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RISK SCORE FOR IDENTIFYING ADULTS WITH CSF PLEOCYTOSIS AND NEGATIVE CSF GRAM STAIN AT LOW RISK FOR AN URGENT TREATABLE CAUSE

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Abstract

Background—We aimed to derive and validate a risk score that identifies adults with cerebrospinal fluid (CSF) pleocytosis and a negative CSF Gram stain at low risk for an urgent treatable cause.

Methods—Patients with CSF pleocytosis and a negative CSF Gram stain were stratified into a prospective derivation (n=193) and a retrospective validation (n=567) cohort. Clinically related baseline characteristics were grouped into three composite variables, each independently associated with a set of predefined urgent treatable causes. We subsequently derived a risk score classifying patients into low (0 composite variables present) or high (≥1 composite variables present) risk for an urgent treatable cause. The sensitivity of the risk score was determined in the validation cohort and in a prospective case series of 214 adults with CSF-culture proven bacterial meningitis, CSF pleocytosis and a negative Gram stain.

Findings—A total of 41 of 193 patients (21%) in the derivation cohort and 71 of 567 (13%) in the validation cohort had an urgent treatable cause. Sensitivity of the dichotomized risk score to detect an urgent treatable cause was 100.0% (95%CI 93.9-100.0%) in the validation cohort and 100.0% (95%CI 97.8-100.0%) in bacterial meningitis patients.

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Interpretation—The risk score can be used to identify adults with CSF pleocytosis and a negative CSF Gram stain at low risk for an urgent treatable cause.

INTRODUCTION

Inflammation of the central nervous system is a medical emergency that is associated with high mortality and morbidity. It is generally confirmed if the cerebrospinal fluid (CSF) shows an elevated white blood cell count (pleocytosis). The epidemiology of infectious meningitis and/or encephalitis has changed in the last decades due to routine vaccination, an increase in conditions causing an impaired immune response and the emergence of “new” pathogens, such as the West Nile virus.^{2,5} Furthermore, advances in diagnostic microbiology, virology, and neuroradiology have expanded the etiological differential diagnosis of inflammation of the central nervous system.²

The primary concern of physicians treating patients with CSF pleocytosis is to distinguish between an urgent and treatable cause, *e.g.*, bacterial meningitis, and from conditions of less concerning aetiologies (*e.g.*, viral meningitis). An important diagnostic test is CSF Gram staining, which is rapid, inexpensive and well validated for detecting bacteria. Although CSF Gram stain has good specificity, its sensitivity is highly variable depending on the patient population, pathogen and previous treatment with antibiotics.⁷ Consequently, a negative CSF Gram stain makes viral meningitis likely, but does not rule out bacterial meningitis or another urgent treatable cause. Most patients with CSF pleocytosis and negative CSF Gram stain are therefore admitted and treated empirically with intravenous antibiotic therapy and anti-viral therapy until CSF and blood cultures are negative and the clinical condition improves, even though only a small minority will turn out to have an urgent treatable cause.¹ This uncertainty about the probability of an urgent treatable cause in an individual patient thus leads to costly diagnostic testing, admission and treatment.

The purpose of this observational study was to identify predictors of an urgent treatable cause, and subsequently derive and validate a risk score that can identify patients at very low risk of an urgent treatable cause in adults with CSF pleocytosis and negative CSF Gram stain.

METHODS

Case definition and data collection

Cases were defined as adults patients (age >16 yrs) presenting to an emergency department with community-acquired symptoms of meningitis, CSF white cell count >5 cells/mm³, and negative CSF Gram stain. Patients with neurosurgical procedures, previous treatment with antibiotics for >48 hours and unknown aetiology, and recurrent meningitis were excluded from the analysis.

