# Clinical Features Suggestive of Meningitis in Children: A Systematic Review of Prospective Data


## abstract

**CONTEXT:** Clinical diagnosis of pediatric meningitis is fundamental; therefore, familiarity with evidence underscoring clinical features suggestive of meningitis is important.

**OBJECTIVE:** To seek evidence supporting accuracy of clinical features of pediatric bacterial meningitis.

**METHODS:** A review of Medline, Embase, the Cumulative Index to Nursing and Allied Health Literature, Web of Science, and PubMed was conducted for all articles of relevance. Articles contained prospective data of clinical features in children with laboratory-confirmed bacterial meningitis and in comparison groups of those without it. Two authors independently assessed quality and extracted data to calculate accuracy data of clinical features.

**RESULTS:** Of 14 145 references initially identified, 10 met our inclusion criteria. On history, a report of bulging fontanel (likelihood ratio [LR]: 8.00 [95% confidence interval (CI): 2.4–26]), neck stiffness (7.70 [3.2–19]), seizures (outside febrile-convulsion age range) (4.40 [3.0–6.4]), or reduced feeds (2.00 [1.2–3.4]) raised concern about the presence of meningitis. On examination, jaundice (LR: 5.90 [95% CI: 1.8–19]), being toxic or moribund (5.80 [3.0–11]), meningeal signs (4.50 [2.4–8.3]), neck stiffness (4.00 [2.6–6.3]), bulging fontanel (3.50 [2.0–6.0]), Kernig sign (3.50 [2.1–5.7]), tone up (3.20 [2.2–4.5]), fever of >40°C (2.90 [1.6–5.5]), and Brudzinski sign (2.50 [1.8–3.6]) independently raised the likelihood of meningitis. The absence of meningeal signs (LR: 0.41 [95% CI: 0.30–0.57]) and an abnormal cry (0.30 [0.16–0.57]) independently lowered the likelihood of meningitis. The absence of fever did not rule out meningitis (LR: 0.70 [95% CI: 0.53–0.92]).

**CONCLUSIONS:** Evidence for several useful clinical features that influence the likelihood of pediatric meningitis exists. No isolated clinical feature is diagnostic, and the most accurate diagnostic combination is unclear. *Pediatrics* 2010;126:952–960



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**KEY WORDS**

bacterial meningitis, children, meta-analysis, systematic review, diagnosis, sensitivity, specificity, likelihood ratio, accuracy, physical examination, history, signs, symptoms


**ABBREVIATIONS**

CSF—cerebrospinal fluid
LP—lumbar puncture
QUADAS—Quality Assessment for Diagnostic Accuracy Studies
LR—likelihood ratio
CI—confidence interval


Drs Curtis, Stobart, and Klassen came up with the study concept and design; Drs Curtis and Stobart acquired the data; Dr Curtis, Mr Vandermeer, and Dr Simel analyzed and interpreted the data; Dr Curtis drafted the manuscript; Drs Curtis and Stobart, Mr Vandermeer, and Drs Klassen and Simel critically revised the manuscript for important intellectual content; Drs Curtis and Vandermeer performed statistical analysis; Drs Curtis and Klassen provided administrative, technical, or material support; and Drs Stobart and Klassen supervised the study.

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Meningitis can be difficult to diagnose clinically, particularly in young infants who do not seem to reliably display the classic features of the disease. Cerebrospinal fluid (CSF) analysis through lumbar puncture (LP) is the most important laboratory diagnostic test. However, LP is invasive and painful and can be challenging to perform and anxiety-provoking for caregivers. It has been commonly associated with adverse events such as headache and backache and rarely associated with infection, cerebral herniation, and subdural and spinal epidural hemorrhage.[1] Furthermore, CSF analysis is not readily accessible in many regions of the world. Thus, it may not be desirable or feasible to perform an LP on every child who presents with the nonspecific symptoms that may be attributable to bacterial meningitis but are much more commonly associated with less serious conditions.

Delay in or failure of diagnosis of meningitis is reflected in reviews of medical malpractice in the pediatric setting. Missed meningitis is the most common diagnosis involved in pediatric emergency malpractice claims and has been associated with the highest median indemnity payments and defense payments for pediatricians.[2,3] Malpractice cases that involve children younger than 2 years and cases in which the child died were most often related to the diagnosis of meningitis. Because incidence rates decline with vaccination uptake, the opportunity for recognition of and familiarity with the clinical features of this disease for practicing physicians and trainees is becoming increasingly rare. However, this devastating disease has an ongoing potential to resurface with occasional outbreaks of known or new organisms.

