focal ulcerative bronchitis and extensive interstitial pneumonitis are most likely the result of infection with the bacillus of Legionnaires' disease.

The histopathologic picture in our patient's specimen from pulmonary biopsy differs from that which is typical of acute bacterial pneumonia and is more consistent with changes characteristically found when viruses, rickettsiae, chlamydiae (bedsoniae), or Mycoplasma pneumoniae organisms are the infecting agents.\(^4,5\) Since the histologic patterns observed in such infections are non-specific, Legionnaires' disease may perhaps be added to the list of infections causing pulmonary interstitial infiltration with mononuclear cells; further differentiation among the diseases in this group by histopathologic examination is at present not reliable.

**REFERENCES**


**Treatment of Pulmonary Melioidosis with Combination of Trimethoprim and Sulfamethoxazole**


Treatment with a combination of trimethoprim and sulfamethoxazole proved lifesaving in a patient with pulmonary melioidosis after therapeutic failure occurred with other antibiotics to which the organisms were sensitive in vitro. Antagonistic interaction of drugs occurred when the combination of trimethoprim and sulfamethoxazole was given along with other antibiotics. The combination of trimethoprim and sulfamethoxazole should be considered a major addition to the pharmacologic armamentarium for the treatment of pulmonary melioidosis.

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The search for the ideal drug in the treatment of melioidosis continues. The organism, Pseudomonas pseudomallei, is not only resistant to therapy with many antibiotics but clinically may fail to respond to those drugs to which it is sensitive in vitro. It has been shown that therapy with the combination of trimethoprim and sulfamethoxazole is effective in vitro, and one patient with pulmonary melioidosis has been treated successfully with this pharmacologic combination. We have recently seen a patient whose infection failed to respond to all other antibiotics to which in vitro sensitivity was shown but whose illness did resolve with therapy with trimethoprim and sulfamethoxazole; however, the therapeutic response occurred only when this combination was given alone (in order to avoid pharmacologic antagonism) and in four times the conventional dosage.

CASE REPORT

This 23-year-old aircraft mechanic was referred to our hospital in June 1976 for evaluation of a persistent pulmonary infection. The patient first became ill in November 1975, with the sudden onset of cough, hemoptysis, chills, and fever. A patchy infiltrate with cavities was seen in the left upper lobe on the chest x-ray film.

Three months of intermittent therapy with various antibiotics, including methicillin, gentamicin, penicillin, and clindamycin, gave inconsistent relief of symptoms. Because of continued severe hemoptysis, the patient underwent left upper lobectomy in February 1976; however, within a few weeks the cough and fever recurred, and he was referred to our hospital.

Physical examination revealed only rales in the left upper pulmonary field. The chest x-ray film showed loss of volume of the left lung and cavitory infiltrates.

Further history revealed that the patient had originally become ill in the Philippine Islands. His duties there included the washing of aircraft wheel wells which were dusty from previous landings in Southeast Asia. These facts, together with the clinical history, suggested the diagnosis of melioidosis, and P pseudomallei was promptly isolated from the sputum. Complement-fixation tests for melioidosis were eventually positive at a titer of 1:256.

Initial minimum inhibitory concentrations for the following antibiotics were noted: tetracycline, 4 μg/ml; chloramphenicol, 16 μg/ml; kanamycin, 32 μg/ml; and trimethoprim and sulfamethoxazole, 1 μg/ml and 19 μg/ml, respectively. There was resistance to all other drugs tested. Therapy with tetracycline (500 mg four times daily) was begun, and the patient improved symptomatically. Growth of P pseudomallei on weekly cultures of sputum changed from "heavy" to "light." During the second month of therapy, symptoms recurred, cultures became strongly positive, and the chest x-ray films showed progression of the left-sided infiltrate, with a new infiltrate in the right lung.

Finally, after several episodes of massive hemoptysis, single drugs and multidrug combinations of tetracycline (750 mg orally every six hours), chloramphenicol (25 mg/kg of body weight intravenously every six hours), and kanamycin (1 gm daily intramuscularly) were administered over three weeks, again without clinical response. Bacteriostatic activity in the serum was noted up to dilutions of 1:8 with various combinations of drugs, but none showed bactericidal activity. Antagonism of drugs occurred when therapy with trimethoprim and sulfamethoxazole was added to the combination of the other three drugs, resulting in the loss of all bacteriostatic activity. Therapy with the combination of trimethoprim (160 mg) and sulfamethoxazole (800 mg) orally twice daily alone also proved unsuccessful. The dosages of these two drugs were then increased to 240 mg and 1,200 mg, respectively, four times daily. Bactericidal activity to dilutions of 1:8 were then noted, with no previous pharmacologic therapy having produced bactericidal activity. Dramatic resolution of symptoms promptly occurred, and cultures of sputum were negative within three weeks. Treatment was continued for a total of seven months, with rapid resolution of the pulmonary infiltrates and only minimal left-sided fibrosis remaining.

