PENICILLIN IN THE TREATMENT OF STAPHYLOCOCCIC SEPSIS

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Extensive staphylococcal cellulitis and staphylococcal cellulitis with bacteriemia have always been considered rather serious infections. Before the modern era of chemotherapy, persons fifty years of age or older who became victims of staphylococcal septicemia had approximately one chance in ten to recover. Mortality statistics gathered from large series of staphylococcal septicemia in which the patients were fifty years of age or older showed a mortality rate of approximately 90 per cent. After the introduction of sulfonamide therapy, mortality rates as low as 30 to 35 per cent were reported by some investigators. In other words, in cases of staphylococcal sepsis in which adequate sulfonamide therapy was employed the mortality rate was reduced from 90 to 30 or 35 per cent. Experience further has indicated that in order to obtain such a low mortality rate one must be certain that the concentration of the sulfonamide in the blood is between 16 and 20 mg. per 100 cc. Unless such a concentration is maintained, the mortality rates in general will be no lower than those observed before the advent of sulfonamide therapy. It may be difficult at times to maintain an adequate concentration of the sulfonamide, and such a high concentration is not without certain well-recognized complications.

After the introduction of the highly antibacterial substance, penicillin, it seemed reasonable to assume that even better results could be obtained in the treatment of staphylococcal sepsis. Compared with the sulfonamides, penicillin is exceedingly more antibacterial for most of the strains of staphylococci, and at the same time it appears to be relatively free of any serious toxic manifestations.

Because of the limited supplies of penicillin available, its use in the treatment of staphylococcal sepsis has, for the most part, been limited to those cases in which previous sulfonamide therapy had failed. The results have not been universally satisfactory, but it seems likely that, with the anticipated increase in the supply of penicillin, it may not be necessary to await sulfonamide failure before instituting penicillin therapy. When this becomes possible, it does not seem unreasonable to assume that far better results can be obtained. Any delay, regardless of trial with sulfonamide therapy or other measures, increases the hazard to the patient suffering from staphylococcal sepsis.
For the past two years we have undertaken experimental and clinical studies on the effectiveness of penicillin against a large variety of bacterial infections including staphylococcic sepsis. Although the number of cases of staphylococcic septicemia is not large, we were able to treat in one group fourteen patients of whom twelve recovered. In the two cases in which the patients failed to recover, sulfonamide therapy had been tried and both patients had evidence of valvular heart lesions at the time the administration of penicillin was started. This complication, in our experience, has not developed under adequate penicillin therapy. When such a complication develops, the prognosis is universally poor because the focus of infection cannot be eradicated.

In the present clinic on the treatment of staphylococcic sepsis, we are presenting two cases of severe staphylococcic septicemia associated with extensive cellulitis and complicated by pneumonia. Pneumonia is not infrequently seen in association with severe staphylococcic bacteriemia. The cases illustrate the problems involved in the successful use of penicillin in the treatment of staphylococcic sepsis.

REPORT OF CASES

CASE I.—The patient was a white man seventy-five years of age. He was admitted to the hospital on March 20, 1943, because of extensive cellulitis which involved the nose and entire left side of the face. Ten days previously, a rather severe infection of the upper part of the respiratory tract had developed. Three days later (seven days before his admission), a furuncle had developed on the septum of his nose. The furuncle had become exceedingly tender and had spread. Three days before his admission, cellulitis had developed in the nose and had involved the upper lid and the left side of the face. The cellulitis subsequently had involved the entire left side of the face and was spreading into the tissues of the neck. The left eye was swollen shut. On the day of his admission, the patient had a chill which was followed by a rather sudden rise in his temperature to 104° F. During the initial phases of the infection, adequate doses of sulfathiazole had been administered.