Ideally, primary clinical assessment should provide an estimate of the probability of disease and help to determine if further diagnostic testing is required. Identification and use of those features that raise the pretest probability of disease in contradistinction to those that do not should improve efficiency and accuracy of clinical assessment. To our knowledge, a systematic synthesis of prospective data pertaining to clinical features suggestive of meningitis has not yet been performed despite the importance of this disease in clinical training and practice.

## METHODS

### Literature Search and Selection

Using a structured search strategy, a review of Medline, Embase, Cumulative Index to Nursing and Allied Health Literature (CINAHL), Web of Science, PubMed, and the Cochrane databases was conducted in June 2009, without time limitations, for all articles of relevance. A meningitis, a diagnostic accuracy, and a pediatric string of search terms were used. Included studies had to describe pertinent historical and physical features of children with LP-confirmed bacterial meningitis and prospectively collected data amenable to calculation of accuracy estimates. Similar data from an LP-negative comparison group also had to be present.

### Assessment of Quality

Two authors assessed quality by using the Quality Assessment for Diagnostic Accuracy Studies (QUADAS)[4] checklist and the guidelines for assigning quality levels of evidence.[5] The QUADAS checklist was developed for quality assessment in systematic reviews of diagnostic-test–accuracy studies. It is a 14-item checklist with "yes," "no", or "unclear" options and examines inclusion population, selection criteria, and the descriptions, timing, independence, and blinding of index and reference tests. Studies were also assessed for the execution of the tests, the consistent use of a single good reference standard (LP), availability of results for all patients, and details of CSF analysis.

### Data Extraction

For both signs and symptoms, if the same word was used to describe a clinical finding in multiple studies, it was assumed that the test was similar enough to combine numerically. The decision to combine terms was reached by consensus after consideration of which terms may reasonably be combined without losing their core meaning.

### Data Analysis

The sensitivity, specificity, and likelihood ratios (LRs) with 95% confidence intervals (CIs) were calculated for symptoms and signs. When data were deemed clinically and methodologically similar enough to warrant meta-analysis, Review Manager (RevMan)[6] was used to calculate summary measures using the generic inverse-variance function. Heterogeneity was estimated by using the $I^2$ statistic, which measures the amount of variance attributable to between-study variance as opposed to within-study variance.[7]

## RESULTS

Figure 1 shows the study flow and selection process. One author screened 14 145 titles and abstracts, which resulted in 760 potentially relevant articles; ultimately, 10 articles met our inclusion criteria (Table 1).[8–17] All studies had a quality level of evidence of 1 or 2 (level 1: $n = 4$; level 2: $n = 6$) and scored $\geq$10 on the QUADAS checklist.

CSF analysis was the gold standard for defining the presence of meningitis. The CSF definition of meningitis varied in detail but included a combination of CSF culture positivity or CSF pleocytosis along with either blood culture positivity or CSF latex agglutination posi-

