

Serum Procalcitonin Level and Other Biological Markers to Distinguish Between Bacterial and Aseptic Meningitis in Children

A European Multicenter Case Cohort Study

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Objective: To validate procalcitonin (PCT) level as the best biological marker to distinguish between bacterial and aseptic meningitis in children in the emergency department.

Design: Secondary analysis of retrospective multicenter hospital-based cohort studies.

Setting: Six pediatric emergency or intensive care units of tertiary care centers in 5 European countries.

Participants: Consecutive children aged 29 days to 18 years with acute meningitis.

Main Outcome Measures: Univariate analysis and meta-analysis to compare the performance of blood parameters (PCT level, C-reactive protein level, white blood cell count, and neutrophil count) and cerebrospinal fluid parameters (protein level, glucose level, white blood cell count, and neutrophil count) quickly available in the emergency department to distinguish early on between bacterial and aseptic meningitis.

Results: Of 198 patients analyzed, 96 had bacterial meningitis. Sensitivity of cerebrospinal fluid Gram staining was 75%. The PCT level had significantly better results than the other markers for area under the receiver operating characteristic curve (0.98; 95% confidence interval, 0.95-0.99; $P = .001$). At a 0.5-ng/mL threshold, PCT level had 99% sensitivity (95% confidence interval, 97%-100%) and 83% specificity (95% confidence interval, 76%-90%) for distinguishing between bacterial and aseptic meningitis. The diagnostic odds ratio between high PCT level and bacterial meningitis was 139 (95% confidence interval, 39-498), without significant heterogeneity between centers.

Conclusions: The PCT level is a strong predictor for distinguishing between bacterial and aseptic meningitis in children in the emergency department. Its combination with other parameters in an effective clinical decision rule could be helpful.

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ACUTE MENINGITIS IN CHILDREN is predominantly aseptic and does not require specific treatment. However, meningitis has a bacterial origin in about 5% of patients¹⁻³ and carries a risk of fatal outcome or severe neurological sequelae, especially when diagnosis and antibiotic administration are delayed.^{4,5} Because distinguishing between bacterial and aseptic meningitis in the emergency department (ED) is sometimes difficult, many recommend that antibiotic treatment be started immediately in children on clinical evidence of acute meningitis and/or cerebrospinal fluid (CSF) pleocytosis and that treatment be continued until bacterial culture results become available 48 to 72 hours later.^{6,7}

These recommendations assure rapid treatment of children with bacterial meningitis but result in systematic hospitalization and antibiotic administration for children with aseptic meningitis, with the morbidity and economic burden that accompany them.⁸⁻¹⁰ Therefore, distinguishing between bacterial and aseptic meningitis in the ED could help to limit unnecessary antibiotic use and hospital admissions. Because the consequences of delayed diagnosis of bacterial meningitis can be severe, any proposed diagnostic tool must achieve near 100% sensitivity.¹¹

Clinical criteria,¹²⁻¹⁴ Gram staining, and bacterial antigen testing of CSF as well as the classic biological markers in blood (C-reactive protein [CRP] level, white blood cell [WBC] count, and neutrophil

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count) or CSF (protein level, glucose level, WBC count, and neutrophil count)^{2,5,7,15} used alone do not offer 100% sensitivity with high specificity for distinguishing between bacterial and aseptic meningitis. Among new markers, serum procalcitonin (PCT) level¹⁶ seems to be one of the most sensitive and specific predictors for discriminating between bacterial and aseptic infections.^{17,18} In a single-center study of pediatric patients, a high serum PCT level on admission to the ED was identified as the best independent predictor of bacterial meningitis.¹⁹ However, because the study included few patients with bacterial meningitis (n=21), the results need further support.

Using a large multicenter study, we sought further evidence that a high serum PCT level is the best biological marker for early discrimination between bacterial and aseptic meningitis in children in the ED.

