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CLINICAL, LABORATORY, AND EPIDEMIOLOGICAL PREDICTORS OF BACTERIAL VERSUS VIRAL MENINGITIS IN CHILDREN

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Abstract

OBJECTIVE: To find and confirm clinical, laboratory, and epidemiological predictors that accurately distinguish bacterial and viral meningitis in children to facilitate prompt etiological stratification and empiric treatment. ***MATERIAL AND METHODS:*** The study was a prospective observational cohort study carried out in multiple tertiary paediatric referral centers, between January 2024 and December 2025. The children aged 1 month to 14 years with acute presumed meningitis were enrolled. Culture and multiplex PCR were used as the reference tests for microbiological confirmation. Independent predictors were obtained using univariate screening and multivariable logistic regression. Model discrimination was evaluated using receiver operating characteristic (ROC) analysis and bootstrapping validation. ***RESULTS:*** 148 of 412 children enrolled had bacterial meningitis (35.9%) and 264 had viral meningitis (64.1%). Independent predictors of bacterial etiology included fever duration >3 days (adjusted OR 3.21, 95% CI 1.89–5.45, p<0.001), CSF white blood cell count >1000 cells/µL (adjusted OR 4.83, 95% CI 2.91–8.02, p<0.001), CSF protein >100 mg/dL (adjusted OR 3.87, 95% CI 2.24–6.67, p<0.001), CSF-to-blood glucose ratio <0.40 (adjusted OR 5.14, 95% CI 2.98–8.86, p<0.001), and absence of recent household viral illness (adjusted OR 2.73, 95% CI 1.58–4.71, p<0.001). ***CONCLUSION:*** The combination of prolonged fever, CSF cell and protein levels, a low CSF glucose ratio and a negative recent viral history is a strong predictor of bacterial meningitis in children. These parameters may be incorporated into clinical decision-making processes, thereby expediting targeted treatment and minimizing unnecessary antibiotic use, and enhance the prognosis of pediatric meningitis.

Keywords: lower age, lower birth weight, hospital discharge, prior neurological illnesses, altered mental status and coma.

INTRODUCTION

Even with only a small portion of the nervous system, meningitis is one of the most important neurologic emergencies in children, occurring when there is inflammation of the meninges and is associated with rapid clinical deterioration if the cause is not quickly identified and appropriate management is not initiated.1 While bacterial meningitis requires urgent broad-spectrum intravenous antibiotic treatment and adjunctive corticosteroid therapy to reduce mortality and the likelihood of any long-term neurodevelopmental sequelae, viral meningitis generally has a benign self-limited course and supportive care with antimicrobials omitted are appropriate.2 Although there is this basic clinical difference, the early symptoms of both disease entities can be similar, especially when both are present in infants and young children who are unable to express classic meningeal symptoms, such as photophobia or neck stiffness.3 The epidemiology of pediatric meningitis has changed significantly over the last 20 years, and the main reasons for the change are the wide-spread immunization campaigns against the group of bacteria Streptococcus pneumoniae, Neisseria meningitidis and Haemophilus influenzae type b.4

The continued threat highlights the importance of fast, precise and easy-to-use diagnostic algorithms to distinguish bacterial from viral disease within the first hours of clinical evaluation. Since then, the CSF exam has been the mainstay of meningitis triage. Classically, bacterial infection is associated with elevated CSF WBC count, neutrophilia, increased protein level and decreased glucose ratio (CSF to serum).5 On the other hand, viral meningitis usually shows mild to moderate lymphocytic pleocytosis, normal or slightly elevated protein and normal glucose.6 The parameters, however, overlap

significantly in early bacterial disease, partially treated infection or atypical viral infection like herpes simplex virus or West Nile virus.7

Additionally, neonates and immunocompromised children often have subdued CSF inflammatory responses, which may further complicate interpretation.8 This has led to the wide-spread practice of empirical treatment of children with suspected meningitis with intravenous antibiotic therapy before culture is obtained (which is lifesaving), but this also results in overuse of antibiotics, higher healthcare costs and disruption of the developing microbiome.9 Developed in pediatric populations, the Bacterial Meningitis Score (BMS) includes parameters of blood Gram stain, CSF neutrophil count, peripheral absolute neutrophil count, CSF protein and seizure at presentation or within 24 hours of presentation.10 It has been validated in a few cohorts but has different performance in different geographic areas, vaccination status and viral circulation timing.11

There are several gaps in knowledge. First, most predictive models are based on retrospective data using different laboratory protocols and gold standard definitions.12 The need to overcome these limitations calls for a prospective, standardized, multi-center study to systematically analyze clinical, laboratory and epidemiological criteria, with modern microbiological confirmation as the reference standard.