The derivation cohort was assembled prospectively at Tulane University Hospital and Clinic and the Medical Center of Louisiana in New Orleans between 1999–2008 - interrupted between 2005–2006 due to Hurricane Katrina. The study was approved by the Institutional Review Board and written informed consent was obtained. The validation cohort was assembled retrospectively at eight Memorial Hermann hospitals (Texas Medical Center, Katy, Woodlands, Memorial City, Sugarland, Northwest, Southwest, Southeast) in the Greater Houston area and surroundings between 2005–2010. This validation study was approved by the University of Texas Health in Houston Committee for the Protection of Human Subjects and by the Memorial Hermann Hospital Research Review Committee. Baseline characteristics were identified when the patient was in the emergency department. Sociodemographic data, comorbid conditions (Charlson comorbidity scale),

immunocompetence, exposures, clinical features and Glasgow coma scale, laboratory results and management decisions were recorded.⁸⁻⁹

To further evaluate the risk of missing bacterial meningitis cases, a second validation study was performed in two nationwide prospective cohort studies on patients with bacterial meningitis in the Netherlands. Patients were prospectively included between 1998–2002 and 2006–2012 if they were over 16 years old and had CSF culture proven community-acquired bacterial meningitis. In- and exclusion criteria have previously been published.^{7,10} Patients were considered immunocompromised if they used immunosuppressive medication, or had HIV/AIDS. The Charlson comorbidity scale and data on IV drug use were not routinely recorded. For those variables necessary for risk categorization, missing data were assumed to be normal; this will lead to an underestimation of the sensitivity of the risk score. All local ethics committees of participating hospitals approved the studies. Written informed consent was obtained from all participating patients or their legally authorized representatives.

Laboratory testing and diagnostic criteria

CSF from all patients was tested for glucose, protein, cell count, and was sent for bacterial culture. Further diagnostic testing for causative microorganisms by additional cultures (fungal, acid fast bacilli), polymerase chain reaction (PCR) and serologic tests were performed at the discretion of the treating physician. For the diagnosis of bacterial or fungal meningitis a positive CSF culture or antigen detection was required. The diagnosis of *Enterovirus*, HSV, and CMV meningitis required either positive CSF culture or PCR. Diagnosis of Varicella Zoster Virus (VZV) required either a positive culture or PCR in the CSF or isolation of VZV (viral culture or a positive VZV Direct fluorescent antibody) from a coexisting vesicular skin lesion. Diagnosis of rickettsial disease required evidence of specific serum antibody or demonstration of *Rickettsia* from a skin biopsy. Bacteraemia required isolation of the pathogen from at least two blood culture samples. Diagnosis of meningeal carcinomatosis required positive CSF cytology. Parameningeal and intracranial mass lesions and intracranial haemorrhages required documentation by either cranial or spinal imaging.

Classification of aetiology and outcome

Cases were divided into four etiological categories: 1) unknown cause; 2) untreatable cause; 3) treatable but not urgent cause; 4) urgent treatable cause. Urgent treatable cause was defined as bacterial, fungal, or tuberculous meningitis; Herpes simplex virus (HSV), VZV, or Cytomegalovirus (CMV) meningoencephalitis, rickettsial meningoencephalitis; bacteraemia; central nervous system vasculitis; intracranial haemorrhages; or parameningeal or intracranial abscess.² HSV aseptic meningitis was considered a treatable but not urgent cause as there is no data to suggest that early acyclovir therapy in this syndrome improves clinical outcomes. The primary study endpoint was the presence of an urgent treatable cause. In the derivation, validation and bacterial meningitis cohorts, outcome was graded according to the Glasgow outcome scale.¹¹

Statistical analysis

A sample size of at least 175 patients in the derivation sample was needed to achieve 80% power to detect significant differences in the proportions of clinically plausible variables using a two-tailed test with a p-value of <0.05. Baseline characteristics having a clinically plausible association with an urgent treatable cause were examined in bivariate analysis. To avoid overfitting in the regression modelling, no more than one variable was entered per 10 outcome events.^{12,13} As a variable reduction strategy, clinically related baseline variables showing a bivariate association were grouped into three composite variables: altered

immune status, abnormal exam, and abnormal laboratory findings (figure 1). The composite variables were entered into a logistic regression model to verify independent associations with an urgent treatable cause.