METHODS

STUDY DESIGN

We conducted a secondary analysis of hospital-based cohort studies. Potential investigating centers were contacted if they had reported on a cohort of patients with meningitis and PCT measurement. Publications were identified by a MEDLINE search of the years 1993 through early 2005 with use of the keywords “procalcitonin,” “child,” and “meningitis” and by a review of abstracts from annual meetings of the Interscience Conference on Antimicrobial Agents and Chemotherapy, the Infectious Diseases Society of America, and the European Society for Paediatric Infectious Diseases from 1995 through 2005. We also contacted members of the French Research Network for Pediatric Epidemiology. Each center selected 1 study period (in the post-*Haemophilus influenzae* type b vaccination era) when children with bacterial or aseptic meningitis routinely underwent PCT measurement on admission to the ED.

PATIENTS

Each investigator received a list of the definitions and inclusion and exclusion criteria for the study protocol and used them to complete data forms. All consecutive patients aged 29 days to 18 years who were admitted for bacterial or aseptic meningitis and had measurements of the main inflammatory markers (including PCT) in blood and CSF quickly available in the ED were eligible for inclusion. Bacterial meningitis was defined as the acute onset of meningitis (CSF WBC count $\geq 7/\mu\text{L}$)^{2,20,21} and documented bacterial infection in CSF (direct examination, culture, latex agglutination, or polymerase chain reaction) or blood culture. Aseptic meningitis was defined as the acute onset of meningitis and the absence of any bacterial meningitis criteria. Data were excluded if patients had any known neurosurgical disease, known immunosuppression, traumatic lumbar puncture (CSF red blood cell count $>10\,000/\mu\text{L}$)^{22,23} or previously treated meningitis or were referred from another hospital because of a diagnosis of meningitis. Patients with missing data essential to the ascertainment of bacterial or aseptic meningitis were also excluded. Data on patients from the previously mentioned single-center study¹⁹ were not included. Institutional review committee approval was obtained by each participating investigator from his or her institution except in Lille, France, where the committee does not require submission of such retrospective studies.

DATA COLLECTION

For each patient, we collected data on clinical, biological (WBC count, neutrophil count, CRP level, and PCT level in blood and WBC count, neutrophil count, protein level, and glucose level in CSF), and microbiological (CSF Gram staining) findings at the time of admission to the ED as well as the results of blood and CSF cultures. These data were retrospectively extracted from existing databases or medical files in each center and sent to the coordinating center. For patients recruited in pediatric departments and intensive care units (ICUs), the values were those measured at the time of admission to the ED. In all centers, the PCT level was determined by a standardized and fully validated immunoluminometric test (Lumitest PCT; Brahms Diagnostica, Berlin, Germany) as previously described.¹⁶ The functional sensitivity of the Lumitest PCT assay was 0.3 ng/mL, with analytical sensitivity of 0.1 ng/mL. The CRP level was determined by standard turbidimetric methods, and the functional sensitivity varied between centers from 0.5 mg/L to 10.0 mg/L.

STATISTICAL ANALYSIS

Statistical analyses used the Stata/SE version 8 (StataCorp, College Station, Texas) and MetaDisc (Creative Commons Attribution, Birmingham, England) statistical software. We first performed a descriptive analysis of the population's characteristics. Then, we used the Mann-Whitney *U* test to compare the distribution of the values of each potential predictor between patients with bacterial and aseptic meningitis. We compared the receiver operating characteristic curves for each potential predictor by the Hanley and McNeil method.²⁴ Each potential predictor was dichotomized by use of a threshold of the rounded first quartile of the distribution among patients with aseptic meningitis from the preceding single-center study.¹⁹ These thresholds are also frequently proposed in the literature^{13,14,23} and are used in day-to-day practice in many centers. Finally, we used these thresholds to calculate sensitivity and specificity (with 95% confidence intervals [CIs]) for each potential predictor. We did not perform multivariate logistic regression because of the very imbalanced distribution of the main predictor identified in the univariate analysis. However, in a meta-analysis, we used the diagnostic odds ratio (DOR) with a 95% CI to measure the relationship between bacterial meningitis and a high PCT level in each center and for the pooled data. Heterogeneity between centers was tested with the *Q* test and *I*² value. Because the admission of some patients to pediatric ICUs may have introduced a strong selection bias related to the stage of disease, we conducted a subanalysis including only patients not admitted to an ICU.