DISCUSSION

Therapy with trimethoprim and sulfamethoxazole in this patient with melioidosis appears to have been life-saving, since administration of the other more commonly used drugs failed to control the infection. Bactericidal levels of tetracycline, chloramphenicol, and kanamycin could not be attained; and, indeed, the patient never showed more than a temporary response to therapy with these medications. Furthermore, it was only with the high dosage of 240 mg of trimethoprim and 1,200 mg of sulfamethoxazole four times daily that in vitro bactericidal activity could be attained. It is of interest that John et al. reported a bactericidal titer of 1:4 with a dosage of 160 mg of trimethoprim and 800 mg of sulfamethoxazole twice daily, with clinical cure of his patient with melioidosis.

A previous laboratory investigation has suggested that pharmacologic antagonism might occur when therapy with a combination of antibiotics is used; and, indeed, that did appear to occur in our patient. When therapy with a combination of trimethoprim and sulfamethoxazole was added to the regimen of tetracycline, chloramphenicol, and kanamycin, no bacteriostatic or bactericidal effect could be noted on testing of the serum. Only when the combination of trimethoprim and sulfamethoxazole was used as a single agent was a bactericidal effect demonstrable. This observation has practical implications, since many authorities have suggested the use of therapy with multiple drugs, particularly in those with disseminated melioidosis.

Our patient was also interesting from the epidemiologic standpoint, as melioidosis is rare in the Philippine Islands. We believe that his infection likely came from cleaning the wheel wells of aircraft which had been used on earthen runways of the Southeast Asian subcontinent, a major endemic area. An aerosol of the dust from the wheel wells was undoubtedly created when they were hosed down, and aerosols are known to induce the disease.

This patient also illustrates the importance of considering this disease in any patient with a respiratory infection who has been exposed to the endemic area. Specimens should be plated on both routine and Sabouraud's agar; and if plates are not kept for 72 to 96 hours, the characteristic wrinkled colonies will not be noted, and the organism may be misidentified. Another
prosthetic cardiac valves is intravenous therapy with high doses of penicillin or ampicillin, with the addition of an aminoglycoside.  

Surgical replacement of the infected prosthesis is recommended when medical therapy fails.  

Despite these measures, a high mortality has been noted for prosthetic valvular endocarditis.  

Whereas endocarditis occurring on a natural valve has been successfully treated with oral therapy, no such information is available concerning the therapy for bacterial endocarditis on a prosthetic valve.

A patient with endocarditis due to S. faecalis on an artificial aortic valve who was unable to tolerate any intravenous therapy was treated successfully with large oral doses of amoxicillin and intramuscular administration of streptomycin. This combination of drugs yielded a satisfactory bactericidal effect on the serum, which correlated with the recovery of the patient.

**Case Report**

A 63-year-old man was admitted to the Chaim Sheba Medical Center, Tel-Hashomer, Israel, because of the recent onset of left hemiparesis following one month of fever and malaise. The patient had undergone an aortic valvular replacement and aneurysmectomy of the ascending aorta for syphilitic cardiovascular disease three years prior to this admission. His postoperative course had been uneventful, and he remained in good health until the present illness. The patient denied any dental or genitourinary manipulations.

On admission the patient appeared to be in no acute distress. His temperature was 38.4°C (101.1°F), the blood pressure was 180/80 mm Hg, and the pulse rate was 68 beats per minute. A grade 3/6 systolic murmur was heard over the aortic area; the murmur did not radiate. A small petechia was observed on the patient's left thumb. Neurologic examination revealed mild paresis of the left arm and leg. The findings from the rest of the physical examination were normal. No other signs of endocarditis were observed.

The results of laboratory tests were as follows: hemoglobin level, 8.7 gm/100 ml; hematocrit reading, 23 percent; white blood cell count, 9,600/cu mm, with a shift to the left; erythrocyte sedimentation rate, 25 mm in the first hour; VDRL test, negative; and Treponema pallidum immobilization test, positive. The rest of the chemical findings on the blood and cerebrospinal fluid were normal. Six consecutive cultures of blood grew S. faecalis, and the minimum inhibitory concentration of ampicillin was 1.75 µg/ml and of amoxicillin 0.5 µg/ml. The minimum inhibitory concentration of streptomycin was 100 µg/ml. Synergism was demonstrated both for the combination of ampicillin and streptomycin and for amoxicillin and streptomycin.

The patient was started on therapy with 12 gm of ampicillin intravenously daily and 1 gm of streptomycin intramuscularly. Very severe thrombophlebitis developed rapidly in all of the veins into which ampicillin was introduced. Intravenous therapy with ampicillin was therefore changed to oral administration of 24 gm of ampicillin daily, and therapy with streptomycin was continued; however, the bactericidal effect in the serum varied between 1:2 and 1:16 on various occasions. Repeated attempts to administer medication intravenously failed because of immediately recurring grave thrombophlebitis. While the patient was receiving oral therapy with ampicillin (total, ten days), atrial fibrillation appeared, and his fever persisted. Therefore, oral administra-