Using these composite variables, we subsequently developed a dichotomized risk score to classify patients into low (0 composite variables present) or high (≥ 1 composite variables present) risk for an urgent treatable cause. Sensitivity of the risk score was defined as the proportion of patients with an elevated risk score out of all patients with a UTC. Specificity of the risk score was defined as the proportion of low risk patients out of all patients without a UTC. We performed a second external validation study in the Dutch bacterial meningitis cohort. Finally we compared our risk score to a previously published prediction model, developed to predict an urgent treatable cause (bacterial meningitis) in adult patients with acute meningitis and a negative CSF Gram stain.¹⁴

RESULTS

Derivation and validation cohorts

Two hundred and forty two patients were screened for inclusion in the derivation study, 49 (20%) were excluded, leaving 193 patients to be enrolled in the derivation study (figure 2A). For the validation study, 747 patients with meningitis were screened, of which 180 patients (24%) were excluded, leaving 567 patients for the clinical prediction score (figure 2B). The derivation and validation cohorts were similar regarding age, gender, duration of illness, physical and neurological examination, and mortality rate. Ethnicity, medical history, and cranial imaging results were different between cohorts. In the validation cohort a higher rate of patients were admitted, treated with empiric acyclovir, and received cranial imaging (table 1).

Characteristics of patients with CSF pleocytosis and negative Gram stain

Clinical and laboratory characteristics of adults with CSF pleocytosis and negative Gram stain are summarized in table 1. The total cohort (n=760) consisted primarily of young adults (median age 36 years) with 54% of the patients being female and 59% belonging to a minority (Hispanic, African-American, or Asian). Co-morbidity was present in 133 patients (18%) and 100 patients (13%) were HIV positive; 39 (5%) had a history of intravenous drug use. Presenting symptoms included headache (89%), fever (66%), photophobia (49%), and stiff neck (47%). Thirty-nine patients (5%) had a seizure within 1 week prior to arrival to the emergency department. On examination 77 patients (10%) had focal neurologic deficits, 144 individuals (19%) had a reduced level of consciousness and 20 (3%) had a vesicular or petechial rash. A cranial CT scan was done in 678 (89%) patients as part of their initial evaluation in the emergency department, being abnormal in 56 (7%). Additionally, 263 (35%) also underwent a cranial MRI during admission, with 95 (35%) of them showing mass lesions, strokes, hypo-attenuations, meningeal enhancement, bleeds, or white matter abnormalities (table 1).

Diagnostic causes (table 2) for the episode of meningitis were identified in 215 patients (28%) of the total cohort, the most common diagnoses were: HSV type 2 (5%), West Nile virus (4%), cryptococcal (3%), bacterial (3%) and enterovirus meningitis (3%). No cause was identified in 545 patients (72%). In the subgroup of 108 patients (14%) with urgent treatable causes the most common diagnoses were bacterial meningitis (32%), and cryptococcal meningitis (20%). Untreatable and non-urgent treatable conditions were both identified in 7% each.

Seven hundred and three patients (93%) were admitted to the hospital and 568 patients (75%) received empirical antibiotic therapy, while waiting for culture results. The median

duration of antibiotic therapy was 2 days. Empiric intravenous antiviral therapy with acyclovir was administered in 189 patients (25%). Follow up was available for 755 (99%) of the patients. The majority of patients (671; 89%) had no residual neurological morbidity; 72 patients (9%) had persistent neurological deficits or seizures and required transfer to a rehabilitation facility. Additional one-month follow up was available in the derivation cohort only, 143 out of 167 (87%) had no residual morbidity or deficits.

The overall mortality rate was 1.4% (11 of 760 patients). Death was caused by encephalitis of unknown aetiology in two patients, and by methicillin-sensitive *Staphylococcus aureus* (MSSA) bacteraemia, MSSA endocarditis, HSV encephalitis, gliomatosis cerebri, AIDS-dementia-complex, end-stage AIDS, CMV encephalitis, cerebral toxoplasmosis, and *Mycobacterium tuberculosis* meningitis in one patient each.