RESULTS

Our search strategy identified 8 published series, and the French Research Network on Pediatric Epidemiology found 1 unpublished series. Six centers²⁵⁻²⁹ from 5 European countries agreed to participate in the study, and all provided complete data files according to the inclusion and exclusion criteria of the protocol (**Table 1**). Data sets were entirely new for 1 center (Lille), partially new for 4 centers,^{25,27-29} and previously reported for 1 center.²⁶ Some patients from 2 of these 6 centers required further admission to a pediatric ICU (n=34, including 24 with bacterial meningitis). Centers varied widely in terms of inclusion dates and prevalence of bacterial meningitis (Table 1). We initially collected data for 232 pa-

Table 1. Population Characteristics at Each Center

Center	Inclusion Dates	Excluded Participants, No. (n=34)	Included Participants, No. ^a (n=198)	Participants With Bacterial Meningitis	
				%	Gram-Positive CSF, %
Pediatric emergency department					
Geneva, Switzerland	2001-2004	1	30	20	100
Lille, France ^b	2004-2005	3	22	27	83
Pediatric department					
Badalona, Spain	1998-2002	9	32	59	79
Elazig, Turkey	2001-2002	5	39	46	50
Rzeszów, Poland	1996-2004	11	41	56	36
Pediatric intensive care unit					
Lille, France ^b	2004-2005	5	15	100	79
Madrid, Spain	2004-2005	0	19	46	50

Abbreviation: CSF, cerebrospinal fluid.

^aData for 115 of the 198 patients have previously been published.

^bUnpublished data.

tients but subsequently excluded information for 34 of them (15%) (mean age, 3.6 years; age range, 0.5 months to 14.1 years; male to female ratio, 2.4), mainly because of missing data: 27 had (or were presumed to have) bacterial meningitis and 7 had aseptic meningitis.

Of the 198 patients who met the inclusion criteria, 96 (48%) had bacterial meningitis and 102 (52%) had aseptic meningitis; 34 patients (17%) were admitted to the ICU, including 10 with aseptic meningitis. The mean age was 4.8 years (median age, 4.1 years; age range, 1 month to 15.9 years) and the male to female ratio was 1:4. The main microorganisms identified were *Neisseria meningitidis* (n=45), *Streptococcus pneumoniae* (n=32), *H influenzae* (n=7), and *Streptococcus agalactiae* (n=4). The CSF Gram staining results showed only 75% (95% CI, 66%-84%) sensitivity for bacterial meningitis (**Table 2**).

The distribution of all blood and CSF biological parameters differed significantly between patients with bacterial and aseptic meningitis (**Table 3**). The PCT level had an area under the receiver operating characteristic curve (AUC) of 0.98 (95% CI, 0.95-0.99), significantly higher than that for the other biological markers ($P = .001$) (**Figure 1**). **Table 4** presents the sensitivity and specificity of each marker, dichotomized at each predefined threshold. Among these markers, a PCT level of 0.5 ng/mL or higher showed the best sensitivity (99%; 95% CI, 97%-100%) and specificity (83%; 95% CI, 76%-90%) (Table 4). The only patient with bacterial meningitis and a PCT level less than 0.5 ng/mL on admission to the ED was a 21-month-old boy with meningitis caused by *N meningitidis* infection in whom the initial PCT level was lower than the level of detection. No threshold of PCT showed 100% sensitivity and good specificity (Figure 1). Meta-analysis of these PCT results shows the significant relationship between bacterial meningitis and PCT level in each center and for the pooled data (**Figure 2**), with a pooled DOR of 139 (95% CI, 39-498) for bacterial meningitis and with no substantial heterogeneity between centers ($Q = 2.0$; $I^2 = 0\%$; $P = .84$). The pooled data also showed a significant relationship between the CRP level and bacterial meningitis (pooled DOR=13; 95% CI, 6-30) without substantial heterogeneity ($Q = 5.0$, $I^2 = 0\%$, $P = .42$) but

