cornell Service at Bellevue Hospital, an average of 75 cases of pneumococcal pneumonia has been treated. In addition to the pneumococcal pneumonias, there is a group, almost as large, in which the etiology is undetermined. These are for the most part presumed to be bacterial in origin. A number of such patients give a history of treatment with penicillin or other agents before admission to the hospital which probably explains the failure to isolate pneumococci from their sputa. The response of both groups of patients to antimicrobial therapy has been satisfactory with a somewhat greater uniformity of response among the patients with known pneumococcal infections. The broad spectrum antibiotics in particular have provided excellent results and it is felt that they can be appropriately used in any usual case of pneumonia. Their effect in complications of pneumonia is at present being evaluated. It should be noted that in a large group of patients under our observation, the serious complication, empyema, has not occurred once after therapy has been thoroughly established.

Typhoid was first effectively treated with chloramphenicol in 1948 by Woodward and Smadel, and their associates (1). Since then a host of reports have appeared which confirm their observations. One of the problems which they and others observed was a latency of effect of drug therapy for as long as 3 or 4 days after start of treatment. In seriously ill patients, this interval was sufficient to permit the grave complications of massive gastrointestinal hemorrhage or perforation of the small bowel to occur. In an effort to avoid this dilemma, Smadel and his associates (2), and Woodward, *et al.* (3), have recently reported the use of cortisone as an adjuvant in the treatment of typhoid. When used in sufficiently large doses in conjunction with chloramphenicol, defervescence occurred in one group

Table 1

ANTIMICROBIAL THERAPY OF ACUTE INFECTIONS*

Disease or Infective Organism	Aureomycin	Chloramphenicol	Terramycin	Other agents or combinations
Hemolytic streptococcus, Group A	II	II?	II	I = Pen
Subacute bacterial endocarditis				
Streptococcus viridans	II	U	U	I = Pen
Streptococcus, Group D	II	U	U	I = Pen + SM
Staphylococcus				
Furunculosis	I	U	U	
Osteomyelitis	II	U	II	I** = Pen; SM; AM; TM; in various combinations
Bacteremia	II	U	U	
Pneumococcal pneumonia	II	II	II	I = Pen
Urinary tract infection				
Escherichia coli	I	I	I	
Aerobacter aerogenes	I	I	I	
Bacillus proteus	III	III	III	Combination with SM may improve results
Pseudomonas aeruginosa	III	II	III	
Typhoid	III	I	III	Cortisone may be valuable adjuvant in critical cases
Bacillary dysentery	II	II	U	
Acute and chronic brucellosis	II	II	II	I = Broad spectrum agent + SM
Plague	II	II	II	I = SM alone, or + SDZ, AM, or CM
Tularemia	II	II	U	I = SM alone, or + AM, CM, or SDZ
Friedlander's bacillus infection	II	II	II	I = SM + one of the broad spectrum agents
Influenza bacillus meningitis	II	II	U	I = CM + SDZ + serum
Pertussis	II	II	U	I = to be determined
Anthrax	II	U	II	I = Pen
Meningococcal meningitis	II	U	U	I = SDZ, Pen = II
Gonorrhea	II	II	II	I = Pen
Syphilis	II	II	II	I = Pen
Lymphopathia venereum	I	I	I	
Primary atypical pneumonia	I	I	I	
Ornithosis-psittacosis	I	I	I?	
Rickettsial infections	I	I	I	
Amebic dysentery (enterocolitis)	II	III	II	AM and TM may prove to be I
Fungus infections	O	O	U	

*Key to symbols:

I - drug of choice
II - effective; requires further evaluation
III - slightly active; not dependable
O - no effect
U - unknown

SM - dihydrostreptomycin or streptomycin
Pen - penicillin
SDZ - sulfadiazine
AM - aureomycin
CM - chloramphenicol
TM - terramycin

**Selection based on *in vitro* sensitivity tests.

of patients, reported by Smadel, in an average period of only 15½ hours after start of treatment. This is an impressive result, and although evaluation of untoward effects after cortisone are not complete, the required interval of cortisone therapy is so short as to suggest that it could be safely employed in patients seriously ill with typhoid.