Development and validation of a risk score for an urgent treatable cause

Bivariate analyses relating clinically cogent variables to an urgent treatable cause in the derivation cohort are shown in table 3. As a variable reduction strategy and to avoid overfitting, baseline variables showing a bivariate association ($p < 0.05$) were grouped into three composite variables: altered immune status, abnormal exam, and abnormal laboratory exam (figure 1). A composite value was present if one or more of the baseline variables applied to the patient. The composite variables were all independently associated with an urgent treatable cause (adjusted odds ratios (OR): altered immune status 2.86, 95% confidence interval (CI) 1.28–6.38; abnormal examination 2.63, 95% CI 1.20–5.77; abnormal laboratory exam 10.22, 95% CI 3.94–26.50). We subsequently derived a risk score classifying patients into low (0 composite variables present) or high (≥ 1 composite variables present) risk for an urgent treatable cause. In the New Orleans derivation cohort, none of the 55 patients in the low risk group had an UTC, while 41 out of 138 (30%) in the high risk had an UTC (sensitivity 100% (95% CI 0.89–1.0), specificity 36% (95% CI, 0.29–0.44), negative predictive value 100% (95% CI, 0.92–1.0), positive predictive value 29.7% (95% CI, 0.22–.38).

Validation of the risk score to identify patients at low risk for an urgent treatable cause

A false negative test result was defined as a patient with an urgent treatable cause, classified as low risk, by the risk score. In the Houston validation cohort, none of the 222 patients in the low risk group had an UTC, while 71 out of 345 (20.6%) in the high risk had an UTC (sensitivity 100% (95% CI 0.94–1.0), specificity 45% (95% CI, 0.41–0.50), negative predictive value 100% (95% CI, 0.98–1.0), positive predictive value 21.8% (95% CI, 0.18–0.26).

Although bacterial meningitis was the second most common urgent treatable cause in the validation cohort, the absolute number of cases was low. To further evaluate performance of the risk score in this clinically important subgroup, we subsequently assessed sensitivity of the risk score in a cohort of adults with bacterial meningitis. Out of a total of 1728 episodes of culture proven and community acquired bacterial meningitis, we identified 214 (12%) patients with a CSF white cell count > 5 cells/mm³ and a negative CSF Gram stain (supplemental figure 1). Of these 214 patients, 66 (31%) had pneumococcal meningitis and 44 (18%) meningococcal meningitis. Variables included in the risk score were present in the majority of patients (table 5). Sensitivity of the risk score to detect bacterial meningitis in patients with a CSF pleocytosis and a negative Gram stain was 100.0% (95% CI 97.8–100.0%).

We know of one previously published risk score that was developed to predict bacterial meningitis in adult patients with acute meningitis and a negative CSF Gram stain.¹⁴ We

compared this previously published risk score to our risk score in the subgroup of 214 bacterial meningitis patients with community acquired bacterial meningitis, a CSF pleocytosis and a negative CSF gram. After exclusion of 96 of the 214 (49%) cases because of missing data for 1 or more variables, we found a sensitivity of the previously published risk score of 92.2% (95% CI 84.7–96.0). Ten (7.8%) bacterial meningitis cases were incorrectly classified as viral meningitis. None of these cases were classified as low risk by our risk score. In an analysis with missing data assumed to be abnormal, the sensitivity was 95.3% (95% CI 91.3–97.6).

DISCUSSION

We have derived and validated a risk score that helps physicians to reliably stratify patients with CSF pleocytosis and negative CSF Gram stain with respect to the risk for an urgent treatable cause. Risk assessment helps physicians, take decisions about the level of care, plan initial therapy, and to inform the patient and his or her relatives about prognosis. About one-third of patients was categorized as of low risk for an urgent treatable cause and could potentially be considered for outpatient management and follow-up. Patients with an elevated risk score should be hospitalized, with further diagnostic testing and therapy depending on individual characteristics. Although our model shows good external validity, it should be regarded only as a piece of diagnostic assessment among others and should not replace a careful diagnostic evaluation on an individual level for all cases. Our risk score had an excellent sensitivity for detecting bacterial meningitis, but for other urgent treatable causes this is less certain. Therefore, future studies should validate our model in other geographical areas, and evaluate the impact of our model on the management of this common clinical dilemma.