MATERIALS AND METHODS

The study was a prospective observational cohort study carried out in multiple tertiary pediatric referral centers. The institutions provided services to a wide catchment area including urban, suburban and rural population demographics. The study protocol was approved by the institutional review board (IRB). Study Population Children were included in the study if they were referred to the emergency department or to the inpatient paediatric unit with clinical suspicion of meningitis, and aged between 1 month and 14 years. Clinical suspicion was met by having any two of the following: fever ≥38.0°C, altered mental status, neck stiffness, bulging fontanelle (in infants) and photophobia, or presence of a new onset seizure.

Exclusion criteria were: (1) prior antibiotic use within 72 hours of presentation (unless culture-proven bacterial meningitis subsequently developed), (2) known immunocompromise or immunosuppressive therapy, (3) presence of ventriculoperitoneal shunt or other CNS device, (4) parental refusal of consent, and (5) CSF with >500 RBC/μL with no reversal of that condition. The purpose of data collection and variables. Demographic, clinical, epidemiological and laboratory data was collected by a standardized case report form at the time of enrollment. Clinical variables recorded were age, sex, fever duration, presence of meningeal signs (neck stiffness, Kernig's sign, Brudzinski's sign), altered mental status (Glascow coma scale <14 or age appropriate behavioural changes), seizure activity, presence of a petechial/purpuric rash and focal neurological deficits.

Epidemiological data gathered: season of presentation, attendance at day care or school, recent viral illness within 14 days of presentation, vaccination status (including pneumococcal conjugate vaccine and meningococcal conjugate vaccine [MenACWY] and H. influenzae type b vaccine [Hib]), recent travel history, and prior antibiotic use. Laboratory Investigations All enrolled children had lumbar punctures (LP) unless contraindicated by clinical instability or coagulopathy. CSF samples were analyzed for: cell count with differential, protein concentration, glucose concentration, Gram stain, bacterial culture, and multiplex PCR panel for common bacterial and viral pathogens. Complete blood count with differential, C-reactive protein (CRP), procalcitonin (PCT), blood culture and serum glucose were collected from blood samples. Microbiological confirmation was used as the reference standard for the etiological classification. Bacterial meningitis was considered to have been diagnosed by either of the following: (1) CSF culture showing growth of a bacterial pathogen; (2) CSF multiplex PCR for bacterial pathogen DNA/RNA; or (3) CSF pleocytosis (≥10 WBC/μL). The diagnosis of viral meningitis was made if CSF pleocytosis occurred with negative bacterial cultures and PCR; or if a viral pathogen was detected by CSF multiplex PCR. Multidisciplinary review of cases resulted in a classification of probable viral meningitis for those cases in which no microbiological study had been done but clinical resolution without antibiotic treatment occurred.

Statistical Analysis: A sample size calculation was performed to detect an odds ratio of 2.5 for the primary predictor (CSF WBC>1000/μL) with 80% power and an alpha level of 0.05, if 30% of patients would have bacterial meningitis, and with 10% attrition expected, 380 evaluable patients were required. Continuous variables were described as mean ± SD or median (IQR); categorical variables as frequencies (percentages). Student's t-test, Mann-Whitney U test or Chi-square/Fisher's exact test was used as appropriate for univariate comparisons for the bacterial and viral meningitis groups. Variables that had $p<0.10$ in univariate analysis were added to a multivariable logistic regression model using backward stepwise selection (likelihood ratio criterion). A clinical prediction score was developed by assigning integer weights proportional to regression coefficients, which was simplified. Two tailed $p<0.05$ was used as the criterion for statistical significance.

RESULTS

The median age was 18 months (IQR 6 – 48) for the bacterial group and 24 months (IQR 9 – 60) for the viral group (p=0.032).

Children with bacterial meningitis were significantly younger than those with viral meningitis and were more likely to have fevers that were prolonged, meningeal signs, altered mental status and seizures, and a petechial rash.

Table 1: shows demographic and clinical characteristics for all participants at baseline (n=412).

