
Article

Validation of a Diagnosis Model for Differentiating Bacterial from Viral Meningitis in Infants and Children under 3.5 Years of Age

F. Jaeger, J. Leroy, F. Duchêne, V. Baty, S. Baillet, J.M. Estavoyer, B. Hoen

Abstract The aim of this study was to validate, in a population of infants and children under 3.5 years of age, a diagnosis model that provides a figure for the probability of bacterial meningitis (pABM), based on four parameters collected at the time of the first lumbar tap: the cerebrospinal fluid (CSF) protein level, CSF polymorphonuclear cell count, blood glucose level, and leucocyte count. The best cut-off value for distinguishing between bacterial and viral meningitis was previously found to be 0.1, since 99% of meningitides associated with $pABM < 0.1$ were viral. The charts of 103 consecutive children aged 0.1–3.5 years who had been hospitalised for acute meningitis were reviewed. Each case was sorted into the following three categories for aetiology: bacterial (positive CSF culture, $n=48$); viral (negative CSF culture and no other aetiology, and no antibiotic treatment after diagnosis, $n=36$); and undetermined (fitting neither of the first two definitions, $n=19$). After computation of pABM values in each case, the predictive values of the model were calculated for different pABM cut-off values. The results confirmed that the best cut-off pABM value was 0.1, for which the positive and negative predictive values in this model were 96% and 97%, respectively. Only one case of bacterial meningitis (lumbar tap performed early in an infant with meningococcal purpura fulminans with negative CSF culture) was associated with a pABM value of < 0.1 . This model is quite reliable for differentiating between bacterial and viral meningitis in children under 3.5 years of age, and it may enable physicians to withhold antibiotics in cases of meningitis of uncertain aetiology.

Introduction

Accurate and rapid diagnosis of acute bacterial meningitis (ABM) is essential for a favourable outcome, especially in infants and children [1]. Although examination of the cerebrospinal fluid (CSF) often provides immediate confirmation of ABM, it sometimes fails to

differentiate between ABM and acute viral meningitis (AVM). Current guidelines recommend starting antibiotics whenever a bacterial aetiology cannot firmly be ruled out [1, 2]. However, the cost of antibiotic therapy and its attendant hospitalization, as well as its potential side effects, have raised concern about unnecessary administration of antibiotics in patients with AVM. Until now, no single CSF or blood parameter has been capable of differentiating between ABM and AVM, since for each potential parameter, the distribution for ABM may overlap the entire range of values found in AVM [3].

We previously elaborated a diagnosis model that proved effective in differentiating ABM from AVM [4]. This model provides a figure for the probability of ABM (pABM), based on four parameters collected at the time of the first lumbar tap: the CSF protein level,

F. Jaeger, J. Leroy, F. Duchêne, S. Baillet, J.M. Estavoyer, B. Hoen (✉)
Service de Maladies Infectieuses et Tropicales,
Hôpital Saint-Jacques, CHU de Besançon, 25030 Besançon,
France
e-mail: bruno.hoen@univ-fcomte.fr

V. Baty
Service de Maladies Infectieuses et Tropicales,
Hôpitaux de Brabois, CHU de Nancy,
54511 Vandoeuvre les Nancy, France

the total CSF polymorphonuclear cell count, the blood glucose level, and the leukocyte count. We determined that 0.1 was the best pABM cut-off value for discriminating ABM from AVM, since the negative predictive value of the model was 99% for this value of pABM – i.e., 99% of meningitides associated with pABM < 0.1 were viral. The study population included patients aged from 0.1 to 83 years, but infants and young children were not specifically selected. The aim of the present study was to validate our model in infants and children under 3.5 years of age, in whom the incidence of ABM is highest.

