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Review

Distinguishing community-acquired bacterial and viral meningitis: Microbes and biomarkers

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SUMMARY

Diagnostic tools to differentiate between community-acquired bacterial and viral meningitis are essential to target the potentially lifesaving antibiotic treatment to those at greatest risk and concurrently spare patients with viral meningitis from the disadvantages of antibiotics. In addition, excluding bacterial meningitis and thus decreasing antibiotic consumption would be important to help reduce antimicrobial resistance and healthcare expenses. The available diagnostic laboratory tests for differentiating bacterial and viral meningitis can be divided microbiological pathogen-focussed methods and biomarkers of the host response. Bacterial culture-independent microbiological methods, such as highly multiplexed nucleic acid amplification tests, are rapidly making their way into the clinical practice. At the same time, more conventional host protein biomarkers, such as procalcitonin and C-reactive protein, are supplemented by newer proteomic and transcriptomic signatures. This review aims to summarise the current state and the recent advances in diagnostic methods to differentiate bacterial from viral meningitis.

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Introduction

Bacterial meningitis is a devastating disease with 5–30% case-fatality despite of antimicrobial treatment and considerable risk of long-term sequelae, including hearing loss, developmental delay, and motor deficits.^{1,2} Rapid initiation of antibiotics is recommended to improve post-infection outcomes.^{3–8} Conversely, rapid diagnosis of viral meningitis can help to reduce hospitalisation rates, length of hospital stay, costs, and detrimental effects of unnecessary antibiotics on antimicrobial resistance and for the host microbiome.^{9–14} Early differentiation between bacterial and viral causes of meningitis is therefore crucial.

The incidence of community-acquired bacterial meningitis has declined steadily following introduction of protein-polysaccharide conjugate vaccines against *Haemophilus influenzae* type b (Hib), and serotype/capsular group specific vaccines against *Streptococcus pneumoniae* and *Neisseria meningitidis* in the past few decades.^{15–18}

S. pneumoniae, *N. meningitidis*, or Hib are now the causative agents in only 3.5% of children aged under 5 years with suspected meningitis in the World Health Organisation (WHO) African region.¹⁹ There is still great geographical variation in the incidence of bacterial meningitis, with highest yearly incidences in sub-Saharan Africa and lowest in high-income countries.²⁰ Vaccination programmes have significantly decreased the incidence of mumps meningitis.²¹ On the other hand, emerging use of nucleic acid amplification tests (NAATs) has increased the detection rate of some neurotropic viruses, such as enteroviruses.²² The dramatic reduction in cases of bacterial meningitis has lowered the probability that a fully vaccinated child with clinical features suggestive of meningitis actually has a bacterial cause and thus makes a high level of accuracy essential for a diagnostic test to be useful.

Current guidelines for bacterial meningitis state that the diagnosis of meningitis should be based on CSF analysis.^{5–7} Clinical prediction rules that include simple laboratory parameters from blood and cerebrospinal fluid (CSF) samples are able to reliably exclude bacterial meningitis in some children with a raised CSF white blood cell (WBC) count (CSF pleocytosis).^{23,24} The most widely studied clinical scoring system, the Bacterial Meningitis Score, was designed to exclude a bacterial aetiology in children with suspected

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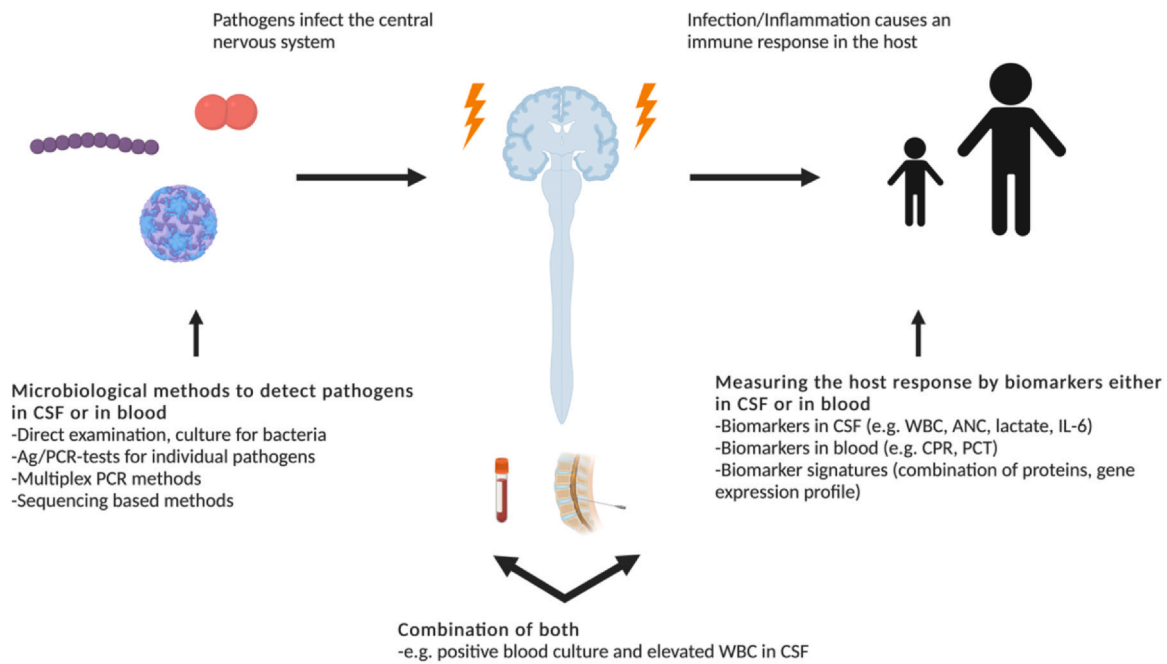


