

Multivariate Approach to Differential Diagnosis of Acute Meningitis

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A previously reported statistical model based on a combination of four parameters (total polymorphonuclear cell count in cerebrospinal fluid (CSF), CSF/blood glucose ratio, age and month of onset) appeared effective in differentiating acute viral meningitis (AVM) from acute bacterial meningitis (ABM). The objectives of this study were to validate this model on a large independent sample of patients with acute meningitis and to build and validate a new model based on this sample. Of 500 consecutive cases of community-acquired meningitis reviewed retrospectively, 115 were ABM, 283 were AVM and 102 were of uncertain etiology. For each of the ABM and AVM cases, the probability of ABM versus AVM (pABM) was calculated for both models. Sensitivity, specificity and predictive values as well as areas under the receiver operating characteristic (ROC) curves were calculated for both models. The original model proved an accurate and reliable diagnostic test. Its area under the ROC curve was 0.981. For pABM = 0.1, its negative and positive predictive values were 0.99 and 0.68, respectively. The new model retained four slightly different independent variables: CSF protein level, total CSF polymorphonuclear cell count, blood glucose level and leukocyte count. Its area under the ROC curve was 0.991 and, for pABM = 0.1, its negative and positive predictive values were 0.99 and 0.85, respectively. In conclusion, both models provide a valuable aid in differentiating AVM from ABM. They should be further evaluated in a prospective appraisal of their contribution to therapeutic decision making.

Accurate and rapid diagnosis is essential for patients with acute bacterial meningitis (ABM). 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). A positive Gram-stained CSF smear is virtually 100 % diagnostic of ABM, but in about 25 % of cases of ABM, the initial Gram-stained CSF smear is negative (1). For years, in cases of difficult differential diagnosis between ABM and AVM, physicians have preferred to treat viral meningitis with antibiotics rather than not to treat a bacterial one. However, the cost of antibiotic therapy and its attendant hospitalization as well as its potential side

effects raised concern about giving unnecessary antibiotics in AVM. Various blood and CSF findings, such as CSF lactate and blood or CSF C-reactive protein, have been proposed as markers for differential diagnosis between ABM and AVM (2-5). Unfortunately, no single value for any CSF or blood parameter has been found to be discriminant, since for each potential parameter the distribution for ABM may overlap the entire range of values found in AVM (5-7). This prompted Spanos et al. (6) to undertake a retrospective study of a large number of both ABM and AVM cases with the aim of assessing whether the final diagnosis could be predicted accurately using a statistical model based on a combination of parameters. They identified four independent parameters for predicting the likelihood of ABM: total polymorphonuclear leukocyte (PMN) count in CSF, CSF/blood glucose ratio, age and the number of months from August 1 at the time of the onset of meningitis. In any case of meningitis,

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the probability of ABM versus AVM (pABM) could either be calculated according to the logistic model equation or estimated from a nomogram derived from this model, given the value of the four diagnostic parameters (6). The complete mathematical expression of Spanos' model was as follows:

$$pABM = \frac{1}{(1 + e^{-L})}, \text{ where}$$

$$L = 0.52 \times \text{number of months from August 1} \\ - 12.76 \times \text{CSF/blood glucose ratio (if ratio} \\ \text{exceeds 0.6 use 0.6)} \\ + 0.341 \times (\text{PMNs in CSF} \times 10^6/\text{l})^{0.333} \\ + 2.29 \times \text{age} + 2.79 \text{ (if age} \leq 1 \text{ year),} \\ - 2.71 \times \text{age} + 7.79 \text{ (if } 1 \text{ year} < \text{age} \leq 2 \text{ years),} \\ - 0.159 \times \text{age} + 2.69 \text{ (if } 2 \text{ years} < \text{age} \leq 22 \text{ years) or} \\ + 0.100 \times \text{age} - 3.01 \text{ (if age} > 22 \text{ years).}$$

If the Gram stain was positive, a probability of 0.99 was assumed.