Table 2. Characteristics of Included Patients

Variable	All Patients (N=198)	Patients With Bacterial Meningitis (n=96)
Age, y		
Mean (median)	4.8 (4.1)	3.2 (1.7)
Range	0.1-15.9	0.1-14.0
Male to female ratio	1.4	0.9
Seizure, No. (%)	34 (17)	21 (22)
Bacterial meningitis, No. (%)	96 (48)	96 (100)
Gram-positive CSF, No. (%)	67 (34)	67 (75)
Positive CSF cultures, No. (%)	76 (38)	76 (79)
Positive for CSF soluble antigens, No. (%)	41 (21)	41 (43)
Positive for CSF soluble antigens alone, No. (%)	NA	12 (12)
Positive blood culture results alone, No. (%)	NA	7 (7)
Positive bacterial PCR results alone, No. (%)	NA	1 (1)

Abbreviations: CSF, cerebrospinal fluid; NA, not applicable; PCR, polymerase chain reaction.

not between the WBC count in the blood and bacterial meningitis (pooled DOR=2; 95% CI, 1-5). Variability between centers for the latter was large ($Q = 11.0$; $I^2 = 56\%$; $P = .046$).

The results did not change when we considered only patients not admitted to the ICU. The distribution of all biological markers differed significantly between patients with bacterial and aseptic meningitis. A PCT level of 0.5 ng/mL or higher still showed the best sensitivity (99%; 95% CI, 92%-100%) and specificity (81%; 95% CI, 72%-88%) and the receiver operating characteristic curve analyses still identified PCT level at admission as the best marker for distinguishing between bacterial and aseptic meningitis (AUC=0.98; 95% CI, 0.96-1.00), statistically better than CRP level (AUC=0.88; 95% CI, 0.82-0.94), CSF protein level (AUC=0.86; 95% CI, 0.79-0.94), or CSF neutrophil count (AUC=0.87; 95% CI, 0.80-0.93) ($P < .001$). Meta-analysis of the pooled data also did not differ, with a significant relationship between bacterial meningitis and PCT level (DOR=98; 95% CI,

Table 3. Distribution of Biological Markers in Children With Bacterial and Aseptic Meningitis

Parameter	Bacterial Meningitis (n=96)		Aseptic Meningitis (n=102)		P Value
	Patients, No.	Median (Range)	Patients, No.	Median (Range)	
Blood					
PCT level, ng/mL	90	21.5 (0.1-156.4)	100	0.3 (0.1-22.4)	<10 ⁻⁶
CRP level, mg/L	95	136.0 (4.9-350.0)	102	14.0 (0.5-330.0)	<10 ⁻⁶
WBC count, / μ L	96	14 730 (2440-42 000)	102	9900 (3290-30 000)	<10 ⁻⁴
Neutrophil count, / μ L	86	11 472 (1176-37 800)	102	6417 (1316-23 000)	<10 ⁻⁶
CSF					
Protein level, g/L	95	1.6 (0.1-10.4)	100	0.4 (0.1-2.9)	<10 ⁻⁶
Glucose level, mg/dL	96	19.8 (0.0-109.9)	99	57.7 (1.8-102.7)	<10 ⁻⁶
WBC count, / μ L	96	1625 (8-22 000)	102	83 (7-1120)	<10 ⁻⁶
Neutrophil count, / μ L	95	1170 (0-19 800)	89	34 (0-720)	<10 ⁻⁶

Abbreviations: CRP, C-reactive protein; CSF, cerebrospinal fluid; PCT, procalcitonin; WBC, white blood cell.
SI conversion factor: To convert glucose level to millimoles per liter, multiply by 0.0555; WBC (blood) to $\times 10^9/L$, multiply by 0.001.