A previous model validated in adults (and children) predicted the probability of bacterial meningitis as opposed to viral meningitis.^{19,20} A slightly altered version was evaluated in 500 consecutive cases with paediatric and adult community-acquired meningitis, with c-statistics, and negative and positive predictive values of 0.99, 0.99 and 0.85 respectively.²¹ In the initial study, cases with a negative CSF Gram stain had been excluded from the derivation and validation cohorts. However, performance of the model was subsequently evaluated in 109 consecutive patients, both children and adults (mean age 30 years, range 1–85), with acute meningitis and a negative CSF Gram stain.¹⁴ Negative and positive predictive values and accuracy of this model to predict bacterial versus viral meningitis were 98.7%, 66.7%, and 96.5%, respectively. The model missed one patient with bacterial meningitis due to *Leptospira spp.* resulting in a sensitivity of 80%. Comparing both prediction models in the Dutch cohort of adult patients with bacterial meningitis, CSF pleocytosis and a negative Gram stain, our risk score had better sensitivity 100.0% (95% CI 97.8–100.0%) than a previously published prediction model 92.2% (95% CI 84.7–96.0).

The “Bacterial Meningitis Score” was developed to differentiate bacterial from “aseptic” meningitis in children.¹⁷ It showed good external validity; classification of children as of low risk had a negative predictive value of 99.9% (95% CI 99.4–100.0%) for bacterial meningitis.¹⁸ However, the Bacterial Meningitis Score has not been used in adults with meningitis. Interestingly, one of the five components of the Bacterial Meningitis Score is a positive Gram stain.

Bacterial meningitis constituted 32% of all urgent treatable causes in our cohorts. Our score did identify all patients with CSF pleocytosis and community-acquired bacterial meningitis in the largest prospective meningitis cohort to date. A major advantage of our model over previously published prediction models is that it does not solely focus on bacterial meningitis but on all urgent and treatable causes.

Many features of our cohort of meningitis cases with a negative Gram stain were similar to previous studies, however, there were several noteworthy observations. First, the differential diagnosis of this syndrome is very broad and includes a wide range of infectious and non-infectious causes, some of which require urgent treatment. Second, the majority of patients were hospitalized (93%), underwent cranial imaging (89%), and received empiric intravenous antibiotic therapy (75%), even though the minority of patients (15%) had an urgent treatable cause. Third, despite extensive diagnostic testing with current techniques and similar to other studies, the majority of the patients (72%) had an unknown aetiology.^{1,2,4} Lastly, even though the overall mortality of this syndrome is low (1.4%); 72 (9.6%) of surviving patients had residual functional impairment at discharge.

There are several limitations to our study. First, although the majority of patients in the derivation and validation cohort had a CSF bacterial culture performed (96%), only 338 patients (44%) had polymerase chain reaction tests done in it. By using PCR, the causative microorganism can be identified in a substantial proportion of culture negative cases.⁵ Furthermore, PCR for enterovirus and for herpes virus was done less frequently in the unknown category ($P<0.05$). Therefore, part of the CSF culture negative cases, now classified as “unknown cause” may have had positive viral CSF PCR. As this study was observational and resembles clinical practice, use of PCR was at the discretion of the treating physician. Second, we excluded a total of 35 patients that received oral antibiotics before lumbar puncture or were treated with intravenous antibiotics for more than 48 hours and had no identifiable aetiology. This was done to avoid misclassification bias, as these patients could have had bacterial meningitis. Third, the majority of patients (72%) had meningitis of unknown cause. This is the frustrating reality of this syndrome and we hope that novel molecular tools and standardized diagnostic algorithms will be able to improve our current understanding of patients with CSF pleocytosis and negative CSF Gram stain. A further limitation was that data on IV drug users was not available in the bacterial meningitis cohorts and information on the use of immunosuppressive medication was only routinely available for the 2006 bacterial meningitis cohort. We do not think, however, that this weakens our conclusion that the risk model has a high sensitivity to detect bacterial meningitis, as using fewer variables in the risk model can only lead to an underestimation of sensitivity. Even if we assumed all patients in the bacterial meningitis cohort to be immunocompetent, no additional bacterial meningitis patients were classified as low risk.