The aims of our study were to validate the model of Spanos et al. (6) on a new sample of patients with meningitis, as suggested by these authors who urged that their model should be validated in other hospitals; and to perform an independent multivariate logistic regression analysis with an objective of determining the most accurate combination of parameters for predicting the likelihood of bacterial meningitis.

Materials and Methods

We reviewed the charts of all patients with a final diagnosis of acute meningitis hospitalized in the Department of Infectious Diseases of the University of Nancy Medical Center, Nancy, France, between August 1983 and December 1991. Cases of meningitis were sought out by the coded diagnoses assigned to each patient file using a computer-assisted research. Like Spanos et al. (6), we selected cases of community-acquired acute meningitis that occurred in patients older than one month. Cases secondary to neurosurgical procedures, cases of neoplastic or tuberculous meningitis and those with missing basic CSF (cell count, protein and glucose) data and blood parameter data needed for multivariate analysis were excluded a priori. Conversely, we retained cases for which outpatient antibiotic treatment was given prior to admission, both to fit Spanos' selection criteria and because this is a common feature at presentation. We also used the same diagnostic criteria as Spanos.

Cases were categorized as ABM if an appropriate etiologic bacterium was cultured from CSF or blood or if bacterial antigen was demonstrated in patients' CSF, blood or urine by latex agglutination. Cases were categorized as AVM if a virus was isolated from culture (on human diploid fibroblasts) 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. Cases that could be categorized neither as ABM nor as AVM according to these definitions were considered of uncertain etiology and were neither considered for Spanos' model validation nor for building our model.

From the initial database that contained 500 cases of meningitis, 102 cases (20.4%) were categorized as meningitis of uncertain etiology. CSF Gram stain was negative in all these cases. In-house antibiotics had been given prior to lumbar puncture to 49% of these 102 patients as compared to 27% of ABM cases and 21% of AVM cases ($p < 0.0001$). Of the 398 remaining cases, 115 were ABM and 283 were AVM. The two groups were compared for their main characteristics using chi-square (χ^2) and Mann-Whitney rank-sum tests for qualitative and quantitative variables, respectively.

For each case of meningitis, we calculated the probability of ABM versus AVM (pABM) according to Spanos' model. For the validation of this model, we calculated the sensitivity, specificity, positive (PPV) and negative (NPV) predictive values of the model for different cut-off points of pABM. Results of these calculations were displayed on a receiver operating characteristics curve (ROC curve) (8) whose area under the curve (AUC) was then calculated according to the rank-sum test method (9). We then performed a stepwise regression analysis (entering and removing limits equal to 0.10 and 0.05, respectively) on the whole sample of cases since no data were missing for any of the 398 cases (10). The analysis was based on the following variables: age, month of onset, blood leukocyte count, blood glucose level, CSF glucose level, CSF/blood glucose ratio, CSF protein level, total and differential CSF leukocyte count and total CSF polymorphonuclear cell count. As did Spanos et al. (6), we entered the variable month as the number of months from the estimated peak incidence of AVM (August 1) and the glucose ratio as follows: $(\text{CSF glucose} + 0.1 \text{ mmol/l})/(\text{blood glucose} + 0.1 \text{ mmol/l})$. Total CSF leukocyte count and total CSF polymorphonuclear count were entered into the model in a slightly modified form $([\text{integer}(\text{CSF-cell count}/100) + 0.5] \times 100)$ in order to decrease the number of covariate patterns for these two variables. As a result, all values within the same hundred were assigned the mean value of the hundred. For example, CSF leukocyte count values of $230 \times 10^6/\text{l}$ and $270 \times 10^6/\text{l}$ were both assigned the mean value $250 \times 10^6/\text{l}$. We did not enter the variable race because all but three patients were Caucasians.