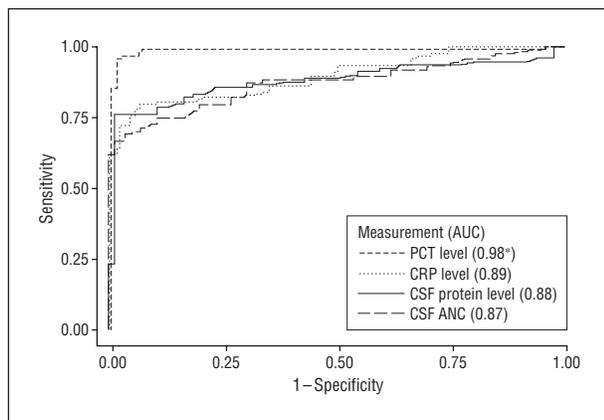


Figure 1. Receiver operating characteristic curves of the best predictors differentiating bacterial from aseptic meningitis. AUC indicates area under the receiver operating characteristic curve; PCT, procalcitonin; CRP, C-reactive protein; CSF, cerebrospinal fluid; and ANC, absolute neutrophil count. * $P=.001$.

25-382) that was stronger than the relationship between bacterial meningitis and other biological markers (data not shown).

COMMENT

In this retrospective data analysis of cohorts from various countries in Europe, we confirmed that a high serum PCT level is the best biological predictor for distinguishing between bacterial and aseptic meningitis in children presenting to the ED. Used alone at a 0.5-ng/mL threshold, PCT level offers the best sensitivity (99%; 95% CI, 97%-100%) and specificity (83%; 95% CI, 76%-90%). Although the sensitivities, specificities, and odds ratios for CRP level, CSF protein level, and CSF neutrophil count were also good, they were significantly lower than those for PCT level. Similar results were obtained when considering only patients not admitted to the ICU, with a slightly wider 95% CI. This study also evaluated the geographical and historical transposability of the predictive power of PCT level given the different study periods and the wide range of bacterial meningitis preva-

lence rates in the different centers, which is an indirect indicator of their different recruitment patterns. These findings confirm high serum PCT level as a very sensitive and specific marker for discriminating between bacterial and aseptic meningitis, consistent with results of previous single-center studies among pediatric^{19,25-30} and adult^{31,32} patients.

The main limitation of this study is its design as a secondary analysis of retrospective cohorts. We mainly searched published reports and abstracts from scientific meetings, which might have resulted in a publication bias because studies with null findings are less likely to have been reported. However, 1 unpublished series (from Lille) was included, and its PCT level had 100% sensitivity and 86% specificity for distinguishing between bacterial and aseptic meningitis at a 0.5-ng/mL threshold. Publication bias is therefore possible but probably limited. The inclusion of the centers was based on voluntary participation, and 3 centers did not agree to participate.^{30,33,34} However, data from all 3 reported that PCT level had better predictive ability than other classic biological predictors of septic shock in pediatric ICUs^{33,34} and of various infections in the pediatric ED.³⁰ Thus, participation bias is unlikely. The high prevalence of bacterial meningitis may suggest the existence of selection bias within each center. This high prevalence may be explained by the inclusion of patients admitted to 2 pediatric ICUs (who are more likely to have bacterial meningitis) and 3 pediatric departments and by the local routine strategy in 2 centers of not performing routine lumbar puncture in pediatric patients with suspected acute aseptic meningitis who appeared well (Elazig, Turkey, and Rzeszów, Poland). This strategy resulted in an overestimation of the frequency of patients with bacterial meningitis (close to 50%). However, it did not influence the sensitivity and specificity values because these results are independent of disease prevalence. This high prevalence may also be explained by an indication bias of PCT measurement. Indeed, although in theory PCT level was routinely measured in every patient with acute meningitis during the study periods that the investigators selected, it might not have been measured in some patients with aseptic meningitis. This indication bias may also explain the differ-