When he was admitted to the hospital, physical examination revealed the furuncle on the nasal septum. There were redness and induration of the upper lip, the left side of the nose and the left cheek. The eyelids on the left side were markedly swollen and edematous. The edema had spread into the tissues of the neck. There was purulent drainage from both sides of the nose (Fig. 66, a). At the time of his admission, the oral temperature was 100.6° F. and the pulse rate was 96 beats per minute. The leukocyte count was 13,700 per cubic millimeter of blood. In spite of the administration of adequate doses of sulfathiazole, the concentration of the drug in the blood was 5.4 mg. per 100 cc. Blood cultures obtained at this time subsequently revealed ten colonies of Staphylococcus aureus per cubic centimeter. Hour by hour the patient’s condition grew worse. Four hours after his admission the rectal temperature was 106° F., although he was still rational. At this time he complained of pain in the left side of the thorax. Physical examination of the thorax revealed evidence of bilateral pneu-
monia, and roentgenograms confirmed the physical findings (Fig. 67, a). The patient's condition subsequently became very critical. He was semicomatose and the rectal temperature remained between 103° and 104° F. At this time the administration of sulfathiazole was discontinued and penicillin therapy was instituted.
Fig. 67.—a, Extensive pneumonia in Case I; b, roentgenographic appearance of lungs after completion of penicillin therapy.
The sodium salt of penicillin was administered by the continuous intravenous drip method, which has been described previously.\textsuperscript{1, 2} Sixteen thousand Oxford units of sodium penicillin dissolved in 1 liter of physiologic salt solution was given every twelve hours. The total daily dose was 32,000 Oxford units. Penicillin therapy was continued in this fashion for twelve days. The patient's general condition improved rather dramatically during the next forty-eight hours of treatment. The temperature subsided gradually, which is usually characteristic in cases of sepsis in which penicillin is used. As is frequently seen when penicillin therapy is used, the edema of the soft tissues subsided rapidly. After this treatment had been continued for forty-eight hours, blood cultures still revealed a few staphylococci; however, cultures that were obtained subsequently failed to reveal any organisms. Improvement continued and the edema of the soft parts was practically gone on the fifth day of treatment (Fig. 66, b). The leukocyte count at this time was 8,600 per cubic millimeter of blood. By the tenth day, the appearance of the patient's face was practically normal (Fig. 66, c).

During the course of penicillin therapy there was evidence of improvement in the physical findings in the thorax. However, a pleural effusion developed on the left side and was slowly absorbed spontaneously. No other treatment was employed except oxygen therapy, which was continued during the first five days of the illness. Because of the pleural effusion which subsided spontaneously, it was necessary to keep the patient in the hospital for a total of twenty-two days. Penicillin therapy, however, was continued for only twelve days. At the time of his dismissal on the twenty-second day, the cellulitis of the face had subsided entirely. There were no physical findings on examination of the thorax. A roentgenogram of the thorax is shown in Figure 67, b. There were no toxic manifestations whatever associated with penicillin therapy administered in the manner described.

The second case is that of a patient also over fifty years of age who had extensive cellulitis of the arm which was complicated by staphylococci septicemia and pneumonia. This patient also had failed to respond satisfactorily to sulfonamide therapy.

\textbf{Case II.—}The patient was a white woman, fifty-seven years of age. She was admitted to the hospital on March 28, 1943, suffering from extensive cellulitis of the left forearm. The cellulitis had developed subsequent to a furuncle in the region of the left elbow. When the patient was admitted to the hospital she was very ill. The lesion resembled a huge carbuncle. The oral temperature was 102.4° F. and the pulse rate was 110 beats per minute. The cellulitis involved the greater portion of the left forearm and elbow. The axillary lymph nodes were not palpable. The leukocyte count was 13,300. Urinalysis revealed a moderate amount of albumin, a few hyaline and granular casts, a few erythrocytes and an occasional leukocyte. Blood cultures revealed the presence of 100 colonies of Staphylococcus aureus per cubic centimeter of blood. Initial treatment consisted of the administration of 15 grains (1 gm.) of sulfathiazole every four hours. Hot packs were applied to the left arm. The following day roentgen therapy was applied to the infected region. Forty-eight hours after admission, in spite of this treatment, the patient was still seriously ill. Her temperature continued to rise daily to 102° F. Administration of sulfathiazole was discontinued and penicillin therapy
Fig. 68.—a, Extensive bilateral bronchopneumonia (more marked on the right side), in Case II; b, roentgenographic appearance of lungs after completion of penicillin therapy.
was instituted by the continuous intravenous drip method. At the time penicillin therapy was instituted, blood cultures still revealed the presence of Staphylococcus aureus. The patient was given 16,000 Oxford units of the sodium salt of penicillin in 1 liter of physiologic salt solution twice daily. This was administered at the rate of 30 drops per minute.

On her fourth day in the hospital, the patient complained of pain in the right side of the thorax. Physical examination revealed signs suggestive of bilateral pneumonia. Roentgenographic examination of the thorax disclosed extensive bilateral bronchopneumonia which was somewhat more extensive on the right side (Fig. 68, a). Oxygen was administered by means of a mask. In spite of the complicating pneumonia, there was marked improvement in the cellulitis of the arm. Blood cultures obtained forty-eight hours after the institution of penicillin therapy revealed the presence of a few colonies of Staphylococcus aureus. Blood cultures taken seventy-two hours after the beginning of treatment were negative. The blood cultures remained negative throughout the convalescence. The patient received a total of 232,000 Oxford units of penicillin in seven days. The extensive cellulitis of the left arm became localized forty-eight hours after penicillin therapy was instituted. A few fluctuant regions were present, and these were incised. Thereafter the patient improved steadily; the blood cultures remained negative, and the pneumonia slowly resolved. A small pleural effusion developed on the right side but was absorbed without any interference. Roentgenograms made at intervals revealed small areas of increased density in both lung fields, but these disappeared and the last roentgenograms revealed only a few localized areas of fibrosis (Fig. 68, b). The total period of hospitalization was seventeen days, and penicillin was administered for seven days. At the time of the patient's dismissal from the hospital, her arm was healed completely.