As we did for the validation of Spanos' model, we calculated sensitivity, specificity, PPV and NPV of our logistic model for various cutpoints of pABM and built a ROC curve whose AUC was calculated and compared to AUC of Spanos' model (11). Finally we assessed the accuracy of both Spanos' and our model in two subgroups of ABM, those with CSF positive on direct Gram stain and those with CSF negative on direct Gram stain.

All the computations were performed using software from BMDP Statistical Software, USA.

Results

Patients' characteristics and blood and CSF findings for both ABM and AVM cases are presented and compared in Table 1. For all studied param-

Table 1: Patients' characteristics and blood and CSF findings in cases of bacterial and viral meningitis. Quantitative variables are expressed as mean with standard deviation and range in brackets.

	Bacterial meningitis (n = 115)	Viral meningitis (n = 283)	P value*
Age (years)	33.7 ± 23.2 (0.1-83)	18.0 ± 13.6 (1-86)	< .0001
Gender (M/F)	59/56	168/115	0.14
Leukocyte count (10 ⁹ /l)	19.9 ± 10.1 (4.5-52.7)	8.9 ± 3.4 (2.9-25.4)	< .0001
PMN count (10 ⁹ /l)	16.3 ± 9.1 (3.9-50.9)	6.2 ± 3.0 (1.2-23.0)	< .0001
Percent PMNs	82.7 ± 13.9 (10.0-97.0)	68.3 ± 13.0 (27.0-91.0)	< .0001
Blood glucose (mmol/l)	9.4 ± 4.8 (2.4-33.0)	5.3 ± 1.2 (2.7-9.6)	< .0001
CSF leukocyte count (10 ⁶ /l)	4990 ± 5000 (2.0-30000)	311 ± 400 (6-3500)	< .0001
CSF PMN count (10 ⁶ /l)	4750 ± 5026 (0-29700)	66 ± 134 (0-1260)	< .0001
Percent PMNs in CSF	83.6 ± 24.4 (0-100)	26.9 ± 29.3 (0-95)	< .0001
CSF protein (g/l)	3.6 ± 3.1 (0.2-20.0)	0.5 ± 0.3 (0.07-2.4)	< .0001
CSF glucose (mmol/l)	2.1 ± 2.2 (0-10.2)	3.1 ± 0.6 (1.1-4.7)	< .0001
CSF/blood glucose ratio	0.2 ± 0.3 (.001-2.3)	0.6 ± 0.2 (0.2-1.3)	< .0001

*p value of Mann-Whitney test for the comparison of quantitative variables and of Pearson's chi-square test for gender.

ters but gender, we showed a strongly significant difference between ABM and AVM cases. However, all of these parameters had a wide distribution range often with a large overlap between ABM and AVM. The distribution of month of onset was also quite different for ABM (peak incidence in January, February and March) than for AVM (peak incidence in June, July and August). Among the 115 ABM cases, 95 (83 %) had a positive CSF culture, 12 had positive CSF Gram stain and CSF antigen latex agglutination tests, and 8 had only a positive CSF antigen latex agglutination test. CSF Gram stain was negative in 53 of the 115 ABM cases (46 %). The 62 positive Gram stains included 30 gram-positive cocci, 24 gram-negative cocci, 7 gram-negative rods and 1 gram-positive rod. The microorganisms responsible for the 95 culture-proven cases were *Neisseria meningitidis* (n = 33), *Streptococcus pneumoniae* (n = 26), *Listeria monocytogenes* (n = 11), *Haemophilus influenzae* (n = 10) and others (n = 15). The 20 microorganisms identified by a positive antigen latex agglutination result were *Streptococcus pneumoniae* (n = 12), *Neisseria meningitidis* (n = 5) and *Haemophilus influenzae* (n = 3). Twelve of these microorganisms were also detected by CSF Gram stain. The breakdown of cases into categories of ABM is shown in Table 2.