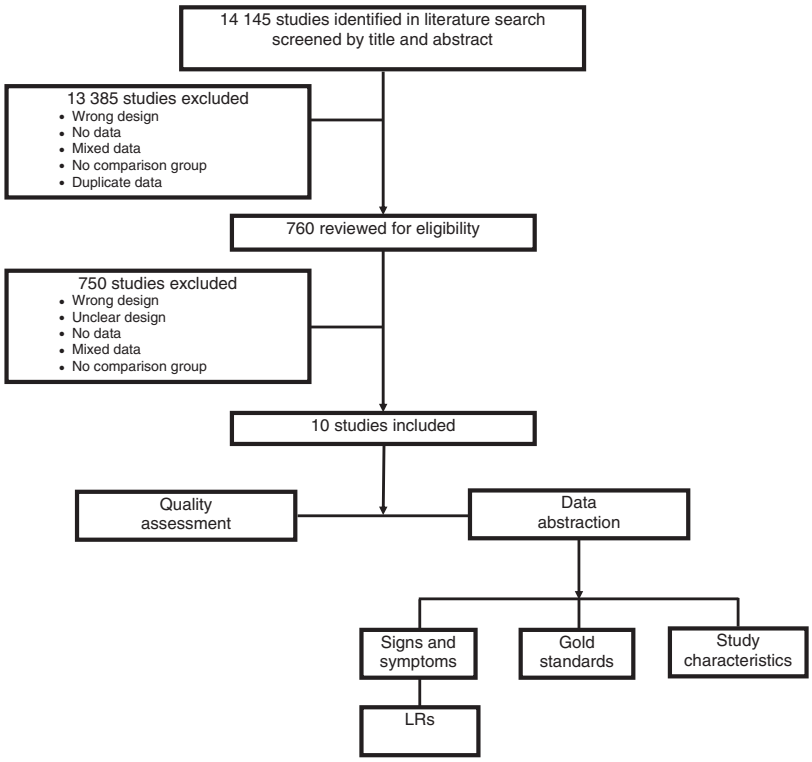


**FIGURE 1**
Study flow diagram.

tivity (Table 2). Normal CSF test results and negative microbiologic study results excluded bacterial meningitis.

Eighteen symptom descriptors and 48 sign descriptors were found and extracted for meta-analysis. Of these descriptors, only 5 symptoms and 21 signs resulted in significant data (Table 3). Nonsignificant findings for both positive and negative LRs are listed in Table 4.

Features were considered to be signs if described by the physician or symptoms if reported on history by caregivers. No studies evaluated the precision of clinical findings, so the focus of the review was on diagnostic accuracy. Only 2 articles reported combinations of findings.[12,17]

## Prevalence of Meningitis

The study (point) prevalence of meningitis varied widely from region to region (Table 1). The high prevalence of meningitis reflects the selected nature of the type of patient studied or seasonal outbreaks of particular pathogens in the various regions of the world. Study inclusion criteria represented 2 categories of children: (1) children with seizure and fever[8,9]; and (2) children with a clinical suspicion of invasive bacterial disease or meningitis.[10–17] Thus, the LRs for the following symptoms and signs should be applied only to these child populations.

## Accuracy of Features of the Clinical History Suggestive of Meningitis

When a caregiver reported that his or her child had a bulging fontanel or neck stiffness, the likelihood of meningitis increased nearly eightfold[10,17] (Table 3). If a child had experienced a seizure but the age of the child was outside that of the typical age range for febrile seizures, the likelihood of meningitis was increased fourfold.[12] A lack of irritability lowered the odds of the disease by half, but the presence of irritability did not strongly signify the presence of meningitis.[17] A child with a history of reduced feeds[12,13,17] had a somewhat increased likelihood of meningitis.

## Accuracy of Features of the Physical Examination Suggestive of Meningitis

### *Seizures*

The presence of complex seizures doubled the risk of meningitis[9–11] (Table 3). When the seizure type was listed as "nonspecific"[13,15] or when multiple seizures[8] were described, the likelihood was weaker. Other seizure descriptors were described in primary studies, but data were not statistically significant (Table 4).

### *Meningeal Signs*

The definition of "meningeal signs" varied (eg, stiffness or rigidity or meningeal irritation or Brudzinski or Kernig sign), and the presence of any 1 of them had a summary LR of 4.50.[8,11,13,16,17] The absence of meningeal signs was more consistent and decreased the likelihood of meningitis. When meningeal signs were defined only as "neck stiffness," the results were more heterogeneous, but the LRs were comparable to the more general term. Only Walsh-Kelly et al[16] evaluated Kernig and Brudzinski signs in isolation. The presence of either sign increased the likelihood of meningitis, whereas the absence of either sign lowered the likelihood.