Fig. 1. Diagnostic tests for meningitis.

meningitis. A meta-analysis reported a negative predictive value of 99.6% and a positive predictive value of 28% for the Bacterial Meningitis Score in a pooled cohort of patients with suspected meningitis and a high prevalence (25%) of bacterial meningitis.²⁵ A recent cohort study included adults with bacterial or viral central nervous system (CNS) infection, negative CSF Gram stain, and CSF WBC count $> 10/\text{mm}^3$. In this cohort, a clinical score comprising of routinely collected clinical and CSF parameters (body temperature, serum WBC count, CSF WBC count, CSF granulocyte count, CSF glucose level, CSF protein concentration) was promising in excluding bacterial meningitis.²⁶ However, clinical prediction rules are not validated in children receiving antibiotics before the lumbar puncture (LP), and only a third of children have a timely LP prior to antibiotic treatment.²⁷ Ideally, biomarkers detectable early from blood and/or CSF in patients pre-treated with antibiotics could overcome these issues (Fig. 1). There have been numerous studies to identify improved biomarkers for differentiation of invasive bacterial infections from other causes of fever. Novel diagnostic approaches are based on quantitating one or more mRNA transcripts or proteins simultaneously in a blood sample comprising a signature characteristic for bacterial or viral aetiology.^{28–39}

The WHO driven campaign, 'Defeating bacterial meningitis by 2030', calls for improved diagnostic methods.⁴⁰ Rapid diagnostic tests would expedite aetiological diagnosis, and thus identify patients who will most likely benefit from the early treatment with effective antibiotics. Point-of-care tests operated independently without the immediate support of a central laboratory could be useful also in helping to reach the microbiological diagnosis of meningitis in a greater proportion of patients than before, especially in remote and low-resource settings, and thereby simplify epidemiological surveillance. This review aims to summarise the existing data on the diagnostic tests for distinguishing between community-acquired bacterial and viral meningitis.

Search strategy and selection criteria

We searched PubMed for articles published from August 1980 to September 2023, by use of the terms: 'meningitis' AND 'aseptic' OR 'viral' AND 'bacterial' AND 'diagnostics', and reference lists of identified

studies. Based on authors' assessment, the most relevant papers for this review were cited. Only papers written in English were included.

Current microbiological diagnostic methods

The increasing use of NAATs is changing microbiological diagnostics of meningitis. Conventional methods, such as direct examination with Gram stain and bacterial CSF culture, are still an essential part of the routine diagnostic work-up but are increasingly supplemented by molecular techniques. Highly multiplexed NAATs and sequencing based metagenomic assays enable a sensitive diagnostic approach based on the clinical syndrome that does not rely on detection of a small, restricted number of pre-specified target pathogens. However, the high sensitivity of NAATs might complicate the interpretation of the results. Application of multiplex PCR NAAT diagnostics to blood and respiratory secretions of children with fever found that for most common bacterial and viral pathogens, a positive detection was insufficient to assign aetiology, as positive viral and bacterial results were not restricted to patients judged to have a viral or bacterial cause of illness, and many pathogens were detected at high frequency in healthy controls.⁴¹

Antigen detection tests have a limited role in the current microbiological diagnosis of meningitis. However, a recent meta-analysis suggested that pneumococcal antigen detection tests in CSF could be useful in excluding pneumococcal meningitis.⁴²

Pathogen-specific NAATs

Enteroviruses are the commonest cause of viral meningitis. Detection of enteroviruses from CSF reduces use of additional diagnostic tests, doses of antibiotics administered, and length of hospital stay.^{9–12} Currently, NAATs are the mainstay of enterovirus diagnosis because of their significantly higher clinical sensitivity and shorter turn-around time than viral culture.^{43,44} For children under 2 years of age, enterovirus polymerase chain reaction (PCR) testing from blood has been recommended in addition to CSF testing because of higher diagnostic yield.⁴⁵ Stool PCR improves the detection rate of enteroviruses in adults with culture-negative meningitis, especially if symptoms have lasted longer than 2 days.⁴⁴ PCR is the method of choice also for diagnosing parechovirus infections and

should be performed in the target population of infants 12 months of age and younger with suspected meningitis.⁴⁶ It is important to note that viral loads in CSF are often low, and some commercial assays have insufficient sensitivity to detect the low copy numbers of enteroviruses, including enterovirus D68, and parechoviruses.⁴⁷