Sensitivity, specificity and predictive values of Spanos' model for different cut-off points of pABM are displayed in Table 3. In the prediction of bacterial meningitis, a high sensitivity and a high NPV are the most important criteria. In an additional search for good specificity and positive predictive value, the cut-off point 0.1 for pABM is associated with sensitivity and NPV values of 97 % and 99 %, respectively, and with a specificity and

PPV of 82 % and 68 %, respectively. In other words, for a patient whose Spanos' model derived pABM is lower than 0.1, one might rule out the diagnosis of ABM with only a 1 % chance of erroneous diagnosis. A cut-off point of 0.2 offers better specificity and PPV for a very mild decrease of NPV which remains as high as 98 %.

Our regression procedure resulted in the identification of four different independent variables. These were CSF protein level, total CSF polymorphonuclear count, blood glucose level and leukocyte count. The complete mathematical expression of our model was as follows:

$$pABM = \frac{1}{(1 + e^{-L})}, \text{ where}$$

$$L = 32.13 \times 10^{-4} \times \text{CSF PMN count (10}^6/\text{l)} \\ + 2.365 \times \text{CSF protein (g/l)} \\ + 0.6143 \times \text{blood glucose (mmol/l)} \\ + 0.2086 \times \text{white blood cell count (10}^9/\text{l)} - 11.$$

The value of the Hosmer-Lemeshow goodness-of-fit statistic (10) computed with BMDP LR program is 4.59, and its corresponding p-value computed with the chi-square distribution is 0.71. This indicates that the model fits quite well (10). Sensitivity, specificity and predictive values of our model for the same cut-off points as defined for Spanos' model are displayed in Table 3. Using a cut-off point of 0.1 pABM is associated with sensitivity and NPV values identical to those found with Spanos' model for the same cut-off point. Moreover, using this cut-off point, PPV is as high as 85 %. A cutpoint of 0.2 is associated with a higher PPV, 90 %, only counterbalanced by a 1 % reduction of NPV. Areas under ROC curves were 0.981 and 0.991 in Spanos' model and our model, respectively, not significantly different from each other.

Table 2: Age and blood and CSF characteristics, grouped by meningitis etiology, expressed as median/range.

	No. of cases	Age (years)	Leukocyte count ($\times 10^9/l$)	Blood glucose level (mmol/l)	CSF leukocyte count ($\times 10^6/l$)	CSF PMN count ($\times 10^7/l$)	CSF protein level (g/l)	CSF glucose level (mmol/l)
Bacterial meningitis	115	35/0.1-83	16,94.5-52.7	8.2/2.4-33.0	4.0/0.02-30	3.6/0-29.7	2.6/0.2-20.0	1.6/0-10.2
<i>N. meningitidis</i>	38	18/05-64	20,9/5.2-43.8	9.5/4.0-25.5	6.5/0.002-29.5	5.9/0-29.2	2.7/0.2-9.1	2.1/0-8.4
<i>S. pneumoniae</i>	38	45/0.6-83	22,6/5.1-52.7	8.1/4.9-33.0	4.3/0.09-30.0	3.6/0.05-29.7	4.0/0.7-14.9	1.1/0-9.3
<i>H. influenzae</i>	13	1.5/0.3-35	13,9/6.4-36.2	5.5/3.9-10.5	4.5/0.12-10	4.1/0.006-10.0	1.4/0.6-5.8	1.8/0-9.8
<i>L. monocytogenes</i>	11	42/27-68	14,3/6.6-20.8	8.3/6.5-10.3	0.9/0.17-10	0.6/0.02-10.0	1.9/0.5-3.8	2.2/0.6-4.4
Others	15	56/0.1-77	12.1/4.5-26.6	7.2/2.4-24.9	0.9/0.1-10	0.5/0-10.0	2.6/0.6-20.0	1.1/0-10.2
Viral meningitis	263	16/1-68	8,3/2.8-25.4	5.3/2.7-9.6	0.2/0.003-3.5	0.02/0-1.2	0.4/0.07-2.4	3.1/1.1-4.7

