Bacterial Meningitis: Some Epidemiologic and Clinical Factors in Diagnosis

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In ancient times all acute delirium states were known as "phrenesis." It was not until the 17th century that inflammations of the meninges and cerebrum were differentiated from each other.[1] By the 19th century meningitis had been described to the extent that a number of epidemics were reported both in the United States and Europe,[2] but it was the development of the lumbar puncture by Quincke in 1893[3] which opened up a new diagnostic era for the disease.

Therapeutically, the history of bacterial meningitis can be divided into three phases (1) that of the pretreatment era (prior to 1906), (2) serological treatment and (3) the antibiotic treatment which began with Domagk in 1932 when sulfonamides were first used.

Etiology

During the latter part of the 19th century and the early years of the 20th century, the meningococcus was considered the only important cause of meningitis other than tuberculosis. Disease caused by *Diplococcus pneumoniae, Haemophilus influenzae* and the streptococcus were considered sporadic and listed along with colon bacilli, Salmonella, *Pasteurella pestis* (plague), and *Pseudomonas mallei* as unusual causes.[4] It soon became apparent that there were other common causes of meningitis besides *Neisseria meningitidis*. In a study by Ward and Fothergill,[5] 83% of their nontuberculous cases were caused by *D pneumoniae, N meningitidis*, or *H influenzae*. Indeed, other early authors, while usually not giving figures, stated these to be the most common agents, and it is extremely interesting that when one looks at recent series[6,7,8] in the antibiotic era, these organisms remain the most common agents of meningitis (Fig 1). Note also that these studies are from three diverse areas of the United States. Not all studies have agreed with them, however; two, one from the Mayo Clinic[9,10] and one from Boston City Hospital,[11] showed an alarmingly high percentage of cases due to *Staphylococcus aureus*. Part of this could be explained in the Mayo series by the large number of patients with neoplastic or congenital disorders. These data were not given in the Boston series, but with half their cases being caused by *S aureus* one wonders whether the meningitis was caused by these disorders or by hospital-acquired infections. In addition the Boston study revealed a number of patients with pneumococcal pleural empyema who developed meningitis yet had sterile cerebrospinal fluid (CSF). The authors did not include these cases in the pneumococcal group although they probably should have.

The importance of hospital-acquired infections is shown by the study of Hodges and Perkins.[12] If one excludes those cases of suspected bacterial meningitis where no organism was isolated, *D pneumoniae, N meningitidis*, and *H influenzae* accounted for 72% of the total cases of meningitis. However, among those infections acquired in the hospital, these organisms accounted for only 7% of cases whereas *S aureus* accounted for 21% and Staphylococcus (all species), Streptococcus, and gram-negative bacilli (especially pseudomonas) accounted for 93% of the cases!

A number of studies have shown that the causative agent depends upon the age of the patient; these

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Etiology	% of Cases		
	Boston (6)	Seattle (7)	Atlanta (8)
D pneumoniae *N meningitidis* *H influenzae*	71	73	77
Others	29	27	23

Fig 1—Percentage of cases of bacterial meningitis due to various etiologies. All studies fall within the era of antibiotic therapy.

studies are consistent in their findings and are summarized in Figures 2 and 3.

The reason for this age variation is not entirely clear. The neonate may be more susceptible to the organisms listed because it is deficient in the immunoglobulin IgM which neither crosses the placental barrier nor is produced by the newborn and which is thought to be the bactericidal immunoglobulin for gram-negative organisms. In addition the phagocytic and bactericidal activity of the leukocytes in newborns may be impaired; as debilitation also affects these functions, this may account for the occurrence of these organisms in the hospital patient and the elderly.

The high incidence of *H influenzae* in young children but not in neonates may be ascribed to the fact that neonates acquire antibodies to *H influenzae* from the mother then lose them within two months, not producing their own until 2 to 3 years of age.

