Proteus Morganii Meningitis Treated with Trimethoprim-Sulfamethoxazole (Co-Trimoxazole)

Charles P. Darby, M.D.,* Otis Hill, M.D.†

ALTHOUGH members of the genus *Proteus* are very common in nature, fortunately they seldom invade the cerebrospinal fluid. The species known as *Proteus morganii* has been well recognized as a cause of meningitis in neonates. It has also been a difficult organism to eradicate from the cerebrospinal fluid, thus giving rise to an extremely high morbidity and mortality in the neonate.[1,2] After the neonatal period *Proteus* meningitis is unusual, being ordinarily associated with some congenital malformation allowing contamination of the cerebrospinal fluid from the exterior. A few instances have followed otitis media and sinus thrombosis. The present childhood case is reported because of the very prompt response to the combination of trimethoprim and sulfamethoxazole, an antimicrobial combination that has recently been introduced in this country.

* Associate Professor of Pediatrics, Infectious Disease Section, Medical University of South Carolina, Charleston, S.C. 29401.

† Fellow in Pediatrics, Infectious Disease Section, Medical University of South Carolina.

Case Report (Fig. 1)

This 2½-year-old boy was transferred to the Medical University Hospital with the diagnosis of *Proteus morganii* meningitis. He first became ill approximately six weeks previously with a headache, stiff neck, and high fever. When he was hospitalized, lumbar puncture revealed findings consistent with a purulent meningitis and the culture grew out *Proteus morganii*. The patient had an 11-day course of carbenicillin, 400 mgm/kg/24 hr, and kanamycin 15 mgm/kg/24 hr with a favorable response. He was discharged and remained home for approximately two weeks completely free of symptoms and afebrile.

Suddenly his symptoms recurred and his fever spiked to 104 F and the patient was reassessed. Again findings were consistent with meningitis and the culture grew out *Proteus morganii*. Sensitivity studies done by the Kirby Bauer technique showed the organism to be "sensitive" to carbenicillin and "intermediate" to kanamycin. The combination of carbenicillin, 600 mgm/kg/24 hr, gentamicin, 7 mgm/kg/24 hr, and chloramphenicol, 100 mgm/kg/24 hr, was prescribed. He showed some improvement in the next few days, followed by a return of high fever spikes, headaches, lethargy, and nuchal rigidity.

A 2 × 3 cm capillary hemangioma was noted over the lower spine at approximately the area of lumbar vertebrae 4 and 5. In the center of this hemangioma was a small dimple.