We then focused our attention on the subgroup of ABM with negative Gram stain, which is probably the most difficult diagnostic situation. We applied both models to this subgroup and to Gram stain positive ABM cases. The results of this analysis are displayed in Table 4. The same proportion of patients received in-house antibiotics prior to lumbar puncture in both subgroups. Laboratory data tended to be less specific for ABM cases with negative Gram stain than in cases with positive Gram stain. Calculated pABMs were significantly greater in Gram stain positive cases. In this subgroup, all the values of pABM were equal to 0.99 using Spanos' model, in which all cases with Gram positive stain were assigned this value. Using our model which did not presuppose the value of pABM in Gram stain positive cases, we found a mean pABM value of 0.97. In cases with negative Gram stain, the mean pABM value was 0.83 for both models, significantly lower than in Gram stain positive cases ($p = 0.03$). However, when applying the models to the only cases of Gram stain negative ABM, the negative predictive value calculated for the cut-off point pABM = 0.1 was 0.99, equal to that calculated when applying the models to the whole group of ABM.

Discussion

At first the present study confirmed that differentiating AVM from ABM is often a difficult task, since in our initial series of 500 cases, 20 % could neither be categorized as ABM nor as AVM according to the case definition used. In most of these cases the final diagnosis had remained uncertain because the patients were given antibiotics for the treatment of Gram stain negative and culture-negative meningitis. We feel that this percentage of 20 % is a good reflection of the proportion of patients with acute meningitis in whom the differential diagnosis is problematic (1). To appraise whether the exclusion of these 102 cases might have biased our results, we compared them to ABM and AVM definite cases. The sex ratio was not different within the three groups. For such quantitative variables as age, CSF and blood laboratory parameters, cases with uncertain etiology had mean values between those found in ABM and AVM cases and a wide range overlapping those of ABM and AVM cases. This was also the case for model derived pABMs (Table 5), either Spanos' or ours, whose distributions were

Table 3: Sensitivity, specificity, positive and negative predictive values of Spanos' model and our model for different cut-off points of the model-derived probability of bacterial versus viral meningitis (pABM).

pABM	Spanos' model				Present model			
	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)
0.05	97	68	55	90	98	87	76	99
0.075	97	70	64	90	97	90	80	99
0.1	97	82	68	99	97	93	85	99
0.2	96	92	83	98	94	96	90	98
0.3	95	94	86	98	93	97	92	97
0.4	94	95	89	98	93	98	95	97
0.5	94	97	92	98	92	99	96	97
0.6	92	97	93	97	90	99	97	96
0.7	90	98	95	96	87	99	97	95
0.8	89	99	96	96	87	100	100	95
0.9	85	99	98	94	86	100	100	95
0.95	83	100	100	93	84	100	100	94
0.99	77	100	100	91	81	100	100	93

Table 4: Proportion of patients treated with in-house antibiotics prior to lumbar puncture (pre-treated), laboratory findings (median/range) and model-derived probability of bacterial versus viral meningitis (pABM) in the 62 cases of gram-positive CSF and the 53 cases of gram-negative CSF bacterial meningitis.

	Gram stain positive (n = 62)	Gram stain negative (n = 53)	P value ^a
Pre-treated, n(%)	18 (28%)	15 (28%)	0.7 ^b
Leukocyte count (x 10 ⁶ /l)	20.1/5.1-62.7	17.0/4.5-47	0.08
Blood glucose level (mmol/l)	8.6/4.0-33.0	7.9/2.4-24.9	0.12
CSF leukocyte count (x 10 ⁶ /l)	4.9/0.12-29.5	2.0/0.002-30.0	0.04
CSF PMN count (x 10 ⁶ /l)	4.5/0.006-29.2	1.7/0-29.7	0.04
CSF protein (g/l)	3.2/0.6-15.7	2.2/0.2-20	0.08
CSF glucose (mmol/l)	1.3/0-9.3	1.8/0-10.2	0.03
Spanos' pABM, mean (range)	0.99 (0.99-1.00)	0.83 (0.007-1.0)	0.03 ^c
Present pABM, mean (range)	0.97 (0.08-1.00)	0.83 (0.01-1.0)	0.03

^a Mann-Whitney rank-sum test unless specified otherwise.

