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EDITORIAL

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How to differentiate bacterial from viral meningitis

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Bacterial meningitis is a rapidly progressive infection whose prognosis depends on prompt initiation of adequate antimicrobial therapy [1, 2]. In case of suspicion of bacterial meningitis blood cultures are needed. Since diagnosis of meningitis depends on signs of inflammation in the cerebrospinal fluid, early lumbar puncture is crucial [3]. However, if there is suspicion of increased intracranial pressure, brain computed tomography must be performed to recognize those patients in whom lumbar puncture is contraindicated [2]. In these cases antibiotic therapy should be initiated prior to CT in order not to loose time until definite diagnosis, since delay in initial administration of antibiotic therapy deteriorates prognosis [3, 4]. In view of this emergency situation antibiotics are frequently given even in patients with suspected viral meningitis. In general this does not harm the individual patient with viral disease. However, it may have an impact on the local frequency of antibiotic resistance, which depends significantly on the amount of antibiotic consumption [5]. Thus, it is not only important to recognize patients who immediately need antibiotics but also those who do not need antimicrobial therapy at all.

The clinical differentiation of bacterial from viral meningitis is difficult and has been studied mainly in children [6]. The classical signs and symptoms of meningitis such as fever, headache, photophobia, nausea, vomiting, and neck and back pain do not allow discrimination between the two origins. Therefore the characteristics of cerebrospinal fluid (CSF) have been used to differentiate between bacterial and viral meningitis [7, 8]. In most studies CSF lactate (>4 mmol/l) is a better predictor of bacterial origin than glucose ratio (less than 0.4), the number of white blood cells in CFS ($>1000\times10^6$/l), and the percentage of polymorphonuclear leukocytes in CSF (>50%) [9, 10, 11].

Since no single CSF or blood parameter has been able to discriminate between bacterial and viral meningitis, a model for the differential diagnosis has been introduced by Spanos et al. [7] and validated in more recent series [12, 13, 14]. Four independent variables are used here to calculate the probability of bacterial (pABM, i.e., odds of bacterial relative to viral meningitis) vs. viral meningitis, namely CSF protein level, total CSF polymorphonuclear count, blood glucose level, and leukocyte count. Setting the cutoff point of pABM is set at 0.1 has been shown to be optimal for the discrimination (Table 1). This is true both for children [13] and for adults [12].

Despite this validated, sophisticated model, it would be an advantage to have clinical criteria to distinguish bacterial from viral meningitis for the following reasons: (a) CSF characteristics are sometimes misleading, especially regarding leukocyte counts and percentage of polymorphonuclear leukocytes [15], (b) in case of suspicion of

Table 1 Performance of the model for a cutoff point of the probability of bacterial meningitis (pABM) of 0.1: $pABM=[1/(1+e^{-L})]$, where $L=32.13\times10^{-4}$ ×CSF PMN count (10^6/l), + 2.365 ×CSF protein (g/l), +0.6143 x blood glucose (mmol/l), +0.2086 ×blood leukocyte count (10^9/l)−11

	Sensitivity	Specificity	PPV	NPV
Jaeger et al. [13]	97.9%	94.4%	95.9%	97.1%
Hoen et al. [12]	97%	93%	85%	99%

increased intracranial pressure antibiotics must be started before CSF puncture, and (c) dexamethasone treatment should be given before starting antibiotics, thus often even before lumbar puncture.

As mentioned above, the initial signs of meningitis are similar regardless of origin. However, bacterial but not viral meningitis rapidly leads to cortical necrosis caused by decreased cerebral blood flow due to oxidative damage and inadequate vasoconstriction. In addition, hippocampal apoptosis occurs via bacterial products directly and through granulocyte products [16, 17]. Thus the bacterial origin of meningitis may be recognized as soon as the first neurological damage clinically appears. Such clinical signs are altered mental status, seizures, and focal neurological deficits. Two large studies by Durand et al. [18] and Aronin et al. [4] found, respectively, that 78% and 83% of the patients with bacterial meningitis had an altered mental status, and that 23% and 13% had seizures. In the study by Durand et al. [18] 28% had focal neurological deficits. In view of these frequent signs of bacterial origin in patients with meningitis, Brivet et al. [19] analyzed the clinical value of signs of severity to differentiate bacterial from viral meningitis in a retrospective cohort study involving 140 adults with different causes of meningitis. They analyzed the role of the initial clinical presentation and the relative diagnositic value of CSF parameters. This study focused especially on signs of severity at referral, including an impaired mental status (Glasgow Coma Scale score less than 14), seizure before or at presentation, focal neurological deficit, and shock. Clinical features were similar in bacterial and viral meningitis, except for headache (63% vs. 94%, p less than 0.01) and signs of severity (99% vs. 7.4%, p less than 0.01). The presence of at least one sign of severity was the only clinical, and CSF neutrophil counts higher than 1000×10^6/l the only laboratory predictor of bacterial origin. In the study by Brivet et al. [19] the hospital mortality decreased from 46% to 24% between the first and the second halves of the study period. Because the data were analyzed only for the whole period, it is not clear whether signs of severity were predictive in each period separately. One could argue that only cases with a long delay before treatment could be clinically recognized as meningitis of bacterial origin. However, since patient characteristics did not differ between the two groups, the delay before antibiotic treatment was probably similar in both groups. According to the receiver operating characteristic curve, the presence of at least one sign of severity at presentation had an excellent accuracy in detecting the bacterial origin of meningitis. With a sensitivity of 0.989, specificity of 0.981, positive predictive value of 0.989, and negative predictive value of 0.981, one would be tempted to withhold antibiotics from patients with meningitis not presenting any sign of severity. The authors were right not to draw this conclusion. As long as their data are not prospectively confirmed in patients with early presentation and a better clinical outcome (less than 20% mortality), most patients with meningitis should still receive antibiotics in the emergency room. In the meantime it is still important to recognize patients in whom antibiotics can be stopped after excluding bacterial origin of meningitis. Rapid and reliable culture techniques for bacteria and polymerase chain reaction techniques for the most important viral agents are important tools for this purpose. In the future the sensitive assay for procalcitonin may allow differentiating patients with bacterial from those with viral meningitis [20].

In conclusion, for the time being, the data of Brivet et al. [19] allow us to recognize patients who rapidly need antibiotics and supportive care in an intensive care unit. However, before antibiotics can be withhold in every patient without signs of severity, this study must be confirmed in patients with very early presentation of bacterial meningitis who take most advantage of early antibiotic therapy.

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