Table 4. Univariate Analyses of Potential Biological Predictors of Bacterial and Aseptic Meningitis

Predictor	Bacterial Meningitis (n=96)		Aseptic Meningitis (n=102)		OR (95% CI)
	No. (%) ^a	(95% CI) ^b	No. (%) ^c	(95% CI) ^d	
Blood					
PCT level, ng/mL					
≥0.5	89 (99)	97-100	17 (17)	76-90	434.5 (57.0 to >1000.0)
<0.5	1 (1)		83 (83)		
CRP level, mg/L					
≥20	79 (83)	76-91	34 (33)	58-76	9.9 (4.8 to 20.8)
<20	16 (17)		68 (67)		
WBC count, /μL					
≥15 000	46 (48)	38-58	22 (22)	70-86	3.4 (1.7 to 6.6)
<15 000	50 (52)		80 (78)		
Neutrophil count, /μL					
≥10 000	49 (57)	47-67	25 (25)	67-84	4.1 (2.1 to 8.0)
<10 000	37 (43)		77 (75)		
CSF					
Protein level, g/L					
≥0.5	84 (88)	82-95	35 (35)	56-74	14.2 (6.3 to 32.7)
<0.5	11 (12)		65 (65)		
Glucose level, mg/dL					
>45.0	64 (67)	58-77	18 (18)	74-89	9.3 (4.5 to 19.3)
≤45.0	31 (33)		81 (82)		
WBC count, /μL					
≥200	76 (79)	71-87	32 (31)	60-78	8.3 (4.1 to 16.9)
<200	20 (21)		70 (69)		
Neutrophil count, /μL					
≥100	78 (82)	74-90	24 (27)	64-82	12.4 (5.8 to 27.0)
<100	17 (18)		65 (73)		

Abbreviations: CI, confidence interval; CRP, C-reactive protein; CSF, cerebrospinal fluid; OR, odds ratio; PCT, procalcitonin; WBC, white blood cell.
SI conversion factor: To convert glucose level to millimoles per liter, multiply by 0.0555; WBC (blood) to $\times 10^9/L$, multiply by 0.001.

- ^aThe first percentage for each marker corresponds to the marker's sensitivity.
- ^bValues are the 95% CIs for sensitivity.
- ^cThe second percentage for each marker corresponds to the marker's specificity.
- ^dValues are the 95% CIs for specificity.