For bacteria, it has been shown that use of NAATs, in addition to blood and CSF bacterial culture, can increase the detection rate of the most common pathogenic bacteria.^{48–50} In infants 7–90 days of age with suspected meningitis, PCR for *Streptococcus agalactiae* was positive in the CSF of 22/2495 (0.9%) infants in comparison bacterial culture that was positive in 5/2495 (0.2%).⁵¹ Culture-independent tests also aid detection of *N. meningitidis* in patients treated with antibiotics prior to LP for several days after starting the treatment.^{52,53} Despite the advantages offered by NAATs, their use in the clinical setting is not universal.²⁷

Multiplexed NAATs for infections in the central nervous system

Recently, a novel NAAT to detect the three pathogens (*S. pneumoniae*, *N. meningitidis*, Hib) directly from samples without nucleic acid extraction has been developed, allowing simplified specimen processing.⁵⁴ More comprehensive syndromic tests for CNS infections are being increasingly developed and implemented. These assays are based on nucleic acid amplification and simultaneously detect multiple important bacterial, viral, and fungal pathogens from CSF. The most widely studied assay, the Biofire Filmarray Meningitis/Encephalitis panel, targets 14 pathogens and delivers results in approximately one hour: six bacteria (*Escherichia coli* K1, Hib, *Listeria monocytogenes*, *N. meningitidis*, *S. agalactiae*, *S. pneumoniae*), seven viruses (cytomegalovirus, enteroviruses, herpes simplex virus 1 (HSV-1), herpes simplex virus 2 (HSV-2), human herpesvirus 6 (HHV6), human parechovirus, varicella-zoster virus), and one fungus (*Cryptococcus neoformans/gattii*). Most studies have found the assay to be sensitive and specific compared with bacterial culture and virus PCR.^{55–62} In comparison with culture-based methodologies, an enhanced detection rate of bacterial pathogens has been reported in antibiotic pre-treated patients.^{57,63,64} The assay seems less useful for diagnosing cryptococcal meningitis in settings where CSF cryptococcal antigen tests are in use: in comparison with antigen testing, the sensitivity of the Filmarray Meningitis/Encephalitis panel for *Cryptococcus* has varied between 52% and 84%.^{55,65,66} Several retrospective studies have found that introducing the Filmarray Meningitis/Encephalitis panel in clinical practice has shortened the duration of antiviral treatment against HSV infections.^{67–70} A retrospective study in children >60 days of age showed that implementation of the Filmarray Meningitis/Encephalitis panel doubled the amount of testing for HSV in the CSF, had no impact on the amount of acyclovir initiation, and decreased the duration of the acyclovir treatment from a median of five to two doses.⁷¹ In considering whether the Filmarray Meningitis/Encephalitis panel is suitable for excluding HSV meningoencephalitis as a standalone test, a recent meta-analysis reported pooled sensitivity of 84% for HSV-1% and 93% for HSV-2 in comparison with HSV PCR.⁷²

Occasional false positive and negative results have been reported with the Filmarray Meningitis/Encephalitis panel, an observation which emphasises the need for caution when novel tests are introduced in clinical practice, especially if used without backup methods.^{60,73–76} In addition to false positive results, pathogens can be detected without certainty of clinical relevance, for example HHV6. When CSF from 262 paediatric patients were tested with the Filmarray Meningitis/Encephalitis panel, HHV6 was the second most frequently detected pathogen (in 9/262 (3%) samples), surpassed only by enteroviruses (in 20/262 (8%) samples). In the age group of 1–12 months, 6/55 (11%) CSF samples were HHV6 positive.⁷⁷ Detection of HHV6 in the CSF of young infants does not always require antiviral treatment.⁷⁸ In a study of 1005 children who were tested with Filmarray Meningitis/Encephalitis panel in their CSF samples,

25 (2%) were positive for HHV6, with only 5/25 (20%) receiving a clinical diagnosis of HHV6 meningitis/meningoencephalitis.⁷⁹ In the same study, chromosomally integrated HHV6 was identified in 3/18 (20%) children. Concerns over the interpretation of HHV6 positive CSF samples have been raised in adult patients as well. In a case series of 12 adult patients with CSF sample positive for HHV6 by the Filmarray Meningitis/Encephalitis panel, the majority of the patients had an alternative explanation for their symptoms.⁸⁰