The treatment of brucellosis has changed radi-

cally since the broad spectrum agents have become available. It has been found that the acute manifestations of the disease are regularly controlled with these agents alone. Relapses have occurred frequently, however, and this presented an additional therapeutic problem. Herrell and Barber (4) have recently met this situation by the administration of streptomycin in combination with one of the broad spectrum agents, aureomycin. No bacteriologic relapses were observed in a 35-case study and in only one instance were symptoms observed which suggested a recurrence of the infection. These results offer convincing evidence of the benefit of this combined therapy and consequently it has been incorporated into table 1.

Anthrax was a serious disease in earlier times in this country and is still an important problem in many parts of the world. Occasional importations of wool or goat hair or other animal products have been followed by localized outbreaks of the infection in the United States. One occurred recently in Philadelphia. Untreated, the disease may be very serious and is often fatal. When appropriately treated, however, the recovery is uniform and rapid. In figure 1 may be seen photographs of a patient with a malignant pustule of anthrax over her left cheek. It developed several days following the slaughter of a beef animal. Cultures yielded a heavy growth of *Bacillus anthracis*. At the time the first picture was taken she was started on terramycin by mouth, 4 gm. daily. In the succeeding two photographs, she is seen at 24 and 72 hours after start of therapy. The rapid clearing of the infection was easily apparent and is evident in the photographs. Cultures of the lesion after start of therapy were negative on several occasions and recovery was entirely uneventful and satisfactory. Penicillin and aureomycin are likewise effective in the treatment of anthrax infections.

One of the most important groups of communicable diseases today for which effective therapy is still not available are the virus infections. Among the more serious are poliomyelitis, influenza, hepatitis, the encephalitides, and the exanthematous diseases. One of the latter, smallpox, periodically causes great apprehension when it appears sporadically in large population centers. In figure 2 may be seen a photograph of a patient with smallpox. This picture was taken about the tenth day of the patient's illness. At the time he was under treatment with terramycin. He improved only gradually following treatment and it was felt that this agent did not influence the course of his illness. Penicillin has similarly been used in the treatment of smallpox and the results of these studies as well as the present observations suggest that antimicrobial therapy is useful only in controlling a secondary infection which may occur in the disease. All of the antimicrobial agents