Age-Related Etiology of Bacterial Meningitis

Age	Predominant Cause
0-2 mo	Gram-negative bacilli Streptococcus, groups B *S aureus*
2 mo-3 yrs	*H Influenzae* *D Pneumoniae* *N Meningitidis*
3 yrs-young adult	*D Pneumoniae* *N Meningitidis*
Elderly	*D Pneumoniae* Gram-negative bacilli Streptococcus, group B *S aureus*

Fig 2—Distribution of bacterial meningitis according to age.

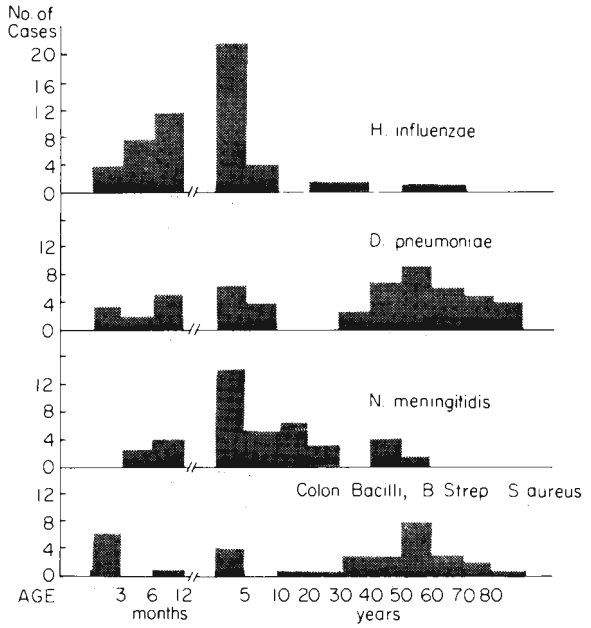

Fig 3—Distribution of bacterial meningitis by age, with number of cases to give relative frequencies.

Children are also born carrying maternal antibodies to the meningococcus which disappear after a few months; antibodies increase again from 2 to 12 years of age. Since the infection is thought to spread via the nasopharynx, this would explain its prevalence in school-age children, its disappearance as these groups develop immunity to the prevalent strain, and its reappearance when new social groups of people are formed as in military camps.

Incidence

There can be no doubt that although the relative frequencies of the different forms of bacterial meningitis have remained fairly constant, the absolute numbers have fallen dramatically since the advent of adequate chemotherapy. During the epidemic of 1904-1906, New York City registered 6,755 cases of meningitis.[4] The census of the city was 4,766,883 in 1910, giving an estimated attack rate of 142/100,000.

Although epidemics have sprung up periodically (Fig 4), with the advent of antibiotics the number of cases of meningococcal meningitis has steadily declined; in 1966, 3,381 cases were reported whereas in 1975 the figure had dropped to 1,478.[13] One must keep in mind that these are reported cases. Since meningococcal meningitis is the only reportable bacterial meningitis this figure is a gross miscalculation

of the total number of cases of bacterial meningitis which have been estimated to be between 10,000 and 20,000 in the United States.[14]

Certain factors are also important in attack rates. For the general population the frequency of the disease is 7/100,000; however, in neonates it jumps to 310/100,000.[15] Prematurity as well as dural defects, trauma, splenectomy, hypogammaglobulinemia, or sickle cell disease predisposes the newborn to meningitis.[6,7,14,16,17] Alcoholism in the adult has a high association with pneumococcal meningitis; it is of interest that this was noted in the preantibiotic era as well. Debilitating diseases, such as tumors (especially lymphoid), and surgery also increase susceptibility to meningitis. The spread of disease to the central nervous system (CNS) or recurrent meningitis can occur with chronic or acute mastoiditis, sinusitis or otitis media, CSF rhinorrhea, bacterial endocarditis, and pneumonia. One often finds that meningitis caused by one of the more unusual organisms is associated with one of these diseases.