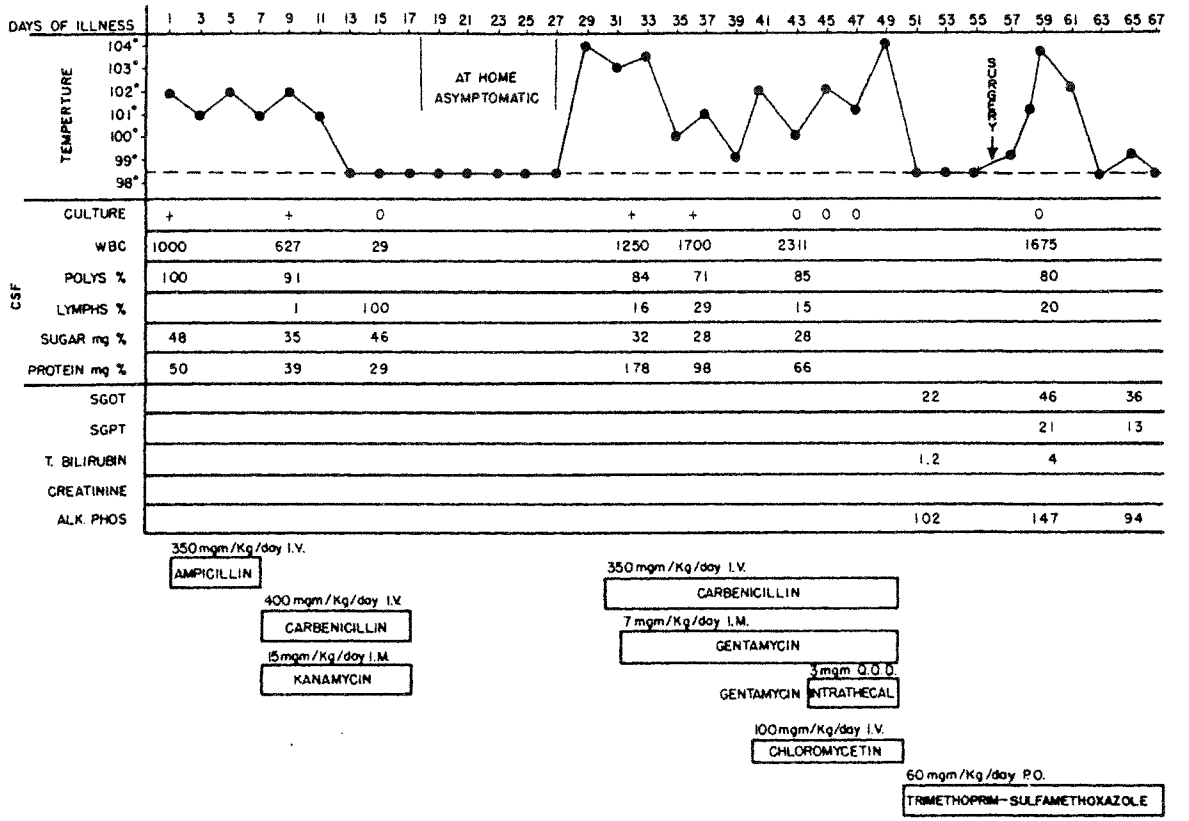

FIG. 1.

A loading dose of co-trimoxazole was started based on 80 mgm/kg of sulfamethoxazole followed by 40 mgm/kg/24 hr given in two divided doses every 12 hours. *In vitro* sensitivities done by the disc method showed the organism to be extremely sensitive to co-trimoxazole. Within 24 hours he became afebrile, alert, and ambulatory for the first time in approximately two weeks. On the fifth day of therapy, a dermal sinus was dissected down to the spinal cord and along with a dural abscess was removed. The patient had a short febrile response for 48 hours after surgery.

The patient now seems to be completely recovered without any neurological sequelae. Co-trimoxazole was continued for three weeks following surgery. No further lumbar punctures were done because the patient continued to be afebrile and asymptomatic.

Discussion

The first episode of meningitis in this child responded well to carbenicillin and kanamycin. However, the same antibiotics failed to control the recurrent infection. On both occasions, the Kirby Bauer technique indicated that the organism was sensitive to carbenicillin.

Ross, *et al.* have reported a similar case of a nine-month old child with *Proteus morganii* meningitis as a complication of a dermal sinus. In this case, it was necessary to excise the sinus and abscess before the patient became afebrile on ampicillin therapy.

Antibiotic treatment of *Proteus* meningitis in infants has not been very successful. Schlerzer reviewed the reported cases up to 1966 and found the overall mortality rate of 53 cases to be 55 per cent. For the 18 cases under one year of age, the rate was 61 per cent. The morbidity is also severe—many cases end up with retardation, hydrocephalus, seizures, or other neurological deficiencies. Schlerzer also reported two successfully treated cases of *Proteus mirabilis* meningitis treated with ampicillin. *Proteus mirabilis* in general has been shown to be sensitive to ampicillin. Ross treated four

TABLE 1. *Experience of Lafaix[8] with Co-trimoxazole, Triple Therapy, and Ampicillin in 844 Cases of Meningitis*

Germ	Per Cent Mortality		
	Sulfamethoxazole Trimethoprim (108 cases)	PNC. g + Chloramphenicol + Sulfamethoxazole (606 cases)	Ampicillin (130 cases)
N. meningitidis	22	13.5	9
D. pneumoniae	55	55	44.5
H. influenzae	33.5	43	9
Enterobacteriaceae	0/1	6/6	5/7
Others	—	5/7	3/8
Gram-negative bacilli	0/1	55	—
Unknown	19.5	39	20.5
Total mortality	28 %	38.5%	27 %