Clinical data describing the diagnostic performance of the Filmarray Meningitis/Encephalitis panel, especially in paediatric patients, are limited. Prospective large-scale studies with adequate numbers of bacterial meningitis cases are needed to allow statistical evaluation of each individual target.⁸¹ In many clinical settings, the low pre-test probability of bacterial meningitis affects the usefulness of diagnostic tests. This is demonstrated by another recent meta-analysis on the Filmarray Meningitis/Encephalitis panel that reported that when the prevalence of bacterial meningitis is 2%, the positive predictive value of a positive bacterial finding in the panel for bacterial meningitis ranges from 42% to 68%, depending on the reference method.⁸²

Novel diagnostic tests should become part of the daily clinical practice when their safety and test parameters have been evaluated and are deemed acceptable, and in addition post-implementation impact should be assessed regarding treatment decisions/outcomes, safety, and cost-effectiveness. In Greece, a randomised controlled trial was performed with 142 children randomised 1:1 for interventional and control arms. The aim was to assess the impact of the Filmarray Meningitis/Encephalitis panel as part of the diagnostic workup of children with suspected CNS infection and CSF pleocytosis (CSF WBC count > 15/mm³).⁸³ The detection rate of pathogens was increased (37/71, 52% versus 16/71, 23%) and length of hospital stay in patients with non-bacterial meningitis (5 versus 8 days), duration of antimicrobial use (4 versus 7 days), and hospitalisation costs (1042€ versus 1552€) were decreased in cases compared with controls.

In addition to Filmarray Meningitis/Encephalitis panel, other syndrome based diagnostic tools for CNS infections or combination of viral and bacterial multiplex assays are available, but not widely validated in different clinical settings.^{84–89} It has been suggested that a multiplex NAAT originally designed for detecting bacteria in positive blood culture could expedite the detection of bacteria in CSF of patients with suspected nosocomial meningitis.⁹⁰

Sequencing based methods to detect pathogens

Nucleic acid sequencing of the bacterial 16S rRNA gene can be used to detect bacterial pathogens directly from CSF, which may be useful especially in patients pre-treated with antibiotics.^{91–94} A meta-analysis reported a sensitivity of 92% and specificity of 94% for detection of bacteria compared with culture. In patients with presumed bacterial meningitis who were CSF culture-negative, 16S rRNA PCR identified a potential cause in 30% of the cases.⁹⁵ However, 16S gene sequencing does not always allow identification of bacteria to the species level, there is still lack of available reference sequence data in gene libraries, and potential contamination of the reagents/samples impair the diagnostic performance of 16S approaches.⁹⁶

Metagenomic approaches to diagnosis rely on sequencing of nucleic acids in a sample and, in context of microbiological diagnostics, removal of the host DNA and RNA reads. Reads from the remaining genomic material are then compared with libraries of known bacterial and viral sequences. Few preliminary studies describe the use of metagenomic sequencing as a diagnostic tool in meningitis patients.^{97–100} A recent study compared the additional information provided by the CSF metagenomic sequencing in comparison with routine clinical testing in children and adults with suspected meningitis and/or encephalitis of unknown origin. In this study, 58 infective agents could be diagnosed in 57/204 (28%)

patients; 13/58 (22%) infections were diagnosed solely by metagenomic sequencing and the findings were thought to have clinical relevance in 8/13 cases. Interpretation of sequencing data is not always straightforward and in this study, treating physicians received support from experts in infectious diseases, microbiology, bioinformatics, and sequencing techniques.¹⁰¹ Sequencing of clinical samples does not need to be slow. A novel rapid metagenomic next generation sequencing method was able to deliver results in only six hours.¹⁰⁰ Novel metagenomic applications focus on detecting microbial cell-free DNA from liquid samples but their clinical utility is not well established yet.^{102,103}

Host-based blood biomarkers

Clinical guidelines do not recommend meningitis diagnosis to be based only on blood test results due to the absence of high quality of evidence to reliably exclude bacterial meningitis.^{5–7} CSF testing enables distinguishing bacterial meningitis from other invasive bacterial infections more accurately, increases specific microbiological diagnosis, and allows antibiotic susceptibility testing for cultured isolates and epidemiological surveillance.

Procalcitonin, C-reactive protein (CRP)

Good availability and short turn-around-time make blood-based, non-specific biomarkers of inflammation, such as procalcitonin or CRP, attractive diagnostic options for supporting the diagnosis of bacterial meningitis in situations where an LP is not possible, for example when it is contraindicated. In small studies, blood procalcitonin has shown potential for distinguishing between bacterial and viral meningitis. A French study enrolled 254 adult meningitis patients with CSF WBC count $> 5/\text{mm}^3$ and negative CSF Gram stain in the emergency department (ED) setting.¹⁰⁴ Patients pre-treated with more than two doses of antibiotics were excluded. A cut-off of 0.28 ng/mL for blood procalcitonin resulted in sensitivity of 95% and specificity of 100% for bacterial meningitis. In two paediatric ED studies, 167 and 50 children with suspected meningitis were recruited.^{105,106} Serum procalcitonin concentration of 0.5 ng/mL was used as the cut-off for bacterial meningitis in both studies and resulted in sensitivities of 89% and 95%, and specificities of 89% and 85%, respectively. Young infants are at risk for invasive bacterial infections including meningitis and sometimes appear without focal signs of CNS involvement. In a recent study of 1821 febrile infants 60 days and younger, a clinical prediction rule including serum procalcitonin level identified patients with low risk for serious bacterial infection (negative predictive value 99.6%) without missing any of the ten infants with bacterial meningitis.¹⁰⁷ Blood CRP performance is inferior to procalcitonin in some studies but may be useful (Table 1).^{108–116} It was proven helpful in differentiating bacterial meningitis ($n = 55$) from viral meningitis ($n = 182$) in children with a negative CSF Gram stain.¹⁰⁹ With the cut-off of 20 mg/L, the measurement had a negative predictive value of 99% for bacterial meningitis.