A very interesting situation developed with regard to the patient's urinary findings. While she still was receiving penicillin she complained of dysuria and the urinalysis revealed 40 leukocytes in each microscopic field as viewed with the high power objective. Cultures of the vesical urine at this time revealed the presence of Escherichia coli. The urinary infection persisted until small doses of sulfathiazole were administered. The urinary infection subsided rapidly under sulfathiazole treatment, but a definite drug fever developed while she was being treated for the Escherichia coli infection. The fever was not associated with penicillin therapy and the temperature quickly returned to normal as soon as the administration of sulfathiazole was discontinued.

This is an excellent example of selective antibacterial activity of penicillin. It is obvious that penicillin was present in the urine in adequate amounts, but since penicillin is ineffective against Escherichia coli, the development of Escherichia coli bacilluria is quite understandable. No toxic manifestations whatever were associated with the administration of penicillin.
COMMENT

These two cases of staphylococcic septicemia are somewhat similar. In one case, the septicemia resulted from a rather severe or extensive localized staphylococcic cellulitis of the face. In the other case, the septicemia was secondary to a very extensive cellulitis of the left arm. Both patients were obviously not responding to sulfonamide therapy. Both patients were over fifty years of age and, as previously pointed out, staphylococcic sepsis in this age group carries a high mortality. In both instances, the staphylococcic septicemia was complicated by rather extensive pneumonia. It must be assumed that the pneumonia was probably staphylococcic in origin. The presence of pneumonia complicating septicemia is a finding of grave prognostic significance. Both patients were treated with penicillin, which was administered by the intravenous drip technic. Thirty-two thousand Oxford units per day was administered in both instances. Both patients were treated early in our experience with penicillin therapy. We believe at the present time that 40,000 to 60,000 Oxford units per twenty-four hours is the most satisfactory dose; however, we have obtained satisfactory results in other cases by using only 32,000 Oxford units in twenty-four hours when the drug is given by the intravenous drip method.

It is of considerable interest that the patient in Case II had evidence of an infection of the urinary tract at the time of her admission to the hospital. She was treated at first with sulfathiazole because of the staphylococcic sepsis. No urinary symptoms were present while sulfathiazole was being administered; however, the staphylococcic sepsis was not responding satisfactorily to this therapy. The administration of sulfathiazole was discontinued and the staphylococcic sepsis was treated satisfactorily with penicillin. While she was receiving penicillin, she evidently had an Escherichia coli infection of the urinary tract, as evidenced by positive cultures. When very small amounts of sulfathiazole again were administered for the Escherichia coli infection, a drug fever developed. This unquestionably was due to an acquired sensitivity to the drug. It is probable that had it been necessary to treat her with sulfathiazole alone she also may have exhibited this toxic manifestation to the drug. Penicillin is very effective against most gram-positive pathogenic bacteria, but as illustrated in Case II it was ineffective against a gram-negative organism. A knowledge of the selective antibacterial activity of penicillin as well as of other chemotherapeutic agents is exceedingly important in the successful treatment of bacterial infections. It should be emphasized that localized collections of pus probably should be drained in conjunction with penicillin...
therapy. Penicillin therapy, or chemotherapy in general, is no substitute for sound medical judgment.

Although we have used the continuous intravenous drip method of administering penicillin for the most part, it must be stated that the intermittent intramuscular method is also satisfactory. We resort to this form of administration when suitable veins are not available. When intramuscular therapy is used the usual dose employed is between 80,000 and 160,000 Oxford units per day.\(^3\) Ten thousand or 20,000 Oxford units of penicillin are dissolved in 4 or 5 cc. of physiologic salt solution and administered intramuscularly into the gluteal or deltoid muscles. The gluteal muscles are more desirable. This method requires eight injections per day; therefore, it places considerable extra demand on the medical personnel. Local regions of induration and pain may occur at the site of intramuscular injection. The only local complication which has been observed after the continuous intravenous treatment with penicillin is the development of venous irritation at the site of injection (so-called penicillin phlebitis). This is probably due to the impurities present in the penicillin now available and is not due to penicillin per se. If a satisfactory preparation of penicillin is available, this reaction will not occur in more than 5 per cent of cases. Moist or dry packs applied locally to the site of irritation will usually result in rapid subsidence of this complication.

Early institution of adequate penicillin therapy in the treatment of staphylococcic sepsis promises to reduce greatly the morbidity and mortality of this rather serious disease. We believe that early and adequate treatment of cellulitis involving the soft parts will prevent not only the development of septicemia but also the development of distant metastatic abscesses and probably osteomyelitis subsequent to infection of the soft tissue.

REFERENCES