Mortality

Prior to serum therapy or antibiotics the mortality from meningococcal meningitis was exceedingly high. In the pandemic of 1904-1909 the fatality rate ranged between 70% to 90% regardless of the city.[4] In a number of outbreaks in various European countries during this time the mortality rate was essentially the same though in some cases it dropped as low as 30% to 40%. Pneumococcal meningitis was thought to be even more lethal with death being the rule and survival being considered a reportable case.

Introduction of serum therapy brightened the outlook at least for meningococcal disease. In a study reported by Flexner,[18] the overall mortality dropped to 31%, certainly a triumph in medical therapy. In the era of antibiotics mortality has greatly changed though it seems to have leveled off at 2000 deaths per year.[13,19] It is very dependent upon the etiology as is seen in Figure 5. Clearly the neonatal group still has an extremely high mortality rate whereas the mortality in *H influenzae* is quite low. The percentage mortality for meningococcus has remained relatively stable for a number of years although pneumococcal deaths remain disturbingly high despite what would appear to be adequate antibiotic therapy. A number of factors come into play including the clinical state of the patient at the time of therapy and the toxins released by the bacteria. An additional noteworthy fact is that one study showed that 28% of fatal cases in children were not diagnosed during life.[20]

MENINGOCOCCAL INFECTIONS—Reported Cases per 100,000 Population by Year, United States, 1920–1975

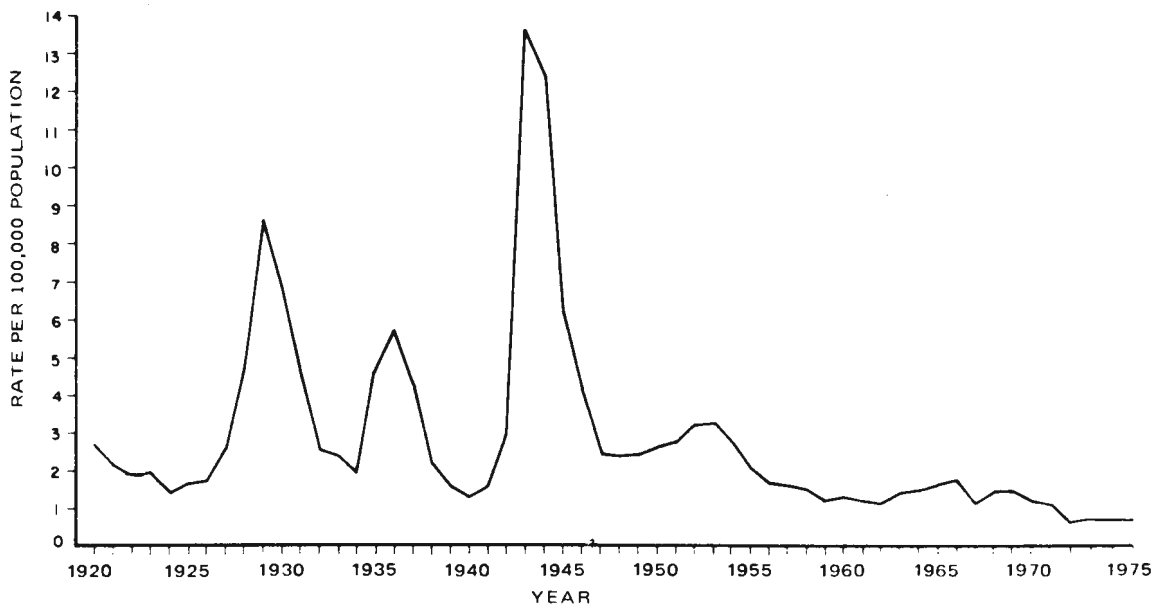

Fig 4—Reported rate of meningococcal infection over the past 55 years. Note the marked dampening of outbreaks following the introduction of penicillin.

Etiology	Percent Mortality for Meningitis					
	Seattle 1950-60 (7)	Boston 1956-62 (6)	Atlanta 1969-72 (8)	Oxford 1969-73 (20)	USA 1966 (19)	USA 1974 (19)
D pneumoniae	59	29	39	16		
H influenzae	18	8	0	6		
N meningitidis	13	15	20	11	26	23
Neonatal Group	64	58	57	44		

Fig 5—Percent mortality for different forms of bacterial meningitis. Note that the series from Oxford included only children which may account for the low mortality with pneumococcus.