cases successfully with carbenicillin. However, *Proteus rettgeri, Proteus morganii,* and *Proteus vulgaris* have usually been resistant to ampicillin but sensitive to carbenicillin. Despite the demonstration of sensitivity *in vitro* to carbenicillin, in this case and others, it is difficult to eradicate the organism from the cerebrospinal fluid. Co-trimoxazole is a fixed mixture of one part trimethoprim to five parts sulfamethoxazole. Trimethoprim blocks the synthesis of tetrahydrofolic acid by bacteria, and the sulfonamide inhibits the conversion of paraaminobenzoid acid to dihydrofolic acid. The combination is synergistic and often bactericidal. It has been used extensively in other parts of the world for a number of years, but only recently has become available in this country with a restricted recommendation that it be used only in urinary tract infections in adults and children over 12 years of age. Studies are being carried out to test its effectiveness with other types of infections and in younger age groups. Both chemicals are relatively small molecules that are rapidly absorbed from the gastrointestinal tract and diffuse readily into the cerebrospinal fluid and other tissue fluids.[4]

Because of the high mortality rate and the apparent effectiveness of co-trimoxazole against enteric organisms, McDonald has recommended adding co-trimoxazole to the antibacterial therapy in neonatal meningitis.

Most strains of enteric and urinary bacteria with the exception of *Pseudomonas aeruginosa* are susceptible to this combination.[5] *Neisseria gonorrhoeae* is usually sensitive and most strains of *Hemophilus influenzae*[6] and one strain of *Pneumococcus*[7] have shown some resistance. Rashes, glossitis and I gastrointestinal upset have been the most common adverse reactions. Steven-Johnson syndrome, long recognized as an infrequent complication of sulfamethoxazole, may likewise occur with the use of the combination of these two drugs.

Lafaix[8] studied the use of co-trimoxazole in the treatment of meningitis in Africa. He found the combination as effective as triple therapy with chloramphenicol, sulfa, and penicillin and ampicillin alone (Table 1). One must keep in mind that these cases were collected in Africa where conditions were severe and admissions were often late in the course of the illness.

Because of the high mortality rate and the apparent effectiveness of co-trimoxazole against enteric organisms, McDonald[9] has recommended adding co-trimoxazole to the antibacterial therapy in neonatal meningitis. Lacoste[10] treated six cases of meningococcal meningitis with co-trimethoxazole. Four of these cases were cured with the drug and two improved but required other antibiotics to eradicate the organisms from the cerebrospinal fluid. The organisms isolated from the two cases that did not respond well were shown to be resistant *in vitro.* These data in

no way imply that co-trimoxazole should be considered a primary drug in treating meningitis caused by common organisms. However, its effectiveness in treating unusual organisms that may be resistant to other antibacterial agents needs to be explored further.

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ter in place for more than a few days sometimes causes thrombosis or emboli. It should therefore be removed as soon as possible. Subsequently (and also if attempts at umbilical artery catheterization fail), arterial blood samples can be obtained by puncture of peripheral arteries.

After the acute phase of severe disease, hypoxia may persist for many days or weeks. At this stage, the main cause of the hypoxia is no longer right-to-left shunting of blood, but uneven ventilation-perfusion relationships in the lungs. Therefore, small changes in inspired oxygen concentration cause large changes in Pa_{O_2}. Measurements of inspired oxygen concentration and Pa_{O_2} should still be performed, until the infant has an adequate Pa_{O_2} when breathing air. Measurements of Pa_{O_2}, as well as of Pa_{CO_2} and pH, are usually made on blood samples obtained intermittently from arteries.

Because the results are often needed immediately, most intensive care units prefer to keep the equipment for blood gas analysis within the unit.

Some authors have suggested that, in the presence of moderate arterial hypoxemia, oxygen release in the tissues may be seriously impaired in infants with hyaline membrane disease. This could be caused by the high affinity of fetal hemoglobin for oxygen, which results from the absence of functionally adequate amounts of 2,3-diphosphoglycerate (2,3-DPG) which is necessary to decrease this affinity (Delivoria-Papadopoulos, Roncevic & Oski, 1971). They have therefore recommended exchange transfusion with fresh adult blood, the red cells of which have a much higher functioning 2,3-DPG content. Since other methods of treatment are so effective, and adverse effects caused by impaired oxygen release (such as the development of a metabolic acidosis) are very unusual provided the Pa_{O_2} is kept above about 35 to 40 mm Hg, it seems unlikely that exchange transfusion to promote oxygen release will find a place in the treatment of hyaline membrane disease except under very rare circumstances.—*E. O. R. Reynolds in Management of Hyaline Membrane Disease,* British Medical Bulletin, *January 1975.*