Patients and Methods

Patients and Setting. We reviewed the medical records of all children aged 1 month to 3.5 years who were admitted to the Department of Infectious Diseases of the University Medical Centre in Besançon, France, from January 1984 to December 1996, and whose final diagnosis was acute meningitis. We excluded cases of tuberculous meningitis, neoplastic meningitis, and meningitis secondary to neurosurgical procedures.

Diagnostic Classification of Cases. In each case, the definitive diagnosis of meningitis was assigned to one of the following three categories, using the same criteria as were used for building the model [4]: (i) bacterial, if an appropriate etiologic bacterium was cultured from CSF or blood, or if a bacterial antigen was demonstrated in the patients' CSF, blood, or urine by latex agglutination; (ii) viral, if a virus was isolated from a human diploid fibroblast culture of blood, stool, or CSF, or if the discharge diagnosis was viral meningitis and no etiology other than viral infection was found and no antibiotics were given for the treatment of meningitis; and (iii) uncertain, in cases matching neither of the above two definitions.

Validation Process. In each case of meningitis, we retrospectively established the computed diagnosis by calculating pABM according to our previously defined model:

$$\text{pABM} = 1/(1 + e^{-L}), \text{ where} \\ L = 32.13 \times 10^{-4} \times \text{CSF PMN count (10}^6/\text{l)} \\ + 2.365 \times \text{CSF protein (g/l)} \\ + 0.6143 \times \text{blood glucose (mmol/l)} \\ + 0.2086 \times \text{leucocyte count (10}^9/\text{l)} - 11$$

The values entered into the model for computing pABM were CSF values of the first lumbar tap and those of blood parameters collected at the same time.

Based on the results of our previous study, we selected 0.1 as the pABM cut-off value for distinguishing between ABM and AVM, as this value was associated with a negative predictive value of 0.99. The computed diagnosis was therefore distributed into two categories: bacterial if pABM was ≥ 0.1 , and viral if pABM was < 0.1 . The definitive diagnoses were cross-tabulated against the computed diagnoses, and the model performance was assessed by calculating its sensitivity, specificity, positive (PPV) and negative (NPV) predictive values, and accuracy. Standard definitions were used for these three parameters [5].

In a second step, we evaluated the performance of the model for other pABM cut-off points, in an attempt to identify a potentially more effective decision rule.

Results

We identified 103 cases of meningitis that occurred in as many patients (mean age 1.74 years; range, 0.1–3.6). There were 48 cases of bacterial meningitis, 36 cases of viral meningitis, and 19 cases of undetermined aetiology. The causative microorganisms are listed in Table 1. The patients' characteristics and the distribution of blood and CSF parameters for ABM and AVM cases are shown in Table 2.

Table 3 shows the cross-tabulation of computed versus definitive diagnoses in the 84 cases of bacterial or viral meningitis: 34 of 36 AVM cases and 47 of 48 ABM cases were correctly classified. The sensitivity, specificity,

Table 1 Distribution of the causative microorganisms in the 103 cases of acute meningitis

Causative microorganism	Cases (n)
Bacterial (n=48)	
<i>Haemophilus influenzae</i>	33
<i>Neisseria meningitidis</i>	11
<i>Streptococcus pneumoniae</i>	4
Viral (n=36)	
Mumps virus	3
Enterovirus	2
Herpes zoster virus	1
Unidentified	30
Undetermined (n=19)	

Table 2 Patients' characteristics and blood and CSF parameters in 48 cases of acute bacterial meningitis and 36 cases of acute viral meningitis. Quantitative variables are expressed as mean \pm standard deviation [range]