The presence of a bulging fontanel increased the risk of meningitis in an infant 3.5 times, but when absent, the risk of meningitis decreased only slightly.[12,13,15–17]

### *Mental Status or Appearance*

The descriptors of a "change in mental status,"[9,12,15,17] "restless or irritable or agitated,"[15,17] "lethargic or

**TABLE 1** Studies That Met Inclusion Criteria for Accuracy of Clinical Features Suggestive of Bacterial Meningitis in Children

| Study | Quality Level | Quality QUADAS Score, of 14 | Country | Setting | Tester | Population Study Prevalence, *n* (%)[a] | Age and Age Subgroup | Inclusion Criteria | No. of Index Tests | Description of Index Tests |
|---|---|---|---|---|---|---|---|---|---|---|
| Akpede et al[8] (1992) | 2 | 12 | Benin, Nigeria | Pediatric ED | Unknown | 522 (4.2) | 1 mo to 6 y; subgroups: 1–6 mo, 6 mo to 2 y, 2–6 y | Seizure and fever | 8 | Insufficient description |
| Akpede and Sykes[9] (1993) | 2 | 10 | Benin, Nigeria | Pediatric ED | Unknown | 92 (15) | 6–14 y | Seizure and fever | 9 | Insufficient description |
| Akpede [10] (1995) | 2 | 12 | Maiduguri, Nigeria | Pediatric ED | Unknown | 341 (19) | 1 mo to 15 y | Fever and seizure or "acutely ill" | 15 | Insufficient description |
| Lembo and Marchant[14] (1991) | 2 | 11.5 | Cleveland, OH | ED/acute care clinic of hospital | Managing physician | 160 (6) | 6 mo (median) | Fever and "could have meningitis" | 2 groups of 4 signs and 4 symptoms | Insufficient description |
| Lehmann et al[13] (1999) | 2 | 13 | Goroka, Papua, New Guinea | Base hospital | Pediatrician | 642 (18) | 1 mo to 5 y | Suspected meningitis | 14 | Insufficient description |
| Walsh-Kelly et al[16] (1992) | 1 | 13 | Wisconsin | Pediatric ED | Pediatric emergency physicians | 547 (10) | 1 wk to 17 y (mean: 30 mo); subgroups: 0–6 mo, 7–12 mo, 13–18 mo, >18 mo | All children undergoing LP | 8 | Well-defined index tests |
| Weber et al[17] (2002) | 1 | 13 | Banjul, the Gambia | Pediatric hospital | Attending physicians | 322 (16) | 2–33 mo | Suspected invasive bacterial disease and member of vaccine trial | 26 | Insufficient description |
| Berkley et al[11] (2001) | 1 | 13 | Kilifi, Kenya | District hospital | Research clinician | 906 (5) | 1 mo to 13 y | Admitted children with suspected meningitis | 3 | Insufficient description |
| Berkley et al[12] (2004) | 1 | 13 | Kilifi, Kenya | District hospital | Clinical officers and pediatric residents | 999 (9) | 3–40 mo (median: 22 mo) | All pediatric admissions with any signs of meningitis, impaired consciousness and prostration, and seizures (other than simple febrile) | 30 | Insufficient description |
| Sigaúque et al[15] (2008) | 2 | 12 | Manhica, Mozambique | District hospital | Trained medical officer | 475 (15) | 0–15 y (13% neonatal) | Admitted children with neurologic signs compatible with meningitis | 9 | Insufficient description |

ED indicates emergency department.

[a] *N* population with both LP results and index-test results available.

drowsy,"[9,17] or being "unconscious or comatose"[8–11,13,16,17] had comparably weak summary LRs that ranged from 1.40 to 1.90. A "toxic or moribund" appearance had a high LR of 5.80, the absence of which would halve the risk of meningitis.[16] The presence of an "abnormal cry" increased the likelihood of meningitis, but its absence had a larger impact on likelihood of meningitis (LR: 0.30).[17]

### *Other Miscellaneous Signs*

The presence of a high fever (≥40°C)[9,10] was useful with a summary LR of 2.90, but the LR for temperatures of <40°C (or not otherwise specified) had a CI that included 1.00. It should be noted that the absence of fever did not rule out meningitis.[13,15,17]

Several other signs have each been evaluated in only 1 study, and their LR results require validation. Among 341 patients with a meningitis prevalence of 19%, the only patients with petechiae ($n = 4$) all had meningitis.[10] Similarly, the presence of jaundice was also notable as a sign of meningitis (positive LR of 5.90) but was less useful for ruling out the disease.[17]

"Tone up" had a clinically useful LR of 3.20.[17] The absence of high tone reduced the likelihood of meningitis by half. The feature of having "staring eyes" had an LR of 2.40, the absence of which only decreased the likelihood of disease by one-third.[13] "Can't or won't feed" seemed to be clinically useful with an LR of 2.10, whereas normal feeding reduced the likelihood of meningitis somewhat.[17]