A discussion of some of the factors affecting mortality should be prefaced by some observations on the clinical picture in meningitis.

Clinical Aspects

Neonatal meningitis. Meningitis in the newborn not only has a different etiology from the other age groups but also different clinical signs.[6,14,21] The signs are often deceptive and may resemble those of other diseases; the best help in making the diagnosis comes simply from having a suspicion that the disease exists.

The usual signs of meningeal infection—neck stiffness and fever—are often absent. The neonate may even be hypothermic, especially if premature. The most consistent signs are those of irritability or listlessness, poor feeding, and vomiting. Bulging of the fontanelle is characteristic but may be a late sign; unexplained jaundice may also occur as may seizures. Examination of the peripheral blood smear is also often unrewarding though either a leukopenia or a leukocytosis should raise suspicion as should a thrombocytopenia. It should be kept in mind, however, that a leukocytosis may be normal in newborns. One clue may be a neutrophilic leukocytosis since lymphocytes predominate in the normal infant for the first three to four years. Blood cultures can be invaluable in identifying the causative agent since they are positive in 70% to 80% of cases; this also applies to the urine.[14] The CSF characteristically shows an elevated protein and cell count with predominant polymorphonuclear cells. The glucose level is reduced but is related to the systemic blood sugar levels so that a simultaneous blood sugar should be obtained. CSF cultures usually yield an organism but 13% of cases[22] in one series and 6% in another[21] did not do so. In the latter study those with negative cultures had positive smears, pointing up the importance of this examination.

Predisposing factors to meningeal infection include difficult deliveries (50% to 65% of cases), remote infections (gastrointestinal, respiratory, skin, omphalitis, catheterization of umbilical vessels), and congenital anomalies (meningomyelocele).[23–26]

Older age groups. In older children and in adults the clinical aspects are much clearer. There is usually a prodromal state with symptoms referable to an upper respiratory infection, ear infection, or nonspecific "flu" symptoms. Medical attention is sought early, usually within 72 hours.[21] In one series all adults and all children older than 2 years save one (who was age 2) had stiff necks,[21] although another series had only a 33% incidence of this phenomenon.[7] Kernig and Brudzinski signs were variable and could not be relied upon as much as the stiff neck. Fever over 38 C is commonly seen as are headache, vomiting, and lethargy—headache is especially frequent in patients over 5 years of age.

In *H influenzae* meningitis, fever was the only symptom present in more than 50% of cases in one series, and in fact Bell and McCormick point out that the symptoms with this agent are often more subtle and less fulminating than with others.[14]

Meningococcal infections are usually preceded by an abrupt onset of fever, chills, vomiting, and headache. Again a stiff neck need not be an early sign; on the other hand, the disease may be so fulminant that the patient goes from apparent health to death within a matter of hours. The skin rash is an indication of meningococcal disease but may be absent in 50% of cases.[6] The rash is usually petechial but may be erythematous or maculopapular; it usually begins over the lower limbs and should be distinguished from the rash of Rocky Mountain spotted fever and viral exanthema. If present, blood smears obtained from the skin lesions or skin scrapings often reveal the organism.[14] Sometimes associated with the meningitis are myocarditis, the Waterhouse-Friderichsen syndrome, and disseminated intravascular coagulation (DIC). Deaths from the Waterhouse-Friderichsen syndrome have been ascribed to adrenal insufficiency; however, this may not always be the case as there have been documented cases of clinical disease where the adrenals were only slightly affected[27] and in others where the serum corticosteroid levels were actually elevated.[28] It is probable that at least in some of the cases, the syndrome is caused by bacterial endotoxin.