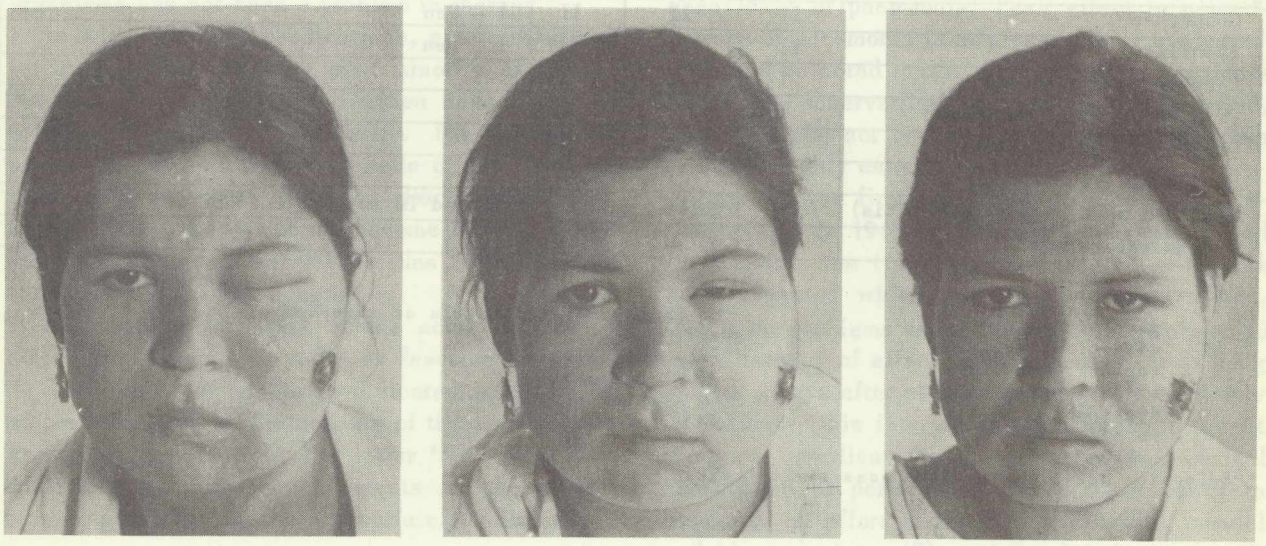

Figure 1. Course of anthrax infection following terramycin. **Left:** Before treatment. Cultures positive for anthrax bacilli, intense inflammatory reaction. **Center:** Twenty-four hours after start of terramycin. Definite reduction in local reaction. Cultures no longer positive for anthrax bacilli. **Right:** At 72 hours, asymptomatic. Recovery uneventful. (Reproduced from Knight, V., N. Y. State J. Med. 50:2177, (Sept. 15) 1950 with permission).

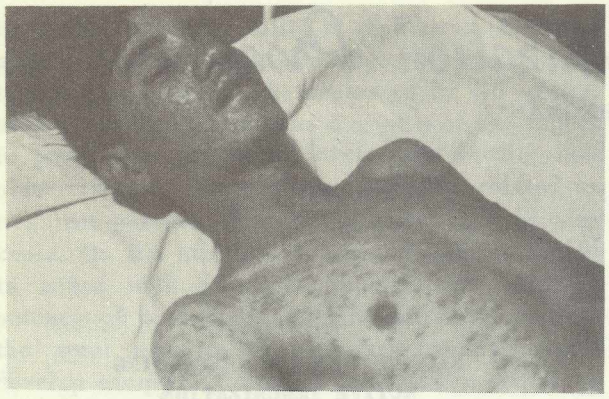

Figure 2. Patient in tenth day of illness with smallpox. He was treated with terramycin without definite evidence of activity although recovery ensued. (Photograph by courtesy of Dr. Amado Ruiz-Sanchez, Guadalajara, Mexico).

have been extensively tried in most of the serious virus infections without any evidence of specific activity. At present it seems best to employ antimicrobial therapy in these diseases only when secondary bacterial infections occur in the course of the illness.

Another problem of antimicrobial therapy which may face any of us is that of caring for the victims of an atomic attack. It is estimated that in such a situation every individual who sustained an injury of any consequence would require some type of antimicrobial therapy. The majority of the cases would likely be flash burns and blast injuries with only about one-fifth of the injuries resulting from exposure to ionizing radiation. The benefits of antimicrobial therapy in the former two groups are well known by experience with burns and blast injuries from other sources and need not be discussed.

Antimicrobial therapy of large numbers of cases of radiation disease is largely predicated upon the results of animal studies. From the standpoint of infection, radiation causes two important types of injury. First, there is widespread destruction of the blood-forming organs and lymphoid tissue; second, the skin and gastrointestinal tract may be so damaged that necrosis and ulceration occur. The effect of these injuries is to deprive the body of defense mechanisms against infection and at the same time provide a pathway for the entrance of pathogenic organisms into the body. Experiments in animals have revealed that the large bowel is a particularly important source of infection in radiation injury, and the causative organisms are frequently Gram-negative bacilli. It was found that streptomycin and the broad spectrum agents, alone and in combination, were helpful in prolonging the life of mice exposed to large amounts of ionizing radiation, and it is anticipated that they would be highly effective in a similar situation in humans. Many other types of infection are known to have complicated radiation disease in humans, and it would be difficult to exaggerate the demands for antimicrobial therapy, or the benefits from its use in the event of an atomic bombing.

In summary, aureomycin or chloramphenicol, terramycin, penicillin, streptomycin, and the sulfonamide drugs provide specific therapy for many of our most serious infectious diseases. Virus diseases, in general, remain outside the range of effective therapy of these and other agents. Cortisone as an adjuvant therapy in typhoid has been described. Finally, the problem of antimicrobial therapy in an atomic disaster is briefly discussed.

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