## DISCUSSION

Information on efficient use of clinical findings is extremely important for clinicians. Useful features for estimation of probability of meningitis are those features that demonstrate the strongest LRs for presence or absence of disease. The LR of a clinical feature is

**TABLE 2** LP (Gold Standard) Definitions Used in Each Study

| Study | Bacterial Meningitis | Presumed Bacterial Meningitis | Aseptic | No Meningitis |
|---|---|---|---|---|
| Akpede et al[8] | >5 WBCs per μL CSF and bacterium on CSF Gram-stain and/or CSF culture | No bacterium in CSF; >5 WBCs per μL and protein > 80 mg/dL and glucose < 40% blood glucose in CSF | — | — |
| Akpede and Sykes[9] | >5 WBCs per μL CSF and bacterium on CSF Gram-stain and/or CSF culture | — | — | — |
| Akpede [10] | Cloudy/turbid CSF, >10 WBCs per μL, organism on Gram-stain/CSF culture and blood culture, and CSF/blood glucose < 50% and CSF protein > 0.8 g/L | — | — | — |
| Lembo and Marchant[14] | Bacterium in CSF culture or bacterium-specific Gram-stain antigen detection in CSF | — | CSF pleocytosis > 10 cells per μL and <1000 RBCs per μL, sterile blood and CSF cultures and negative CSF Gram-stain and bacterial antigen tests when no oral antibiotic treatment | — |
| Lehmann et al[13] | Bacterium in CSF culture | CSF culture-negative but bacterium in blood culture or Hib antigen in urine and either CSF glucose < 50 mg/dL or CSF WBCs > 7 μL with 70% polymorphs | — | — |
| Walsh-Kelly et al[16] | CSF latex agglutination-positive or Gram-stain–positive or CSF culture-positive | | CSF WBCs > 10/μL neonate; >5/μL child with negative CSF Gram-stain and/or latex agglutination and normal CSF culture | — |
| Weber et al[17] | CSF culture-positive | CSF culture-negative; antigen detection-positive or WBCs > 5/μL | — | CSF culture-negative, CSF antigen-negative, WBCs < 5/μL |
| Berkley et al[11] | CSF culture-positive or positive latex agglutination test or organism on CSF Gram-stain | CSF WBCs > 5/μL or CSF/blood glucose ratios of ≤0.1 | — | CSF WBCs ≤ 10/μL, glucose CSF/blood ≥ 0.67, CSF protein ≤ 0.45 g/L |
| Berkley et al[12] | Positive CSF culture or positive CSF latex agglutination test or bacteria seen on Gram-stain or a CSF leukocyte count of >50 cells per μL or a CSF/blood glucose ratio of <0.1 | — | — | — |
| Sigaúque et al[15] | Bacterial growth in CSF culture | — | — | — |

WBCs indicates white blood cells; RBCs, red blood cells; Hib, *Haemophilus influenzae* type b.

the probability of that finding in patients with disease divided by the probability of the same feature in patients without disease (LRs range from 0 to infinity). Features with LRs equal to 1.00 have no diagnostic value, because it is equally likely to find the feature in those with the disease as in those without the disease. Features with LRs of >1.00 support the diagnosis of interest in magnitude of increasing numerical value. For features with LRs between 0 and 1.00, the smaller the LR, the less likely the disease.[18,19]

Valuable features found in this review are listed in Table 3. On history, in order of decreasing magnitude, a caregivers' report of neck stiffness, bulging fontanel, seizures (outside the febrile-convulsion range), or reduced feeds raise concern about the presence of meningitis. On physical examination, in order of decreasing magnitude, the presence of jaundice, being toxic or moribund, or having meningeal signs, neck stiffness, bulging fontanel, Kernig sign, tone up, fever of >40°C, or Brudzinski sign all raise the probability of meningitis to varying degrees in the patient. Several other clinical features with LRs between 1.30 and 2.40, are less strong but warrant further study. Note that the sign petechiae is strong with an LR of 37.00 but was surprisingly only examined in a single small prospective study, and only 4 patients displayed the feature. Thus, relevance of this well-known feature is currently uncertain, and systematic prospective evaluations of it among large numbers of patients would provide clarity.