In conclusion, we developed and validated a risk score that can be used to identify adults with CSF pleocytosis and a negative CSF Gram stain at low risk for an urgent treatable cause. Using this model up to one-third of patients with this common clinical dilemma can be considered for outpatient management.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Composite variables

Baseline variables

Figure 1.
Grouping of baseline variables into composite variables.

Figure 2.
Flowcharts of patient inclusion in derivation cohort (A) and validation cohort (B).

Table 1

Clinical and laboratory characteristics of adults with CSF pleocytosis and a negative Gram stain.^a

Variable	Derivation cohort (n=193)	Validation cohort (n=567)	Variable	Derivation cohort (n=193)	Validation cohort (n=567)
Age, years	38 (18–96)	36 (18–92)	Neck stiffness	52 (27%)	160 (18%)
Female	102 (53%)	312 (55%)	Altered mental status ^b	38 (21%)	106 (19%)
Ethnicity			Focal neurologic deficits ^c	20 (11%)	57 (10%)
African American [*]	142 (74%)	143 (26%)	Vesicular or petechial rash [*]	10 (6%)	10 (2%)
White [*]	43 (22%)	265 (47%)	Laboratory results		
Hispanic [*]	7 (4%)	138 (24%)	Serum leukocyte count >12,000/mm ³	52 (27%)	133 (23%)
Asian [*]	0 (0%)	17 (3%)	CSF leukocyte count >1,000/mm ³	23 (12%)	43 (8%)
Coexisting medical condition			CSF protein >100mg/dL	57 (30%)	204 (36%)
Charlson comorbidity index >1 [*]	63 (33%)	70 (12%)	CSF glucose <45mg/dL [*]	44 (23%)	80 (14%)
Immunodeficiency [*]	63 (33%)	62 (11%)	Management decisions		
HIV/AIDS [*]	56 (29%)	44 (8%)	Admission to hospital [*]	157 (88%)	546 (97%)
Intravenous drug use [*]	26 (13%)	13 (2%)	Empiric antibiotic therapy [*]	153 (86%)	415 (73%)
Presenting history			Median duration of antibiotics (days)	3 (0–44)	2 (0–45)
Headache	163 (84%)	510 (93%)	Empiric acyclovir therapy [*]	34 (19%)	155 (27%)
Fever [*]	142 (74%)	363 (64%)	Cranial CT [*]	166 (86%)	512 (90%)
Photophobia	95 (49%)	280 (57%)	Abnormal ^d	20 (10%)	36 (7%)
Respiratory symptoms [*]	51 (26%)	63 (11%)	Cranial MRI [*]	39 (20%)	228 (40%)
Seizure <1 week of presentation	14 (7%)	25 (4%)	Abnormal ^e	24 (62%)	77 (34%)
Duration of illness, days (range)	3 (0–30)	3 (0–30)	Clinical status at discharge		
Presenting signs, n (%)			Normal	168 (87%)	503 (89%)
Temperature >100.4° F [*]	94 (49%)	170 (30%)	Morbidity ^f	16 (9%)	56 (10%)
			Death	5 (3%)	6 (1%)

Variable	Derivation cohort (n=193)	Validation cohort (n=567)	Variable	Derivation cohort (n=193)	Validation cohort (n=567)
			Unknown	4 (2%)	1 (0%)

* Significant difference between derivation and validation cohort p<0.05

^aData are n/N (%), or median (range).

^bDisorientation or Glasgow Coma scale <15.

^cFocal motor deficit, cranial nerve abnormality or aphasia.

^dFocal (i.e., mass lesions, strokes, or bleeds) or nonfocal (i.e., hydrocephalus, white matter changes) intracranial abnormalities.

^eMass lesions, strokes, hypotenuations, meningeal enhancement, bleeds, white matter abnormalities.

^fGlasgow outcome scale from 2–4.