^b Pearson's chi-square test.

^c t test for the comparison of sample mean to expected mean.

both clearly bimodal, with one mode for pABM values lower than 0.1 and a second mode for pABM values greater than 0.9. We can therefore reasonably assume that cases with uncertain etiology included viral and bacterial meningitis in a proportion not very different from that of the 398 cases with definite diagnosis. As a result, if a bias had been introduced by our analysis process, it should have been only minor.

We then showed once again that no single parameter could rule out the diagnosis of bacterial meningitis since the distribution of all but one of the CSF parameters tested overlapped the entire range of values found in AVM. The exception concerned CSF protein level for which some values found in AVM were lower than the lowest value found in ABM. Among blood parameters

this was also the case for leukocyte count and PMN count. Not surprisingly, CSF protein level and leukocyte count were retained in the multivariate model.

In a further step we validated Spanos' model on a new, large and independent sample of patients with acute meningitis. We confirmed that pABM, the parameter generated by Spanos' model, could be used as an accurate diagnostic test since the area under ROC curve for this parameter was very close to 1, even higher than that found by Spanos et al. in their test sample. For the cut-off point pABM = 0.1, sensitivity and NPV of the model were quite high. Specificity was only 82 %, meaning that for this cut-off point, up to 18 % of AVM cases would be categorized as ABM according to Spanos' model. In our model, for the

Table 5: Mean values and range of probability of bacterial versus viral meningitis (pABM) according to Spanos' model and ours, for proven cases of bacterial and viral meningitis as well as for cases of uncertain etiology.

pABM	Bacterial meningitis (n = 115)	Viral meningitis (n = 283)	Uncertain (n = 102)
Spanos' model mean	0.92	0.07	0.39
range	0.007-1	0.0003-0.93	0.0005-1
Present model mean	0.91	0.04	0.35
range	0.01-1	0.0005-0.80	0.001-1

same cut-off point $pABM = 0.1$, we found roughly the same sensitivity and NPV values, whereas specificity was better since less than 7 % of AVM were categorized ABM. However, it should be mentioned that calculating sensitivity, specificity, predictive values and area under the ROC curve of our model on the same data set used to build it may artificially favor our model. These performance indexes might well decrease if our model were tested with independent data, as it was for our validation of Spanos' model.

With both models, 3 of 115 patients with ABM had a pABM value lower than 0.1. The responsible pathogens were *Streptococcus pneumoniae*, *Haemophilus influenzae* and *Staphylococcus epidermidis*. In all three patients, pABMs were calculated based on the results of the first CSF examination, as planned in the design of the study. In these patients, the first lumbar tap was done early in the course of the disease and was not suggestive of bacterial meningitis at that time. A second lumbar tap, performed within 24 hours of the first one, was then typical of bacterial meningitis.

We found that both predictive models accurately differentiated ABM from AVM in the subgroup of ABM with negative Gram stain in which differential diagnosis is the most difficult. The diagnosis of ABM can be ruled out with good confidence (1 % chance of error) in negative Gram stain meningitis when model derived pABM is equal to 0.1 or lower.

The fact that the distribution of causative microorganisms in ABM was different in our series as compared to Spanos' (more *N. meningitidis* and less *H. influenzae*) does not seem to have altered the validity of the clinical prediction rule.