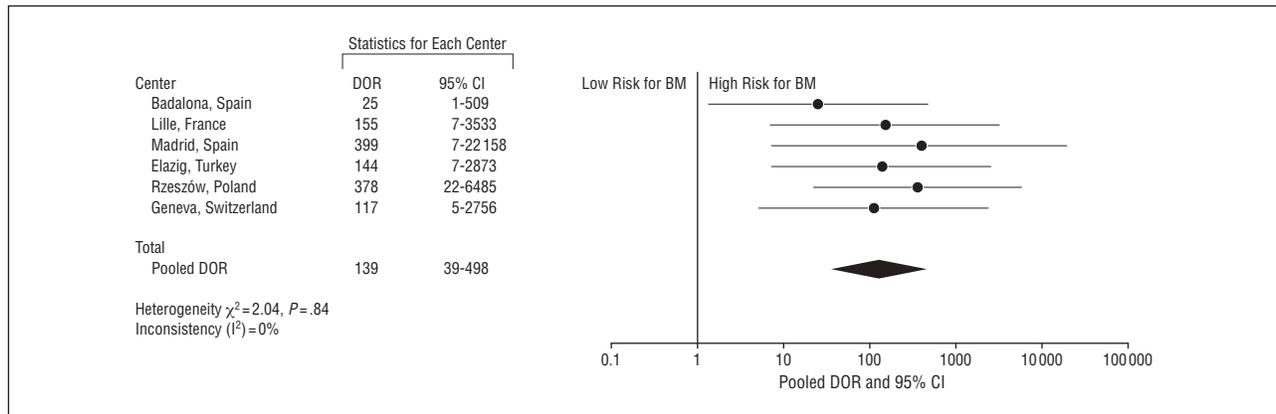


Figure 2. Meta-analysis of the relationship between bacterial meningitis and procalcitonin level in each center and for the pooled data. DOR indicates diagnostic odds ratio; CI, confidence interval; and BM, bacterial meningitis.

ence in PCT level sensitivity between our initial single-center study (89%; 95% CI, 67%-97%) and this multicenter analysis (99%; 95% CI, 97%-100%).^{19,25-30} Retrospective record review may have also introduced classification bias. For example, some parameters such as pre-treatment with antibiotics in the previous 48 hours may have been missed. However, the strength of our results is consolidated by the large size of our population, particularly for bacterial meningitis cases. Moreover, the

meta-analysis of PCT level results did not identify significant heterogeneity between centers that could have been observed when pooling data from different centers and thus reinforces our results.

Although PCT level is probably the best biological predictor currently available to distinguish between bacterial and aseptic meningitis, it cannot be used alone with 100% sensitivity and good specificity regardless of the threshold chosen. Some rare pediatric^{19,25} and adult³⁵ patients with

bacterial meningitis may have an initially low PCT level and some investigators have not found the PCT level to be this sensitive, especially in adult populations.^{31,36} The use of a recently developed and more sensitive PCT assay (Kryptor; Brahms Diagnostica) and a follow-up measurement (within hours after admission) may increase the sensitivity of the PCT level. Another way to increase the sensitivity of a diagnosis tool while retaining high specificity might be the combination of PCT level at admission with other predictors in a clinical decision rule. One study³ showed that the best of 5 published rules was the Bacterial Meningitis Score.² According to the Bacterial Meningitis Score, outpatient management may be considered for children with meningitis (CSF WBC count $\geq 7/\mu\text{L}$) in the absence of all of the following 5 criteria at arrival in the ED: (1) history of seizure with the illness; (2) blood neutrophil count of 10 000/ μL or higher; (3) CSF gram-positive results; (4) CSF protein level of 80 mg/dL or higher; and (5) CSF neutrophil count of 1000/ μL or higher. However, the broad validation of the Bacterial Meningitis Score failed in part because a few patients with bacterial meningitis were not detected by this rule.³⁷ Introducing PCT level into a modified Bacterial Meningitis Score to avoid misdiagnosis would be of interest. For example, in a previous single-center study,^{19,38} no patients with bacterial meningitis had a PCT level lower than 0.5 ng/mL and a CSF protein level lower than 0.5 g/L. Further studies are necessary to confirm this encouraging preliminary finding. Validation by prospective studies is needed before PCT level can be routinely included as part of a rule to decide on admission and/or treatment in cases of pediatric meningitis, for such changes in practice require caution.

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Announcement

Trial Registration Required. In concert with the International Committee of Medical Journal Editors (ICMJE), *Archives of Pediatrics and Adolescent Medicine* will require, as a condition of consideration for publication, registration of all trials in a public trials registry (such as <http://ClinicalTrials.gov>). Trials must be registered at or before the onset of patient enrollment. This policy applies to any clinical trial starting enrollment after July 1, 2005. For trials that began enrollment before this date, registration will be required by September 13, 2005, before considering the trial for publication. The trial registration number should be supplied at the time of submission.

For details about this new policy, and for information on how the ICMJE defines a clinical trial, see the editorials by DeAngelis et al in the September 8, 2004 (2004;292:1363-1364) and June 15, 2005 (2005;293:2927-2929) issues of *JAMA*. Also see the Instructions to Authors on our Web site: www.archpediatrics.com.