Variable	Bacterial Meningitis (n=148)	Viral Meningitis (n=264)	p-value
Age, months, median (IQR)	18 (6–48)	24 (9–60)	0.032
Male sex, n (%)	82 (55.4)	138 (52.3)	0.521
Fever duration >3 days, n (%)	98 (66.2)	89 (33.7)	<0.001
Neck stiffness present, n (%)	76 (51.4)	98 (37.1)	0.004
Altered mental status, n (%)	64 (43.2)	51 (19.3)	<0.001
Seizure at presentation, n (%)	41 (27.7)	38 (14.4)	0.001
Petechial/purpuric rash, n (%)	33 (22.3)	12 (4.5)	<0.001
Daycare/school attendance, n (%)	89 (60.1)	178 (67.4)	0.132
Household viral illness (≤14 days), n (%)	28 (18.9)	142 (53.8)	<0.001
PCV vaccination complete, n (%)	112 (75.7)	218 (82.6)	0.089
Prior antibiotics (≤72h), n (%)	31 (20.9)	67 (25.4)	0.312

Statistically significant (p<0.05). IQR: Interquartile range, PCV: pneumococcal conjugate vaccine.

All CSF and inflammatory markers were significantly different between bacterial and viral meningitis with highly significant differences.

Table 2: Cerebrospinal Fluid and Serum Laboratory Parameters by Etiology

Laboratory Parameter	Bacterial (n=148)	Viral (n=264)	p-value
CSF WBC count, cells/µL, median (IQR)	1,240 (485–2,890)	185 (68–412)	<0.001
CSF neutrophils, %, median (IQR)	82 (65–94)	28 (12–54)	<0.001
CSF protein, mg/dL, median (IQR)	142 (98–215)	48 (32–71)	<0.001
CSF glucose, mg/dL, median (IQR)	38 (28–51)	58 (49–68)	<0.001
CSF:Blood glucose ratio, median (IQR)	0.32 (0.24–0.41)	0.68 (0.58–0.79)	<0.001
Serum CRP, mg/L, median (IQR)	86 (42–158)	18 (8–34)	<0.001
Serum procalcitonin, ng/mL, median (IQR)	3.8 (1.2–9.4)	0.3 (0.1–0.7)	<0.001
Peripheral ANC, cells/µL, median (IQR)	12,450 (8,210–18,900)	6,840 (4,120–9,750)	<0.001

Statistically significant (p<0.05). WBC: White blood cell; ANC: absolute neutrophil count; CRP: C-reactive protein.

Table 3. CSF:blood glucose ratio <0.40 and CSF WBC >1000/µL were the best predictors with odds ratio of ~5-fold increased risk. Epidemiological context was still important and highlights the importance of incorporating exposure history into diagnostic algorithms.

Statistically significant (p<0.05). OR: Odds ratio; CI: Confidence interval; WBC: White blood cell.

Table 4: Individual parameters had good discriminatory ability; combined multivariable model had excellent discrimination with an AUC of 0.94.

Table 3: Multivariable Logistic Regression Analysis for Predictors of Bacterial Meningitis

Predictor Variable	Adjusted OR (95% CI)	p-value
Fever duration >3 days	3.21 (1.89–5.45)	<0.001
CSF WBC >1000 cells/µL	4.83 (2.91–8.02)	<0.001
CSF protein >100 mg/dL	3.87 (2.24–6.67)	<0.001
CSF:Blood glucose ratio <0.40	5.14 (2.98–8.86)	<0.001
Absence of household viral illness	2.73 (1.58–4.71)	<0.001
Altered mental status	1.89 (1.04–3.43)	0.036
Petechial/purpuric rash	2.41 (1.18–4.92)	0.016

Table 4: Diagnostic Performance of Individual Predictors and Combined Model

Predictor / Model	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	AUC (95% CI)
CSF WBC >1000/µL	78.4	85.6	76.3	87.1	0.86 (0.82–0.90)
CSF protein >100 mg/dL	72.3	88.2	78.9	84.5	0.84 (0.80–0.88)
CSF:Glucose ratio <0.40	81.1	91.3	85.2	88.9	0.91 (0.88–0.94)
Fever >3 days + rash	64.9	79.5	65.8	78.9	0.76 (0.71–0.81)
Combined model	**89.2**	**92.8**	**88.5**	**93.1**	**0.94 (0.91–0.96)**

Score 0–2: Low risk (<5% probability of bacterial meningitis) Score 4–6: Medium risk (46-65% probability) Score 5: Medium risk (>50% probability)

Table 5: A simplified integer-based scoring system was developed from regression coefficients for ease in application at the bedside.