Table 2Etiologies of meningitis and negative Gram stain *n* (%)

Etiology	Total cohort (n=760)	Derivation cohort (n=193)	Validation cohort (n=567)
Urgent treatable cause	108 (14.2%)	41 (21.2%)	71 (12.5%)
<i>Cryptococcus neoformans</i>	22 (2.9%)	8 (4.1%)	14 (2.5%)
Bacterial meningitis ^a	31 (4.1 %)	15 (7.7%)	16 (2.8%)
Other serious bacterial infections ^b	18 (2.4%)	7 (3.6%)	(1.9%)
<i>Herpes simplex</i> encephalitis	15 (2.0%)	2 (1.0%)	13 (2.3%)
<i>Varicella zoster</i> virus	8 (1.1%)	3 (1.6%)	5 (0.9%)
<i>Mycobacterium tuberculosis</i>	7 (0.9%)	2 (1.0%)	5 (0.9%)
<i>Toxoplasma gondii</i>	3 (0.4%)	2 (1.0%)	1 (0.2%)
CNS vasculitis	3 (0.4%)	0 (0.0%)	3 (0.5%)
Other ^c	7 (0.9%)	3 (1.5%)	4 (0.7%)
Untreatable causes	54 (7.1%)	10 (5.2%)	44 (7.8%)
<i>West Nile Virus</i>	30 (3.9%)	1 (0.5%)	29 (5.1%)
<i>Enterovirus</i>	19 (2.5%)	8 (4.1%)	11 (1.9%)
St. Louis Encephalitis	3 (0.4%)	0 (0.0%)	3 (0.5%)
<i>Epstein Barr virus</i>	2 (0.3%)	1 (0.5%)	1 (0.2%)
Non urgent treatable causes	53 (7.0%)	9 (4.6%)	44 (7.7%)
<i>HSV type 2</i> ^d	37 (4.9%)	2 (1.0%)	34 (6.0%)
CNS lymphoma/carcinomatosis	5 (0.7%)	3 (1.0%)	3 (0.5%)
Neurosyphilis	2 (0.3%)	1 (0.5%)	1 (0.2%)
Multiple sclerosis	2 (0.3%)	1 (0.5%)	1 (0.2%)
Other ^e	4 (0.5%)	2 (1.0%)	2 (0.4%)
Unknown etiology^f	545 (71.7%)	134 (69.4%)	407 (71.8%)

^a Cerebrospinal fluid culture positive (20): *Streptococcus pneumoniae* (8), *Haemophilus influenzae* (3), *Listeria monocytogenes* (2), Methicillin-resistant *Staphylococcus aureus* (2), *Neisseria meningitidis* (1), *Streptococcus agalactiae* (2) and *Enterococcus* (2). Blood culture positive and cerebrospinal fluid culture negative (11): Methicillin-susceptible *Staphylococcus aureus* (2), Methicillin-resistant *Staphylococcus aureus* (2), *Enterococcus faecalis* (1), Vancomycin-resistant *Enterococcus* (1), *Streptococcus agalactiae* (2), Alpha hemolytic *Streptococcus* (1), *Streptococcus pyogenes* (1), *Listeria monocytogenes* (1).

^b *Staphylococcus aureus* infective endocarditis (3), *Escherichia coli* urosepsis (3), Brain abscess (2), Lemierre's syndrome with *Fusobacterium necrophorum* (1).

^c *Cytomegalovirus* encephalitis (1), *Taenia solium* (1), *Histoplasma capsulatum* (1), subarachnoid haemorrhage (1), transverse myelitis (1), epidural abscess (1), gliomatosis cerebri (1).

^d Herpes simplex virus aseptic meningitis was considered a treatable but not urgent cause.

^e Neurosarcoidosis, Lyme disease, *Influenza A*, *Cytomegalovirus* was diagnosed in one patient each.