Characteristic	Bacterial meningitis (n=48)	Viral meningitis (n=36)	P value*
Age (years)	1.3 \pm 0.8 [0.1–3.3]	2.3 \pm 0.8 [0.6–3.5]	< 0.0001
Sex (M/F)	25/23	26/10	0.06
Leukocyte count (10 ⁹ /l)	15.2 \pm 8.0 [2.8–33.6]	11.6 \pm 3.9 [5.8–20.3]	< 0.0001
Blood glucose (mmol/l)	5.8 \pm 1.8 [2.7–11.7]	5.1 \pm 1.0 [3.2–8.1]	< 0.0001
CSF leukocyte count (10 ⁶ /l)	3445 \pm 4131 [27–19000]	305 \pm 329 [9–1300]	< 0.0001
CSF PMN count (10 ⁶ /l)	3152 \pm 3976 [25–18620]	49 \pm 75 [0–312]	< 0.0001
CSF protein (g/l)	1.5 \pm 1.0 [0.2–5.0]	0.4 \pm 0.2 [0.1–1.2]	< 0.0001
CSF glucose (mmol/l)	1.6 \pm 1.3 [0–4.6]	3.2 \pm 0.7 [1.8–5.3]	< 0.0001
CSF/blood glucose ratio	0.3 \pm 0.2 [0–0.9]	0.7 \pm 0.2 [0.3–1.4]	< 0.0001

* P value in the Mann-Whitney test for the comparison of quantitative variables and of Pearson's chi-square test for sex

Table 3 Computed diagnosis versus definitive diagnosis in 48 cases of acute bacterial meningitis and 36 cases of acute viral meningitis

Computed diagnosis	Definitive diagnosis		
	Bacterial	Viral	Total
Bacterial	47	2	49
Viral	1	34	35
Total	48	36	84

Table 4 Performance of the model for different cut-off points of the probability of bacterial meningitis (pABM). All values are expressed as percentages

pABM	Sensitivity	Specificity	PPV	NPV	Accuracy
0.05	97.9	88.9	92.2	97.0	94.0
0.1	97.9	94.4	95.9	97.1	96.4
0.2	91.7	97.2	97.8	89.7	94.0
0.3	89.6	100	100	87.8	94.0

PPV: positive predictive value; NPV: negative predictive value.

ty, positive and negative predictive values, and accuracy of the model were 97.9%, 94.4%, 95.9%, 97.1%, and 96.4%, respectively (Table 3).

The only case of bacterial meningitis that was computed as viral by the model was that of an 8-month-old girl who was admitted to the emergency room with febrile purpura fulminans. A CSF sample obtained from the lumbar tap performed on arrival showed the following results: leucocytes, 104/mm³ (PMNs, 31/mm³), protein, 0.25 g/l, and glucose, 3.1 mmol/l; both the CSF Gram stain and culture were negative. Only blood cultures yielded *Neisseria meningitidis*.

The sensitivity, specificity, positive and negative predictive values, and accuracy of the model for cut-off points of pABM other than 0.1 are shown in Table 4. Although a pABM value of 0.3 was associated with a positive predictive value of 100%, negative predictive values associated with pABM values greater than 0.1 were unacceptably low. Consequently, we found again that the best cut-off point for discriminating ABM from AVM is 0.1, which is associated with the highest NPV and accuracy values of the model; virtually no bacterial meningitis is associated with a pABM value of <0.1.

Discussion

In spite of advances in diagnosis and treatment, bacterial meningitis is still responsible for substantial mortality and permanent neurological sequelae in children. It is widely accepted that rapid diagnosis and treatment of bacterial meningitis are essential for curing the disease. Although the clinical findings and

initial examination of the CSF most often provide rapid diagnosis of acute bacterial meningitis, they fail to differentiate between bacterial and viral meningitis in about 20% of cases [4, 6]. The present study confirms that differentiating between bacterial and viral meningitis may be difficult. In fact, even after the patients had been discharged, it remained impossible to categorize 18% of the cases as either ABM or AVM. In all of these cases, the diagnosis remained undetermined because no bacteria were cultured from the CSF and antibiotics had been administered for at least 24 hours after the diagnosis of meningitis.