Table 5: Simplified Clinical Prediction Score for Bacterial MeningitisRisk Stratification

Variable	Points Assigned
CSF:Blood glucose ratio <0.40	3
CSF WBC count >1000 cells/µL	2
CSF protein >100 mg/dL	2
Fever duration >3 days	1
Absence of household viral illness	1
Petechial/purpuric rash	1
Total Score Range	**0–10**

DISCUSSION

In this prospective multicenter study, a strong clinical, laboratory and epidemiological set of determinants were identified and validated that help differentiate bacteria from viral meningitis in children. Our findings support and build on previous studies to show that adding the epidemiological context substantially improves predictive accuracy along with CSF parameters and clinical features.13

The overall model performed very well in terms of discrimination (AUC 0.94), suggesting its prospects for use in emergencies and inpatient settings for rapid triage. Our results are similar and complementary to the current clinical prediction rules. The Bacterial Meningitis Score (BMS) was sensitive and showed some inconsistent specificity in its validation studies 14 and focused on CSF neutrophils, peripheral ANC and CSF protein. WBC >1000/µL and protein >100 mg/dL in CSF held up as strong independent predictors in our cohort, like BMS components. We noted, however, that inclusion of CSF:blood glucose ratio (less than 0.4) in the original BMS greatly enhanced model performance, as has been recently reported, suggesting that glucose dynamics are important discriminatory parameters.15,16

In addition, our use of fever duration >3 days as an independent predictor overcomes a weakness of previous scores, in that prolonged fever has not been widely used in previous scores, although it is biologically plausible in the pathogenesis of bacteria.17 The major contribution of this study was the epidemiological factors having significant predictive value. However, children with recent (≤ 30 days) viral illness in the household were significantly less likely to have bacterial meningitis (adjusted OR 0.37), suggesting that exposure history can be an important factor to alter pretest probability .18

The finding has practical implications: in a community with a high level of viral spread (e.g., during an enterovirus season), a child with meningeal symptoms and possible contacts in the home should be managed with watchful waiting until PCR results are available, while a lack of exposure should increase a suspicion for bacterial etiology. These observations are congruent with recent guidelines that have placed stress on the importance of contextually assessing the risk in pediatric febrile illness.19,20

Our combined model (sensitivity 89.2%, specifically 92.8%) is comparable with previously published rules. The Meningitis Score for Emergencies (MSE) has been validated in 2023 with sensitivity of 92.9% and specificity of 65.2% at the optimal cut-off.21 It may be that our higher specificity is due to the inclusion of epidemiological variables and the use of contemporary multiplex PCR for reference standard classification, which helps to minimise misclassification bias. Importantly, our simplified scoring system (Table 5) preserves high accuracy while at the same time making the system clinically more usable, which is a crucial element to implement in resource variable settings.22 There are a few things to consider, though. First, our study was conducted in tertiary referral hospitals and may not be applicable to community hospitals with different pathogen epidemiology or diagnostic capabilities. Lastly, we must validate our prediction score in independent cohorts, especially in low-resource environments, before its widespread use.

We have simplified our score (Table 5) to be applicable at the bedside without complex calculations, making it more feasible for rapid time sensitive emergency evaluations. Further studies are needed to examine the impact of our prediction model in the clinical setting on clinical outcomes, antibiotic use and costs. In addition, the introduction of new biomarkers, such as CSF interleukin-6, and molecular diagnostics that can be performed at the bedside, such as serum procalcitonin kinetics, could improve predictive accuracy.23 Electronic health record (EHR) data might be used to develop machine learning tools that provide dynamic and personalized risk prediction, which would need to be carefully validated before clinical use.24

CONCLUSION

A combination of prolonged fever, high CSF protein, low CSF to blood glucose ratio, and no recent household viral illness in children with suspected bacterial meningitis is highly predictive of the actual diagnosis of bacterial meningitis. The clinical prediction score is derived from excellent discriminatory performance (AUC 0.94) and developed to be used for clinical bedside use. The incorporation of such validated predictors could help fast-track targeted therapy, decrease overuse of antibiotics and enhance outcomes for pediatric meningitis patients. External validation and implementation studies are warranted to ensure generalizability and impacts in real-world practice in different healthcare settings.

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