All four variables retained in our model were laboratory parameters obtained from patient's blood or CSI immediately after his or her admission to hospital. They were independent of the

patient's age and month of onset. In fact, although the likelihood of developing a bacterial versus viral meningitis does vary with the period of the year, it seems odd that, once defined by its clinical and laboratory characteristics, the diagnosis of meningitis could switch from viral to bacterial depending on the month of onset. An advantage of not using the date of onset in the model is that the clinical prediction rule could be used anywhere in the world, not just in the northern hemisphere.

The following case report illustrates this fact. A 55-year-old woman was admitted on 12 November 1992 with acute meningitis. Initial lumbar puncture showed 310 leukocytes/mm³ with 95 % lymphocytes, protein and glucose levels of 0.8 g/l and 2.04 mmol/l, respectively. CSF Gram stain was negative. Blood leukocyte count was $4.6 \times 10^9/l$ and blood glucose level was 5.61 mmol/l. She was treated with antibiotics. Two days after admission she developed herpes zoster. Later on CSF viral cultures grew varicella-zoster virus. The calculated pABM values according to Spanos' model and our model were 0.62 and 0.01, respectively. Should the same patient have presented an identical zoster meningitis in August, her Spanos' pABM would have been 0.32. Owing to the results of our model ($pABM = 0.01$), one might have decided not to treat the patient since negative predictive value of the model for this cut-off point is greater than 99.5 %. Even in the 'August version,' pABM calculated according to Spanos' model was too high for ruling out the diagnosis of ABM. This is probably due to the patient's age, at which a bacterial meningitis is more likely to occur than a viral one.

CSF polymorphonuclear count was the only variable common to both Spanos' model and ours. In our model this variable predicted ABM better than either the percentage of polymorphonuclear cells in the CSF or the total CSF leukocyte count. This may not be surprising since it is the product

of the two. Nye et al. (12) has previously shown that CSF differential leukocyte count was a better guide to diagnosis than the total count. However, they did not appraise the diagnostic value of the total polymorphonuclear cell count.

CSF protein level was the first step-entered parameter of the model. After this first regression step, CSF glucose level and CSF/blood glucose ratio dramatically lost capability of improving the model while this was not the case for blood glucose level. One explanation is that CSF glucose is strongly inversely correlated to CSF protein, as evidenced in our series ($r = -0.416$, $p < 0.001$). In addition, blood glucose level which is known to be elevated in ABM (12, 13) appeared in this study as an independent predictor of bacterial meningitis, irrespective of CSF glucose level.

The results of our study support the accuracy of Spanos' model. Although we found another model based on slightly different variables, we can consider that this approach of combining basic, routinely and immediately available parameters is clinically valuable. Other investigators have previously demonstrated that a combination of parameters is much more helpful than any single parameter (2, 12). The multivariate model provides a valuable aid in differentiating AVM from ABM with both high negative and positive predictive values and consequently with good confidence. The predictor pABM proved accurate in excluding bacterial in favor of viral meningitis. So far, no single CSF or blood parameter could achieve this goal although the reverse (excluding viral in favor of bacterial meningitis) was quite possible.

Recently McKinney et al. (14) have also validated Spanos' model on a retrospective series of 62 ABM cases and 98 AVM cases which originated from five hospitals in Dallas, Texas, and Milwaukee, Wisconsin, USA. They showed that the clinical prediction rule proved robust when applied to a geographically distinct population of adults, irrespective of patients' age.

However, both Spanos' model and ours should be further validated in a prospective appraisal of their contribution to therapeutic decision making. We started such an evaluation in our institution, as illustrated in the following case report. A 32-year-old male doctor complained of fever, headache and vomiting for about 12 hours when he was admitted to our hospital on 15 June, 1992. His neck was stiff. Lumbar tap revealed a slightly cloudy CSF containing: leukocytes $700 \times 10^6/l$ (PMN = 75%), protein 0.43 g/l glucose