Until recently, no single CSF or blood parameter was found to be capable of distinguishing between bacterial and viral meningitis, since for each potential parameter the distribution for bacterial meningitis may overlap the entire range of values found in viral meningitis [7–10]. Plasma procalcitonin recently proved sensitive and specific for differentiating between viral and bacterial meningitis in children, with no overlapping values between bacterial and viral meningitis [11, 12]. However, these results are preliminary and need to be confirmed, and procalcitonin assays are not widely available. The current clinical practice is therefore to start antibiotic treatment in all patients in whom bacterial meningitis cannot be firmly excluded [13].

This is why we elaborated a diagnosis model aimed at helping clinicians to distinguish between viral and bacterial meningitis accurately. Our diagnosis model was elaborated using a multivariate logistic regression analysis in a previous study of 500 consecutive cases of acute community-acquired meningitis that had been reviewed retrospectively [4]. The previous study was primarily intended to validate a similar approach reported by Spanos et al. [6]. Of the 500 cases of meningitis reviewed, 398 were documented as either AVM ($n=283$) or ABM ($n=115$), and 102 were of undetermined etiology. The performance indices for this model were quite satisfactory: its area under the receiver operating characteristic (ROC) curve was 0.991, and its negative predictive value was 0.99 for a pABM cut-off value of 0.1 [4]. In addition, the validity of our model and the relevance of pABM=0.1 as a cut-off for therapeutic decision-making have been confirmed by independent investigators in retrospective series of acute meningitis [14, 15].

We deemed it wise to evaluate the accuracy of our model in a population of infants and children under 3.5 years of age, in whom both the incidence of bacterial meningitis and the frequency of antibiotic treatment for acute meningitis are higher than in patients at any other age [16, 17]. Although the vaccine-related decline in meningitis caused by *Haemophilus influenzae* has been responsible for a dramatic drop in the incidence of bacterial meningitis in infants and young children in industrialised countries [18], in our series,

bacterial meningitides were more frequent than viral cases, and *Haemophilus influenzae* was the most frequent causative organism. This is due to the fact that most of the cases were recorded before *Haemophilus influenzae* immunisation programs had started in our country.

The present study confirms that our model can effectively help distinguish between viral and bacterial meningitis in children under 3.5 years of age. We found that the negative predictive value of our model was as high as 97.1% when using a pABM cut-off value of 0.1. The accuracy of the model was also very high (96.4%). Only one case of bacterial meningitis was computed as viral by the model, preventing the negative predictive value from reaching 100%. In this case of meningococcaemia with purpura fulminans, the clinical diagnosis was obvious, and antibiotics were started even before the results of the lumbar tap were obtained.

In summary, the model used in this study proved accurate and reliable when applied in infants and children under 3.5 years of age. It is easy to use and provides the results of pABM calculation within seconds after the CSF and blood parameters have been entered into the computer. However, we would emphasise that results obtained using this model should be regarded as one piece of diagnostic information among others and should never entirely take the place of a careful diagnostic evaluation targeted at each individual case. In addition, we have shown in another study that the decision on whether to withhold or stop antibiotic treatment early can be made according to the results of our model-derived pABM computation, which has been confirmed as accurate for this type of therapeutic decision-making process [19]. The model can help physicians identify patients in whom antibiotics can be withheld safely, and it can therefore contribute to reducing the inappropriate use of antibiotics, which are still used too often and for too long a time in acute meningitides of uncertain aetiology. In our center, we have been using this model routinely in such situations for more than 3 years, in adults and children, with the same level of effectiveness as described in our prospective validation study [19].

Acknowledgements This work was presented in part at the 37th Interscience Conference on Antimicrobial Agents and Chemotherapy, Toronto, Ontario, Canada, September 28–October 1, 1997 (no. K124).