As an example of applicability, assuming statistical independence, a pretest probability of disease of 10%, and using the LR nomogram,[20] a combination of the presence of meningeal signs (LR: 4.50), a bulging fontanel (LR: 3.50), and a high fever (LR: 2.90) (thus, a combined LR of 45.60) raises an infant's

**TABLE 3** Accuracy of Clinical Features

| | No. of Patients | Summary Sensitivity, % | Summary Specificity, % | Summary LR+ (95% CI) | $I^2$, % | Summary LR− (95% CI) | $I^2$, % |
|---|---|---|---|---|---|---|---|
| Symptom | | | | | | | |
| Bulging fontanel[17] | 284 | 14 | 98 | 8.0 (2.40–26.00) | — | 0.88 (0.79–0.98) | — |
| Neck stiffness or bulging fontanelle[10] | 341 | 20 | 98 | 7.7 (3.20–19.00) | — | 0.82 (0.73–0.93) | — |
| History of seizures outside febrile-convulsions age range[12] | 965 | 32 | 93 | 4.4 (3.00–6.40) | — | 0.73 (0.64–0.85) | — |
| Reduced feeds[12,13,17] | 1890 | 52 | 70 | 2.0 (1.20–3.40) | 92 | 0.66 (0.54–0.81) | 54 |
| Irritability[17] | 284 | 82 | 34 | 1.3 (1.10–1.50) | — | 0.52 (0.28–0.97) | — |
| Sign | | | | | | | |
| Petechiae[10] | 341 | 6 | 100 | 37 (2.00–680.00) | — | 0.94 (0.88–0.99) | — |
| Jaundice[17] | 2059 | 6 | 99 | 5.9 (1.80–19.00) | — | 0.95 (0.89–1.00) | — |
| Toxic or moribund[16] | 172 | 49 | 92 | 5.8 (3.00–11.00) | — | 0.56 (0.42–0.73) | — |
| Meningeal signs[8,11,13,16,17a] | 2399 | 64 | 89 | 4.5 (2.40–8.30) | 94 | 0.41 (0.30–0.57) | 69 |
| Neck stiffness[11–13,15–17] | 3118 | 51 | 89 | 4.0 (2.60–6.30) | 90 | 0.56 (0.43–0.72) | 87 |
| Bulging fontanel[12,13,15–17] | 2247 | 36 | 90 | 3.5 (2.00–6.00) | 84 | 0.74 (0.61–0.89) | 82 |
| Kernig sign[16] | 172 | 53 | 85 | 3.5 (2.10–5.70) | — | 0.56 (0.41–0.75) | — |
| Tone up[17] | 284 | 59 | 82 | 3.2 (2.20–4.50) | — | 0.50 (0.36–0.70) | — |
| Fever > 40°C[9,10] | 433 | 19 | 93 | 2.9 (1.60–5.50) | 62 | 0.81 (0.55–1.20) | 66 |
| Brudzinski sign[16] | 172 | 66 | 74 | 2.5 (1.80–3.60) | — | 0.46 (0.31–0.68) | — |
| Staring eyes[13] | 640 | 42 | 82 | 2.4 (1.80–3.20) | — | 0.70 (0.60–0.82) | — |
| Can't or won't feed[17] | 284 | 61 | 70 | 2.1 (1.50–2.80) | — | 0.56 (0.39–0.79) | — |
| Complex seizures[9–11b] | 1400 | 27 | 82 | 2.0 (1.20–3.40) | 84 | 0.86 (0.70–1.10) | 45 |
| Lethargic or drowsy[9,17] | 376 | 40 | 79 | 1.9 (1.30–2.90) | 48 | 0.58 (0.20–1.70) | 67 |
| Unconscious or coma[8–11,13,15–17] | 3313 | 23 | 86 | 1.8 (1.20–2.70) | 69 | 0.94 (0.85–1.10) | 83 |
| Abnormal cry[17] | 284 | 84 | 52 | 1.8 (1.50–2.10) | — | 0.30 (0.16–0.57) | — |
| Restless/irritable/agitated[15,17] | 758 | 37 | 79 | 1.6 (1.20–2.10) | 0 | 0.77 (0.50–1.20) | 81 |
| Multiple seizures[8] | 522 | 64 | 57 | 1.5 (1.10–2.10) | — | 0.62 (0.36–1.30) | — |
| Seizures, nonspecific[13,15] | 1095 | 54 | 63 | 1.4 (1.20–1.70) | 0 | 0.75 (0.48–1.20) | 87 |
| Change in mental status[9,12,15,17c] | 1815 | 72 | 47 | 1.4 (1.20–1.70) | 74 | 0.54 (0.34–0.87) | 71 |
| Fever (°C not otherwise specified)[15–17] | 885 | 76 | 34 | 1.2 (0.98–1.40) | 62 | 0.7 (0.53–0.92) | 66 |

$I^2$ is a measure of heterogeneity.