Blood RNA transcriptome and proteome

Blood transcriptome profiles in the host are increasingly studied to identify gene expression signatures that are specific for either bacterial or viral infections. Recently, an international research consortium reported 100% sensitivity and 96% specificity for distinguishing bacterial (including bacterial-viral co-infections) from viral infections in febrile children by using a two transcript RNA signature of the host.³⁰ Another study on RNA signature profiles in febrile infants 60 days or younger reported 87% sensitivity and 89% specificity for distinguishing between bacterial non-bacterial aetiologies.²⁹ A separate analysis combined transcriptional expression datasets from 8 published studies and used computational machine learning methods to create a 'rule-out' signature of bacterial

infection. The signature was combined with a gene expression signature for viral infection and validated in a prospective cohort of febrile ED patients. The combined signature had sensitivity of 94% and specificity of 93% for bacterial infection and receiver operating characteristic area under the curve of 0.95.¹¹⁷ Before novel tests can be helpful in a larger scale or prove their impact at the point-of-care, useable and affordable platforms must be developed.^{118,119} Gene expression profiling of multiple biomarkers simultaneously holds potential to diagnose a wide range of causes of fever (bacterial, viral, inflammatory) simultaneously in a single multiclass test.¹²⁰

Another approach for the same objective is to combine blood levels of protein biomarkers. Oved et al. screened potential host response biomarkers in blood and developed a combination of three proteins.³² In an external validation study in young children with lower respiratory tract infection or with fever without a source, proteome based host signature discriminated bacterial from viral infection with sensitivity of 87% and specificity of 91%.³¹ At the present time, results from studies focusing specifically on differentiating bacterial and viral meningitis are lacking but studies in both children and adults imminent.^{121,122}

Host-based CSF biomarkers

Elevated CSF WBC count and protein concentration, and decreased CSF glucose all support the diagnosis of bacterial meningitis. In a prospective study in adults with bacterial meningitis at least one of these laboratory findings was present in 88% of the patients.¹²³ In a study of 9111 LPs in neonates, cut off of 21 WBCs/ mm^3 in the CSF had sensitivity of 79% and specificity of 81% for bacterial meningitis.¹²⁴ In a retrospective study in US paediatric EDs among children with CSF pleocytosis (CSF WBC count $\geq 10/\text{mm}^3$) not requiring immediate admission and not pre-treated with antibiotics, only 121/3295 (3.7%) children had bacterial meningitis.²³ In the current post-vaccine era, conventional CSF tests are not sufficient as the only rationale for clinical decision making.

Defensin and lactoferrin, lactate dehydrogenase (LDH), lactate, soluble triggering receptor expressed on myeloid cells-1 (sTREM-1)

Antimicrobial peptides such as defensin and lactoferrin, enzymes including LDH, and metabolic products including lactate have all been studied. Defensin and lactoferrin are secreted mainly by neutrophils, and are elevated in blood and in CSF during the inflammatory response to bacterial infection.^{125,126} As a catalyst of lactate metabolism, LDH is elevated in various CNS pathologies including bacterial meningitis.¹²⁷ CSF lactate concentration is considered to increase as a result of anaerobic metabolic conditions induced by bacterial meningitis. For defensin, lactoferrin, and LDH there are only few reports and no well-designed clinical studies on their diagnostic performance.^{127–130} In contrast to CSF glucose concentration that is proportional to blood glucose concentration, CSF lactate concentration seems not to be a direct consequence of the blood lactate concentration.^{131,132} Results from the earlier studies on the diagnostic utility of CSF lactate concentration in meningitis are controversial (Table 1).^{133–138} Pretreatment with antibiotics complicates the interpretation of CSF lactate results in the diagnosis of meningitis: 2 meta-analyses and one more recent adult study reported sensitivities of 94–96% for CSF lactate for differentiating bacterial from culture-negative meningitis in non-pretreated patients.^{104,139,140} However, in studies that did not exclude antibiotic pretreated patients, the sensitivity of CSF lactate to detect bacterial meningitis was only 49%.¹³⁹ The optimal cut off value for CSF lactate concentration derived from the meta-analysis was 3.5 mg/L or 3.9 mmol/L.¹³⁹ CSF lactate is not a perfect biomarker for differentiation between bacterial and viral meningitis: it requires CSF sampling and cannot give the exact microbiological diagnosis. However, it is readily available, relatively inexpensive, and performs

Table 1
Main biomarkers to distinguish bacterial meningitis from other aetiologies.