References

1. Feigin RD, McCracken GH Jr, Klein JO: Diagnosis and management of meningitis. *Pediatric Infectious Disease Journal* (1992) 11:785–814
2. Tunkel AR, Scheld WM: Acute bacterial meningitis. *Lancet* (1995) 346:1675–1680
3. Bonadio WA: The cerebrospinal fluid: physiologic aspects and alterations associated with bacterial meningitis. *Pediatric Infectious Disease Journal* (1992) 11:423–432
4. Hoen B, Viel JF, Paquot C, Gérard A, Canton P: Multivariate approach to differential diagnosis of acute meningitis. *European Journal of Clinical Microbiology & Infectious Diseases* (1995) 14:267–274
5. Fletcher RH, Fletcher FW, Wagner EW: Diagnostic test. In: *Clinical epidemiology: the essentials*. Williams & Wilkins, Baltimore (1982) pp 41–58
6. Spanos A, Harrell FE, Durack DT: Differential diagnosis of acute meningitis: an analysis of the predictive value of initial observations. *JAMA* (1989) 262:2700–2707
7. Arevalo CE, Barnes PF, Duda M, Leedom JM: Cerebrospinal fluid cell counts and chemistries in bacterial meningitis. *Southern Medical Journal* (1989) 82:1122–1127
8. Baker RC, Lenane AM: The predictive value of cerebrospinal fluid differential cytology in meningitis. *Pediatric Infectious Disease Journal* (1989) 8:329–330
9. Hansson LO, Axelsson G, Linne T, Aurelius E, Lindquist L: Serum C-reactive protein in differential diagnosis of acute meningitis. *Scandinavian Journal of Infectious Diseases* (1993) 25:625–630
10. Lindquist L, Linne T, Hansson LO, Kalin M, Axelsson G: Value of cerebrospinal fluid analysis in the differential diagnosis of meningitis: a study in 710 patients with suspected central nervous system infection. *European Journal of Clinical Microbiology & Infectious Diseases* (1988) 7:374–380
11. Gendrel D, Raymond J, Assicot M, Moulin F, Iniguez JL, Lebon P, Bohuon C: Measurement of procalcitonin levels in children with bacterial or viral meningitis. *Clinical Infectious Diseases* (1997) 24:1240–1242
12. Gendrel D, Raymond J, Assicot M, Avenel S, Lefevre H, Ravilly S, Moulin F, Lacombe C, Palmer P, Lebon T, Bohuon C: Procalcitonine, protéine C-réactive et interleukine 6 dans les méningites bactériennes et virales. *Presse Médicale* (1998) 27:1135–1139
13. Swinger G, Delport S, Hussey G: An audit of the use of antibiotics in presumed viral meningitis in children. *Pediatric Infectious Disease Journal* (1994) 13:1107–1110
14. Leblebicioglu H, Esen S, Bedir A, Günaydin M, Saniç A: The validity of Spanos' and Hoen's models for differential diagnosis of meningitis. *European Journal of Clinical Microbiology & Infectious Diseases* (1996) 15:252–253
15. Hoen B: The validity of Spanos' and Hoen's models for differential diagnosis of meningitis. *European Journal of Clinical Microbiology & Infectious Diseases* (1996) 15:253–254
16. Wenger JD, Hightower AD, Facklam RR, Gaventa S, Croome CV, and the Bacterial Meningitis Study Group: Bacterial meningitis in the United States, 1986: report of a multistate surveillance study. *Journal of Infectious Diseases* (1990) 162:1316–1323
17. Schlech WF III: The epidemiology of bacterial meningitis. *Antibiotic Chemotherapy* (1992) 45:5–17
18. Schuchat A, Robinson K, Wenger JD, Harrison LH, Farley M, Reingold AL, Lefkowitz L, Perkins BA: Bacterial meningitis in the United States in 1995. *New England Journal of Medicine* (1997) 337:970–976
19. Baty V, Viel JF, Schuhmacher H, Jaeger F, Canton P, Hoen B: Prospective validation of a diagnosis model as an aid to therapeutic decision in acute meningitis. *European Journal of Clinical Microbiology & Infectious Diseases* (2000) 19:422–426