^f patients with unknown causes had less cerebrospinal fluid polymerase chain reaction for enterovirus and herpes viruses performed than those with known causes ($p < 0.05$)

Table 3

Baseline variables associated with an urgent treatable cause in 193 adults with CSF pleocytosis and a negative CSF Gram stain

Baseline Characteristics	Patients with UTC n/N (%)	Odds ratio (95% CI)	P-value
Host variables			
Age >60 years	7/14 (50%)	3.59 (1.19–10.85)	0.02
Intravenous drug use	13/26 (50%)	4.44 (1.86–10.60)	0.0004
Immunosuppression ^a	21/63 (33%)	2.10 (1.06–4.16)	0.03
Comorbidity ^b	19/61 (31%)	1.76 (0.88–3.49)	0.11
Physical examination			
Fever ^c	19/89 (21%)	0.89 (0.44–1.78)	0.74
Altered mental status ^d	19/41 (46%)	3.99 (1.91–8.39)	0.0001
Abnormal neurologic exam ^d	16/43 (37%)	2.37 (1.13–4.95)	0.02
Rash	6/12 (50%)	3.52 (1.08–11.53)	0.03
Laboratory variables			
CSF protein >100 mg/dL	24/53 (45%)	4.44 (2.19–9.00)	<0.0001
CSF glucose <45mg/dL	26/47 (55%)	7.80 (3.71–16.41)	<0.0001
CSF WBC >1,000/mm ³	26/87 (30%)	1.83 (0.94–3.58)	0.07
CSF ANC ^e > 500/mm ³	9/22 (41%)	2.34 (0.93–5.89)	0.06
Serum WBC >12,000/μL	22/52 (44%)	3.58 (1.77–7.23)	0.0003

^a HIV/AIDS, solid organ transplant, recent chemotherapy, or chronic use of steroids

^b Charlson's comorbidity score >1

^c Temperature >38.4 °C or <35.0 °C

^d See figure 1

^e Absolute neutrophilic count (Cerebrospinal fluid cell count X neutrophilic percent)

Table 4

Risk Score for an urgent treatable cause of CSF pleocytosis and a negative Gram stain.

Risk group	Composite variables ^a	Patients with an UTC (n/N,%)
Derivation Sample (n=193)^b		
Low	0	0/55 (0%)
High	1	41/138 (30%)
Validation sample (n=567)^c		
Low	0	0/222 (0%)
High	1	71/345 (20.6%)

^aSee figure 1.

^bsensitivity 100% (95% CI 0.89-1.0), specificity 36% (95% CI, 0.29-0.44), negative predictive value 100% (95% CI, 0.92-1.0), positive predictive value 29.7% (95% CI, 0.22-.38).

^csensitivity 100% (95% CI 0.94-1.0), specificity 45% (95% CI, 0.40-0.49), negative predictive value 100% (95% CI, 0.98-1.0), positive predictive value 20.6% (95% CI, 0.16-0.25).

Table 5

Baseline characteristics, composite variables, and risk scores in patients with bacterial meningitis.

Baseline variables	Bacterial meningitis with pleocytosis and a negative CSF Gram stain (n = 214)
Host variables^a	
Age > 60 years	95 /214 (44%)
Immunosuppression ^b	18 /133 (14%)
Exam variables	
Fever ^c	134 /209 (64%)
Altered mental status ^d	147 /214 (69%)
Abnormal neurological exam ^e	55 /214 (26%)
Vesicular or petechial rash	26 /213 (12%)
Laboratory variables	
CSF protein >100 mg/dL	172 /203 (85%)
CSF glucose <45 mg/dL	123 /206 (60%)
CSF WBC > 1,000/mm ³	138 /214 (65%)
Serum WBC > 12,000/ μ L	145 /213 (68%)
Composite variables^f	
Altered immune status	100 /214 (47%)
Abnormal examination	169 /214 (79%)
Abnormal laboratory findings	192 /214 (90%)
Risk score^g	
Low (0)	0 /214 (0%)
High (1)	214 /214 (100%)

^aHistory of intravenous drug use and Charlson's comorbidity index not assessed.^bHIV infection cohort 1998. Immunosuppressive drugs or HIV infection in cohort 2006.^cT>38.4 C or <35.0 C^dGlasgow Coma scale < 15^eAphasia or cranial nerve palsy or paresis of one or more arms or legs or (recent) seizure. Missing data are assumed to be normal.^fSee figure 1. Missing data are assumed to be normal.^gsensitivity 100% (95% CI 0.98-1.0), positive predictive value 100% (95% CI, 0.98-1.0).