[a] Stiffness or rigidity or meningeal irritation or Brudzinski or Kernig sign.

[b] Focal or multiple or >15-minute duration or complex.

[c] Lethargic/agitated/impaired consciousness.

probability of meningitis to 84%. Although the presence or absence of these findings, in combination or separately, hardly confirms or refutes a diagnosis of meningitis, they raise the probability high enough that an LP must be performed.

Each physician routinely incorporates a sense of the probability of disease through careful consideration of the clinical assessment, experience, and estimates of disease prevalence in the population. All of the studies included patients with a suspicion of meningitis or severe illness. The point prevalence of meningitis ranged from 4.2% to 19% across these studies; each prevalence reflects the clinical impression of possible meningitis (via initial inclusion in each study). The summary prevalence of these studies is 10%. This summary prevalence could be viewed as the posttest probability of the overall clinical examination, because all of the children were judged sick enough to undergo definite testing for meningitis. Assuming a prevalence of disease of 1%, the LR for the clinical impression of meningitis as its own independent "test" would be 11.00. Thus, the clinical suspicion of disease that a health care provider derives from clinical history and examination may, in itself, be a useful test that warrants follow-through to further diagnostic testing. However, although necessary for rapid comprehensive synthesis of complex clinical information, much is unknown about the process of clinical judgment and decision-making. Clinical impressions are prone to error, and efforts to minimize error by maximizing pretest probability through accurate clinical prediction or decision rules will offer improved patient care.[21–25]

It seems clinically sensible that the combinations of some findings listed in Table 3 would have a greater impact on the probability of meningitis than the individual findings. Only 2 studies examined combinations of findings. It is unfortunate that original subject data from statistical models used in these studies were unavailable; thus, LRs could not be calculated. Nonetheless, Weber et al[17] and Berkley et al[11,12] had constructed logistic regression models of varying combinations of features in an attempt to obtain sets of predictor variables with an optimal balance of sensitivities and specificities. The best combination model in the

**TABLE 4** Unsupported Features of Pediatric Meningitis: Clinical Features From Prospective Studies With Statistically Insignificant Results

| Symptoms (13) | Signs (28) |
|---|---|
| Lethargic or drowsy[10] | Simple seizures[10] |
| Cough[13,17] | Focal seizures[8,9] |
| Cyanosis[12,13] | Fever not otherwise specified[13,15,17] |
| Family history of seizure[9] | Tachypnea[13,17] |
| History of seizures outside febrile-convulsion age range[12] | Chest indrawing[13,17] |
| History of difficulty breathing[17] | Low oxygen[17] |
| History of vomiting[12,17] | Shock[10,16] |
| History of diarrhea[10] | Severe malnutrition[10,15] |
| Fever for <3 d[10] | Dehydration[10] |
| Fever for >3 d[10] | Age 1–6 mo[10] |
| Male gender[10] | Age <2 y[10] |
| Female gender[10] | Age 6–10 y[10] |
| Chest pain[17] | Age 10–14 y[10] |
| | Palpable spleen[15] |
| | Palmar pallor[11,17] |
| | Tachypnea[13,17] |
| | Cyanosis[13] |
| | Crepitations[17] |
| | Delayed capillary refill[12] |
| | Hypothermia[12] |
| | Respiratory distress[13,17] |
| | Palpable temperature gradient[12] |
| | Severe wasting[12] |
| | Malaria parasite on slide[12,17] |
| | Extracranial focal infection[8,9] |
| | Appears sick[17] |
| | Opisthotonos[15] |

These features were examined in 1 or more articles of this review as referenced, but data were statistically insignificant (CIs for LRs crossed 1).