About ten years ago another complication of meningococcal disease was noted, that of disseminated intravascular coagulation. In the study by McGehee and Rapaport[29] all patients on the communicable disease service were evaluated. Of 19 patients with meningococcus infection, 6 had evidence of coagulopathy using platelet count, prothrombin time, partial thromboplastin time, fibrinogen, and Factor V, VII and VIII studies. Of the six, all but one died. The survivor had only equivocal evidence of coagulopathy when treatment was instituted. The authors concluded that probably all patients with fulminant meningococcemia with shock have DIC, a fact which is reflected in the underdiagnosis of DIC in encephalopathy associated with widespread tumors.[30] The point illustrated by the latter study is that frequently only one of the many coagulation tests may be abnormal in proven cases.

In pneumococcal meningitis the onset of symptoms is also usually abrupt and the frequency of the initial symptoms is variable[6,7,14,31]; these usually consist of fever, headache, stiff neck, and vomiting. A significant number are alcoholics[7] and many have an associated pneumonia[7,31] or infection of the ears or sinuses.[6,7] In one study[31] fibrinogen degredation products were found in the CSF, again raising the question of DIC in this disorder.

Neurologic Signs

Other than the stiff neck and headache, neurologic signs usually consist of generalized dysfunction, the most common being altered states of consciousness which occur in 80% to 87% of cases.[6,7] Seizures are also surprisingly frequent, especially in infants, and are associated most commonly with *H influenzae* and least commonly with meningococcus.[6]

Focal signs are unusual in nontuberculous bacterial meningitis although they do occur. The most common are visual defects, particularly of the oculomotor variety.[6,7] Surprisingly hemiparesis also occurs[6,7] although this is probably a Todd's paralysis since in most cases it is very transient. One is probably talking about less than 10% to 15% of cases for these focal signs, however.

Laboratory Tests

Examination of the CSF is the most important laboratory test to be performed; the findings are summarized in Figure 6 and are compared with aseptic, tuberculous, and fungal meningitis. Both a Gram's stain smear and culture should be done. As noted for the neonatal group, the smear may be positive and yet the CSF not grow any organisms. Cultures are positive in about 90% of cases[6,7] and in Swartz and Dodge's series[6] this included meningococcus which probably reflects care in handling the sample. Blood cultures can also be helpful. In one series[6] *H influenzae* was grown from blood in 79% of cases, *D pneumoniae* in 56%, and meningococcus in 33%. Peripheral leukocyte counts are also usually elevated with polymorphonuclear cells predominating, a differentiating point from viral in-

Disease	Appearance[a]	Cell Count	Differential	Protein	Glucose[c]
bacterial meningitis	often opalescent	10-20,000 +	Predominantly Polymorphonuclear	Mildly to Markedly Elevated	Reduced
viral meningitis	clear	5-2000	Predominantly Mononuclear[b]	N1-Elevated (usually 150)	Normal[d]
tuberculous meningitis	often opalescent	5-2000	Predominantly Mononuclear	Mildly to Markedly Elevated	Reduced
cryptococcal meningitis	usually clear	5-2000	Predominantly Mononuclear	N1-Elevated	Reduced

Fig 6—CSF findings in different forms of meningitis: a) if the protein is very high, the fluid will become xanthochromic; b) early in the disease polymorphonuclear cells may predominate; c) in relation to blood sugar; d) can be reduced in meningitis due to *Herpes simplex* or mumps.