3.5 mmol/l. Blood leukocyte count was $6.3 \times 10^9/l$, and serum glucose was 7 mmol/l. CSF Gram stain was negative. On one hand the patient had no clinical evidence of ABM, but on the other hand CSF was cloudy and contained more than 500×10^6 PMN/l. Calculated pABM according to Spanos' model and ours was 0.065 and 0.069 respectively, both far lower than 0.10, the value of pABM associated with a NPV of 99%. We hypothesized that the patient had AVM with predominant PMN in CSF due to early lumbar tap. Accordingly, we decided to delay the administration of antibiotics. The patient became afebrile without treatment and 48 hours after admission, lumbar tap showed a clear CSF containing 500×10^6 lymphocytes/l. The diagnosis of AVM was accepted, although CSF viral culture remained negative, and the patient was discharged on the fourth day.

In this case report, the model provided an aid in deciding not to treat the patient. The pABM cut-off point value that allows ruling out the diagnosis of bacterial meningitis may be chosen individually by each clinician, according to the NPV associated with a given pABM. In our ongoing prospective study, we considered that a pABM value equal to 0.10 might be an accurate cut-off point, both discriminant and harmless since it is associated with a NPV equal to 99%. For a different management strategy, other clinicians might choose other cutpoint values using the data given in Table 3.

Finally, we share the opinion of Spanos et al. (6) that a probability is only a probability, not the final answer. We likewise recommend that pABM should be regarded as one piece of diagnostic information among others and should never be substituted entirely for a careful diagnostic evaluation of each individual case.

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References

1. Geiseler PJ, Nelson KE, Levin S, Reddi KT, Moses VK: Community-acquired purulent meningitis: a review of 1,316 cases during the antibiotic era, 1954-1976. *Reviews of Infectious Diseases* 1980, 2: 725-745.
2. Landaas S, Von der Lippe B: Chemical analyses for early differential diagnosis between bacterial and viral meningitis. *Scandinavian Journal of Clinical and Laboratory Investigations* 1985, 45: 525-529.

3. Briem H: Comparison between cerebrospinal fluid concentrations of glucose, total protein, chloride, lactate, and total amino acids for the differential diagnosis of patients with meningitis. *Scandinavian Journal of Infectious Diseases* 1983, 15: 277-284.
4. BenGershöm E, Briggeman-Mol GJJ, de Zegher F: Cerebrospinal fluid C-reactive protein in meningitis: diagnostic value and pathophysiology. *European Journal of Pediatrics* 1986, 145: 246-249.
5. Lindquist L, Linné 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.
6. Spanos A, Harrell FE, Durack DT: Differential diagnosis of acute meningitis. An analysis of the predictive value of initial observations. *Journal of the American Medical Association* 1989, 262: 2700-2707.
7. Baker RC, Lenane AM: The predictive value of cerebrospinal fluid differential cytology in meningitis. *Pediatric Infectious Disease Journal* 1989, 8: 329-330.
8. Fletcher RH, Fletcher FW, Wagner EW: Diagnostic test. In: *Clinical epidemiology, the essentials*. Williams & Wilkins, Baltimore, 1982, p. 41-58.
9. Hanley JA, McNeil BJ: The meaning and use of the area under a receiver operating characteristics (ROC) curve. *Radiology* 1982, 143: 29-36.
10. Hosmer DW, Lemeshow S: *Applied logistic regression*. John Wiley, New York, 1989, p. 140-145.
11. Hanley JA, McNeil BJ: A method of comparing the areas under receiver operating characteristic curves derived from the same cases. *Radiology* 1983, 148: 839-843.
12. Nye FJ: The value of initial laboratory investigations in the management of meningitis. *Journal of Infection* 1983, 7: 31-38.
13. Swartz MN, Dodge PR: Bacterial meningitis - a review of selected aspects. *New England Journal of Medicine* 1965, 272: 779-787.
14. McKinney WP, Heudebert GR, Harper SA, Young MJ, McIntire DD: Validation of a clinical prediction rule for the differential diagnosis of acute meningitis. *Journal of General Internal Medicine* 1994, 9: 8-12.