	Study setting and population	Pretreatment with antibiotics	Number of bacterial and viral meningitis cases, n (%)	Main results (cut-off, sensitivity, specificity for bacterial meningitis)
<i>Blood PCT</i>				
<i>Children</i>				
Kuppermann et al. ¹⁰⁷ (n = 1821, of whom LP in n = 1399)	Prospective study in infants < 60 days evaluated for serious bacterial infection	Excluded if pretreatment with antibiotics in < 48 hours	Bacterial meningitis: n = 10 (0.7%) Viral: not reported	Cut-off 1.71 ng/mL (as part of a clinical prediction rule) Sensitivity 100%
Dubos et al. ¹⁰⁵ (n = 167)	Retrospective study in children hospitalised with meningitis	Excluded if pretreatment with antibiotics in < 48 hours	Bacterial: n = 21 (12.6%) Viral: n = 146 (87.4%)	Cut-off 0.5 ng/mL Sensitivity 89% Specificity 89%
<i>Adults</i>				
Viallon et al. ¹⁰⁴ (n = 254)	Prospective study in adults at the ED with meningitis and negative direct CSF examination	Patients with > 2 preceding doses of antibiotics were excluded	Bacterial: n = 35 (13.8%) Viral: n = 181 (71.3%)	Cut-off 0.28 ng/mL Sensitivity 95% Specificity 100%
<i>Blood CRP</i>				
<i>Children</i>				
Sormunen et al. ¹⁰⁹ (n = 237)	Prospective study in children with bacterial meningitis and negative direct CSF examination. Retrospective cohort of children with viral meningitis	Excluded if pretreatment with antibiotics	Bacterial: n = 55 (23.2%) Viral: n = 182 (76.8%)	Cut-off 20 mg/L Sensitivity 96% Specificity 93%
Roine et al. ¹¹⁰ (n = 83)	Retrospective study in children with meningitis	Not reported	Bacterial: n = 67 (80.7%) Viral: n = 16 (19.3%)	Cut-off 20 mg/L Sensitivity 96% Specificity 88%.
<i>Children and adults</i>				
Hansson et al. ¹¹³ (n = 235)	Retrospective study in both children and adults with suspected CNS infection	8/60 (13.3%) of the patients categorised as bacterial meningitis (culture-negative) pretreated with antibiotics	Bacterial: n = 60 (25.5%) Viral: n = 146 (62.1%)	Cut-off 50 mg/L Sensitivity 88%
<i>CSF lactate</i>				
<i>Children</i>				
Ruuskanen et al. ¹³⁵ (n = 447, of whom n = 104 with meningitis)	Retrospective study in children with CSF lactate results available	Not reported	Bacterial: n = 32 (7.2%) Culture-negative meningitis: n = 72 (16.1%)	Cut-off 3.0 mmol/L Sensitivity 94% Specificity 92%
Rutledge et al. ¹³⁸ (n = 185, of whom n = 116 with meningitis)	Retrospective study in children with CSF available for lactate measurement	Pretreatment with antibiotics in 8/29 (27.6%) of those with bacterial meningitis	Bacterial: n = 29 (15.7%) Culture-negative meningitis: n = 87 (47.0%)	Cut-off 3.0 mmol/L Sensitivity 93% Specificity 84%
<i>Adults</i>				
Viallon et al. ¹⁰⁴ (n = 254)	Prospective study in adults at the ED with meningitis and negative direct CSF examination	Patients with > 2 preceding doses of antibiotics were excluded	Bacterial: n = 35 (13.8%) Viral: n = 181 (71.3%)	Cut-off 3.8 mmol/L Sensitivity 94% Specificity 97%
<i>CSF IL-6</i>				
<i>Children</i>				
Srinivasan et al. ¹⁵⁰ (n = 684)	Prospective study in infants younger than 180 days receiving LP	Pretreatment with antibiotics in 522/684 (76.3%)	Bacterial: n = 11 (1.6%) Viral: n = 3 (0.4%)	Cut-off 790 pg/mL Sensitivity 82% Specificity 99%
<i>Adults</i>				
Takahashi et al. ¹⁵¹ (n = 70)	Retrospective study in critically ill adults admitted in the ICU with suspected bacterial meningitis	Not reported	Bacterial: n = 13 (18.6%) Viral: n = 6 (8.6%)	Cut-off 644 pg/mL Sensitivity 92% Specificity 90%

PCT = procalcitonin; LP = lumbar puncture; ED = emergency department; CSF = cerebrospinal fluid; CNS = central nervous system; ICU = intensive care unit.

moderately well, with the prerequisite of usage only in patients without prior antibiotic treatment (Fig. 2).