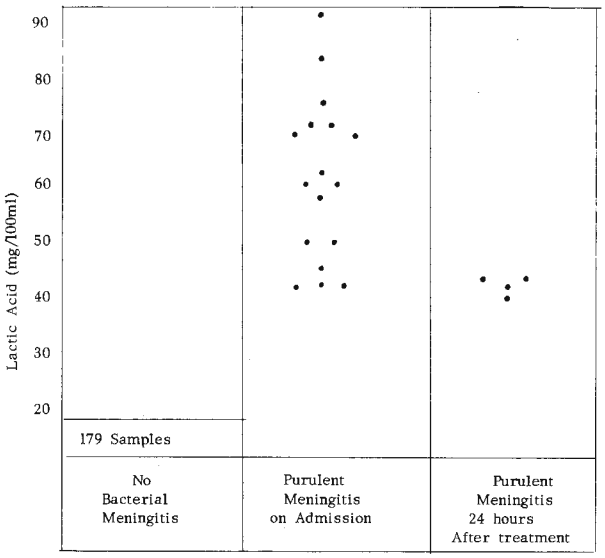

Fig 7—CSF lactate levels in noninfected patients and patients with bacterial meningitis. In other studies including viral meningitis their levels fall in with the control group.

fections. Nasopharyngneal, sputum, and urine cultures may also be valuable in establishing the etiology.

In the past few years some additional laboratory aids have been devised to help in the diagnosis of bacterial meningitis, some of which will be summarized here.

Nitroblue tetrazolium dye test (NBT). This test is based on the ability of phagocytizing leukocytes to reduce nitroblue tetrazolium to an insoluble purple particle which can be seen inside the leukocyte. Early reports were enthusiastic about the test in differentiating bacterial diseases from viral, tuberculous, and other conditions, but as more experience accumulated, the incidence of false-positives and false-negatives rose to such a level as to make the test almost useless, particularly as an occasional bedside test.[32,33]

Limulus test. This test is based on the property of gram-negative endotoxin to cause a gel to form in a lysate from the horseshoe crab *Limulus polyphemus*.[34] It is subject to some of the same problems as the NBT test, that is, operator technique and the fact that old material may become contaminated and give a false-positive test. In addition it is only useful for gram-negative meningitis which would make a negative test uninformative, particularly in adults.

Counter-immunoelectrophoresis. This is an immunologic test for the detection of bacterial antigens in either blood or CSF.[35,36] It is quite sensitive though in some series is no better than routine smear and culture even in partially treated meningitis.[37] In addition one would have to have antigens from all possible bacteria before a negative test could be considered certain.

CSF lactic acid. Elevations of CSF lactate in bacterial meningitis have been known since 1924[38] but have only been used recently to differentiate bacterial from viral meningitis. Bland et al found the CSF lactate to be elevated in bacterial meningitis until full treatment was completed, while the CSF in viral meningitis remained the same as normals.[39] In another study using a more sensitive gas chromatographic determination in 1.0 ml samples of CSF,[40] elevated CSF lactates were found in all 21 patients with bacterial meningitis from various agents (even in five who had already been started on therapy), while 0/179 controls showed an elevation (Fig 7). The disadvantage of this test is the need for special handling of the samples to avoid false elevation of the lactate.

CSF enzymes. A word should be said about the enzymes of the CSF in meningitis. Both lactic dehydrogenase and glutamic-oxaloacetic transaminase are elevated in bacterial meningitis but not in the viral form, a fact which some have attempted to use clinically.[41–44] For some reason, however, these tests have not become popular although they appear to be useful.

Factors Influencing Mortality

In a number of studies the prognostic value of various signs and tests has been evaluated.[6,7,41] In general, patients at the extremes of life, those with coexisting serious illnesses, those in whom therapy was delayed, and those who developed seizures—all had a poor prognosis. Mental state on admission also had a profound effect on outcome with one study showing a 52% mortality if the mental status was worse than simple lethargy and 35% if it was better,[7] while another series showed the difference to be 34% and 10% respectively.[40] Interestingly, the absence of nuchal rigidity was found to be a bad sign.[41] Changes in the CSF may also give some clues to outcome; the higher the protein, the worse the prognosis.[41] This might be expected since an elevated protein level reflects either blood-brain barrier breakdown or tissue destruction, that is, the severity of the infection. In a similar manner, an elevated bacterial antigen level was also a poor sign.

Summary

The advent of antibiotic therapy has decreased the number of patients with bacterial meningitis, yet it remains a significant problem. An attempt has been made to present some of the factors influencing etiology and prognosis as well as some of the clinical and laboratory findings.

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