Weber et al study,[17] which combined a history of seizures, being lethargic or unconscious, or having a stiff neck, had a sensitivity of 98% and specificity of 70%.[17] This combination of features is a simplified Integrated Management of Childhood Illness referral criteria, a set of guidelines initially developed by the World Health Organization to identify sick children in need of referral.[17,26]

However, Berkley et al[11] later tested this same model and found it to be only 85% sensitive and 59% specific. Further models from Berkley et al[12] included 1 with a high sensitivity of 97% but low specificity of 44% and combined nonmalarious fever with any 1 of the following: bulging fontanel; neck stiffness; cyanosis; seizures (outside of febrile seizure age range); partial seizures; and impaired consciousness. Another model combined impaired consciousness with any 1 of the following: bulging fontanel; neck stiffness; partial seizure; cyanosis; seizure (outside of febrile-seizure age range); it was found to be less sensitive (79%) but more specific (80%).[12] With a life-threatening highly morbid condition, diagnostic models that maximize sensitivity are essential. However, population overassessment, resulting from application of low-specificity models, is also of concern, particularly for regions in which distance or resource restrictions limit access to further care. Thus, the ideal clinical model for pediatric meningitis is still unclear, and prospective evaluation and validation of known and new prediction models in varying populations are imperative.

Although many of the symptoms and signs with available data demonstrated poor accuracy (Table 4), these findings have not been otherwise studied in combination. In addition, many other widely described features, otherwise reported in textbooks or review articles, have not been examined for validity in prospective studies. These commonly described clinical features warrant further prospective examination to confirm soundness of continued use in the context of meningitis.

When considering the results of this systematic review, clinicians should remain prudent regarding decision-making for young infants and particularly should not rely on the absence of archetypal features as reassurance of absence of disease. Several investigators from the included studies noted infants with meningitis who displayed few or no classic features of the disease. It is well accepted clinically that young infants with nonspecific yet concerning features such as fever, lethargy, poor feeding, or irritability, among others, must be approached with a high index of suspicion regardless of how well they appear, because the incidence of serious bacterial infection in this age group is much higher than that in older infants.

## LIMITATIONS

This review was limited by heterogeneity in study settings, patient age, comorbidities, inclusion criteria, gold standard, and index-test definitions. However, the weight of each of these features on clinical heterogeneity is variable and uncertain. All studies were similar in that they examined unwell children initially encountered as outpatients in hospital emergency departments or hospital acute care clinics. All children had a spectrum of illness that raised the suspicion of meningitis, none were pretreated with antibiotics, and all had LPs performed. Nevertheless, the degree of tolerance for increasing heterogeneity must be balanced with potential diminution of accuracy in overall summary measures. Results of this meta-analysis should be applied with prudent consideration of its limitations and to patient

populations that resemble those of the included studies (Table 1).

Ideally, meta-analyses of clinical features in pediatrics would provide accurate summary reports of the usefulness of clinical features in clinically relevant age groups reflective of changing pediatric physiology. It is unfortunate that this meta-analysis can only provide single summary data for the child (age not defined), because precise age categorization of findings were either absent or dissimilar. This leaves uncertainty, for example, as to when the examination of an older child begins to reflect that of an adult or how the examination of a neonate differs from that of an older infant.

Other notable limitations are the insufficient a priori definitions of the individual clinical findings. When viewed as separate diagnostic "tests" each clinical feature, as in any diagnostic-accuracy study, requires precise definitions to ensure reproducibility and a standardized interpretability. For example, neck stiffness may have varied from slightly stiff or tender for 1 set of researchers to rigid for other researchers. Tone up may mean increased muscle tone or hypertonicity, but it was not specifically defined in the original article. Even fever had variable descriptions, and the finding showed no utility when it was not quantified by actual temperature. For future research, careful attention must be paid to clear definitions and precision ratings of clinical findings to standardize performance of the physical examination and ensure reproducibility.

## CONCLUSIONS

Several useful clinical features that are more likely to be present in children with meningitis compared with those without disease have been identified and are supported, with limitations, by prospectively collected data. Many other described features of meningitis are currently unsupported by available data and warrant further definitive examination. No clinical feature is diagnostic in isolation, and the most accurate combination of clinical features to raise or lower suspicion of meningitis is still unclear.

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Noted by JFL, MD and WVR, MD

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