The expression of sTREM-1 is upregulated in phagocytes following exposure to microbial products. In addition to other bacterial infections, sTREM-1 concentration in CSF has been studied as a biomarker for bacterial meningitis.^{141,142} In a retrospective study with 92 adults with community-acquired meningitis a cut-off level of 20 pg/mL had the sensitivity of 73% and specificity of 77% for bacterial meningitis. It was also noted that among patient with bacterial meningitis, higher levels of sTREM-1 were associated with higher mortality.¹⁴¹

Procalcitonin in CSF

Measuring the procalcitonin level in the CSF has not been shown to offer an advantage over serum measurement. The superiority of serum procalcitonin over CSF procalcitonin as a biomarker for

bacterial meningitis was shown in a study with adults with either bacterial meningitis or tick-borne encephalitis.¹⁴³ A threshold of 0.5 µg/L for serum and CSF procalcitonin concentrations had sensitivities of 90% and 55% and specificities of 100% for bacterial meningitis, respectively. In a prospective study in 120 adults in the ED with suspected meningitis without antibiotic pre-treatment, a CSF procalcitonin cut-off of 0.74 µg/L had sensitivity of 69% and specificity of 100%, and a serum procalcitonin cut-off of 0.88 µg/L had sensitivity of 87% and specificity of 100% for detecting bacterial meningitis.¹⁴⁴ A systematic review and meta-analysis included 2058 study subjects in 22 different studies and reported overall sensitivities and specificities of 86% and 80% for CSF procalcitonin and 97% and 95% for blood procalcitonin for diagnosing bacterial meningitis, respectively.¹⁴⁵ A more recent report from a neurological tertiary unit reported better discriminatory value for procalcitonin in CSF than in blood between adult patients with bacterial meningitis in

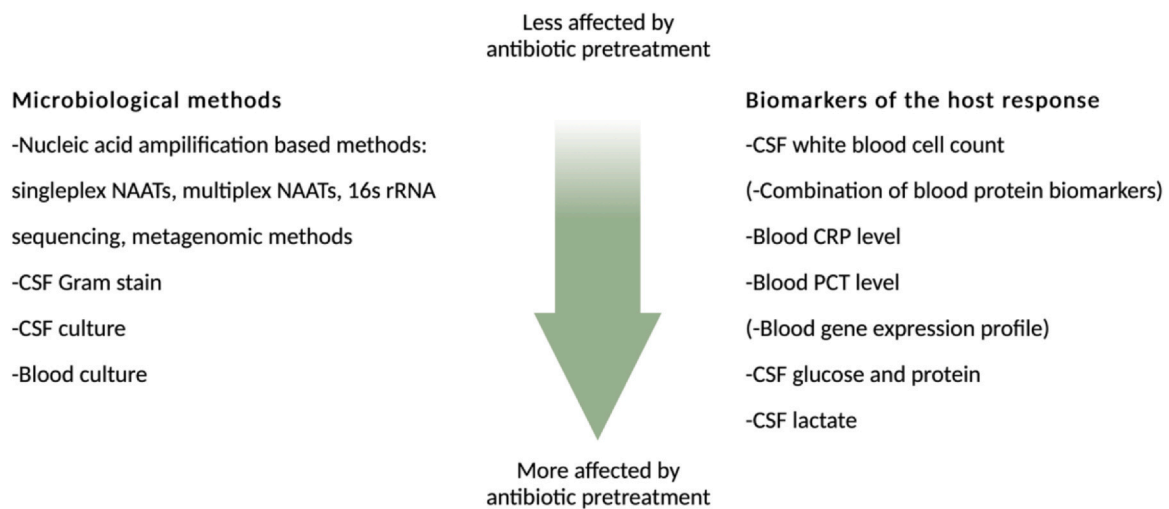


Fig. 2. An approximation of the effect of antibiotic pretreatment on the capability of diagnostic tests to detect bacterial meningitis.

comparison with tuberculous meningitis, viral meningitis, auto-immune meningitis/encephalitis, or non-inflammatory conditions. It is of note that 89% of the patients, including all the patients in the bacterial meningitis group, had received pre-treatment with antibiotics for a median of 8 days. The results suggest that in patients with bacterial meningitis pre-treated with antibiotics, procalcitonin concentration in CSF might normalise later than in blood.¹⁴⁶ CSF procalcitonin has also been suggested to be useful in differential diagnosis of neonates with suspected meningitis and traumatic LP¹⁴⁷ and in the diagnosis of post-neurosurgical bacterial meningitis.¹⁴⁸ In a prospective study with 50 children with suspected meningitis and CSF pleocytosis, CSF or serum procalcitonin levels were not found to be useful in differentiating bacterial and viral meningitis.¹⁴⁹ In an ED setting, CSF procalcitonin seems to be of limited diagnostic value.

CSF cytokines

Other biomarkers in the CSF have also been investigated to differentiate bacterial and non-bacterial meningitis. A study of 684 infants < 6 months of age who had an LP investigated the diagnostic accuracy of six different cytokines to predict culture positive bacterial meningitis.¹⁵⁰ Definite bacterial meningitis was diagnosed in 11/684 (2%) infants of whom 9/11 (82%) were antibiotic pre-treated. A pro-inflammatory cytokine interleukin 6 (IL-6) and an anti-inflammatory cytokine IL-10 had the best discriminatory power between culture-proven and antibiotic non-pretreated, culture-negative cases. Elevated levels of IL-6 in the CSF have been associated with bacterial meningitis in other studies (Table 1).¹⁵¹⁻¹⁵³ Additionally, several biomarkers in the CSF have been investigated to assist in the diagnosis of Lyme neuroborreliosis.^{154,155} The most promising and widely studied is C-X-C Motif Chemokine Ligand 13 (CXCL13). An elevated level of CXCL13 in the CSF is closely related to intrathecal production of *Borrelia burgdorferi* antibodies and is therefore helpful for diagnosing neuroborreliosis.^{154,156-160} Also neurosyphilis can cause elevation of CXCL13 level in the CSF.¹⁶¹

Future perspectives

Microbiological aetiology remains unclear in approximately half of the patients with a clinical diagnosis of meningitis. Some reports have suggested that additional methods could facilitate more rapid identification of causative bacteria including direct CSF examination by matrix-assisted laser desorption/ionisation time-of-flight mass spectrometry in smear positive patients or by microarrays that target multiple pathogens simultaneously.^{162,163} In terms of treatment decisions, the exact microbiological aetiology might not always be required immediately and

host-based biomarker results could point out the right direction. It can be hypothesised that a combination of the two above mentioned approaches, the host-based and the molecular microbiology based, could overcome the major diagnostic obstacles, e.g. decreased sensitivity of host-based biomarkers very early in the disease and the low diagnostic yield of microbiological assays in antibiotic pretreated patients. There is no perfect diagnostic test with 100% sensitivity and specificity. As more tests enter use that have multiple parallel host or pathogen targets, then interpretation of the results will require careful consideration of the pre-test probabilities, potentially through integration of clinical data with test results, in order to avoid over-calling of false-positive results.

As stated in WHO 'Defeating bacterial meningitis by 2030' campaign, rapid molecular microbiology assays hold promise of identifying pathogens in emerging outbreaks early. In this respect, it is reassuring that the most widely used NAAT assay, the Filmarray Meningitis/Encephalitis panel, was successfully implemented for diagnostic use in an Ethiopian centre without previous experience of molecular microbiological assays¹⁶⁴ and could improve the detection rate of pathogenic bacteria and viruses in children with suspected meningitis as demonstrated by a retrospective study from Nigeria.¹⁶⁵ The costs of rapid molecular assays still restrict their use but increasing competition in the market, and the emergence of platforms based on new technologies, could improve the price trajectory and thus enable wider adoption.

Limitations

Bacterial meningitis can co-exist with bacteraemia or other forms of invasive bacterial infection. For completeness of the data, we have included some studies in this review that did not focus solely on meningitis. Also, the definition of meningitis that was used in different studies was highly variable reflecting real world differences of managing patients with suspected meningitis. The clinical utility of diagnostic tests depends on their sensitivity, specificity, and the pretest probability of the target condition. Screening tests typically require a high sensitivity, whilst targeted diagnostics require high specificity. For conditions that are rare, or for populations with a low pretest probability, the development and introduction of tests requires careful consideration of the population that is suitable for testing, to avoid unacceptably high rates of false positive tests. With discovery pipelines delivering potential biomarkers for a wide range of sometimes rare conditions, there is a need for new strategies, for instance using artificial intelligence approaches, that can define and identify the subset of patients with a higher pre-test probability based on their clinical characteristics - ie those patients suitable for testing in clinical use.

Conclusions

In addition to clinical scores and conventional laboratory parameters, there is moderate quality of evidence for additional tests in differentiating bacterial and viral meningitis. Based on our literature review, blood procalcitonin concentration, blood CRP concentration, and CSF lactate concentration might be useful in selected clinical settings. Host transcriptomic and proteomic approaches will soon be part of the routine diagnostic methods in the search for different infection aetiologies. NAAT based microbiological tests are under-used despite their advantages in clinical care. Rapid diagnostic multiplex tests have great potential, and their use will likely increase. Clinical use of metagenomic methods in CNS infections has just started but it offers a powerful diagnostic tool especially for the most complex cases.

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Declaration of Competing Interest

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MS and LI conceptualised the manuscript. LI did the literature search and analysis with support from MS and JH. LI wrote the first draft of the manuscript. All authors contributed equally to critical revision of the manuscript and approved the final version.

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