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Bacterial Meningitis: An Overview of Immunologic and Biochemical Markers for Diagnosis.

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Abstract:

Background: Bacterial meningitis is a severe central nervous system (CNS) infection with high mortality and morbidity rates, especially in low-resource settings. Clinical symptoms often overlap with other illnesses, necessitating precise diagnostic methods.

Aim: This study reviews immunologic and biochemical markers for the early and accurate diagnosis of bacterial meningitis, with a focus on differentiating it from viral meningitis.

Methods: A comprehensive analysis of diagnostic assays, including cerebrospinal fluid (CSF) examination, Gram staining, and molecular methods like polymerase chain reaction (PCR) and next-generation sequencing (NGS), was conducted. Biomarkers such as protein, glucose, lactate, and bacterial antigens were also evaluated for their sensitivity and specificity in meningitis diagnosis.

Results: Bacterial meningitis is characterized by elevated CSF white blood cell counts, increased protein levels, decreased glucose ratios, and high lactate concentrations. Gram staining shows variable sensitivity (25%-97%), while bacterial culture remains the diagnostic gold standard despite limitations in low-resource settings and post-antibiotic administration. Molecular techniques, including PCR and NGS, significantly enhance sensitivity and specificity, with PCR showing near-perfect accuracy for targeted pathogens. Emerging biomarkers like CSF lactate demonstrated 93% sensitivity and 99% specificity at a cutoff of ≥35 mg/dL.

Conclusion: Early diagnosis of bacterial meningitis is critical for initiating effective treatment and reducing complications. Immunologic and biochemical markers, combined with advanced molecular diagnostics, show promise for overcoming limitations in traditional methods. Integrating these approaches can improve patient outcomes, particularly in resource-constrained settings.

Keywords: Bacterial meningitis, cerebrospinal fluid, biomarkers, polymerase chain reaction, next-generation sequencing, diagnosis.

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Introduction:

The term "meningitis" describes inflammation of the meninges, which is mostly brought on by bacterial, viral, or fungal infections [1]. Meningitis incidence and prevalence vary greatly over time and between geographic locations [2]. A comprehensive study of bacterial meningitis in low-, middle-, and high-income areas found that death rates varied from 5% to 30%, with differences in healthcare access, medical infrastructure, and resource availability playing a major role [3], [4]. *Streptococcus pneumoniae, Neisseria meningitidis (meningococcus), Haemophilus influenzae, Streptococcus agalactiae (Group B Streptococcus), Escherichia coli, and Listeria monocytogenes* are the most common bacterial infections linked to meningitis [5].

N. meningitidis and S. pneumoniae were shown to be the most frequent causal agents in a meta-analysis of 61 papers published between 2012 and 2017 that looked at the incidence of bacterial meningitis in various age groups and geographical areas. Depending on the region and age group, the weighted frequency means for these infections varied from 3.2% to 47.0% and 9.6% to 75.2%, respectively [6]. Despite the fact that the blood-brain barrier (BBB) protects the central nervous system (CNS), several organisms that cause meningitis have been shown to be able to pass across the BBB, which can lead to colonization and inflammation of the CNS [7]. Fever, stiff neck, headache, anorexia, vomiting, exhaustion, lightheadedness, seizures, purpuric rash, photophobia, and behavioral abnormalities are the classic signs of meningitis [8], [9]. Neurological consequences, including developmental delays, hearing impairment, and neuropsychological abnormalities, might affect as many as 50% of survivors [10]. In order to reduce mortality and morbidity, prompt diagnosis and treatment are essential [11]. Long-term disabilities, including as organ damage, vision impairments, seizures, brain damage, and hearing loss, may also be experienced by survivors [5, 12].

Because meningitis can overlap with other disorders, clinical presentation alone is not enough to diagnose it; therefore, cerebrospinal fluid (CSF) investigation is essential. Despite its drawbacks, such as low sensitivity and a minimum two-day turnaround time, CSF culture is still the gold standard for diagnosis [13], [14], and [15]. Inadequate laboratory facilities and previous antibiotic use, which can lead to false negatives, further undermine the effectiveness of culture-based approaches in low-resource settings [16]. Therefore, lowering mortality requires starting antimicrobial treatment as soon as bacterial meningitis is suspected, ideally after acquiring blood and CSF samples for culture [17]. False-negative CSF culture results may result in inappropriate treatment of aseptic meningitis or delayed or inadequate antibiotic delivery for bacterial meningitis [18]. On the other hand, viral meningitis seldom causes serious problems and usually resolves on its own. With a usually good prognosis, management concentrates on symptom relief [19]. However, extended hospital stays and unnecessary use of antibiotics in viral cases might lead to hazardous side effects, microbial resistance, or allergic reactions, as well as increase healthcare expenses [20], [21]. Early and adequate antibiotic medication is essential for the effective management of bacterial meningitis, since it minimizes the severity of the disease and greatly increases survival rates [5, 22, 23]. It is still very difficult to distinguish between bacterial and viral meningitis, which emphasizes the need for diagnostics with high sensitivity and specificity [24]. By using microscopy, biochemical analysis, and culture, CSF—which is collected through lumbar puncture—allows for etiological identification. Nevertheless, current biomarkers are unable to accurately differentiate bacterial from viral meningitis in isolation, and early-stage culture data may be unavailable or inconclusive [25].

The importance of immunologic biomarkers for early diagnosis and distinction of meningitis etiology has been highlighted by advancements in diagnostic procedures. These indicators exhibit potential for laboratory diagnoses and are enhanced during bacterial infections [26]. However, a number of factors, including the origin of the infection, inclusion criteria, patient characteristics, detection techniques, and specimen collection time, affect their sensitivity and specificity [27]. The potential of several immunologic indicators to reliably detect bacterial meningitis and distinguish it from viral infections is investigated in this work. It can be difficult to accurately diagnose and differentiate between different kinds of meningitis based solely on clinical symptoms, especially in juvenile populations where presentations are frequently vague. In order to confirm meningitis diagnoses, laboratory examination of CSF is essential [28]. As listed below, several diagnostic assays using biosensors and indicators exhibit varying diagnostic efficiency.

Diagnostic Assays for Meningitis Etiology

Normal cerebrospinal fluid (CSF) contains 0–5 white blood cells (WBCs) per microliter, predominantly lymphocytes, with protein levels between 0.15 and 0.45 g/L, a CSF-to-serum glucose ratio of 0.6, and negative culture results. In bacterial meningitis, WBC counts often exceed 103 per microliter, predominantly neutrophils, with protein levels ≥1.0 g/L, a CSF-to-serum glucose ratio ≤0.5, and positive culture results. Viral meningitis typically presents with WBC counts below 103 per microliter, primarily lymphocytes (which may shift to neutrophilic dominance within the first 48 hours), protein levels below 1.0 g/L (though levels ≥1.0 g/L may occur in cases caused by *Herpes simplex virus* or *Varicella zoster virus*), and a CSF-to-serum glucose ratio of 0.6, with negative culture results. Tuberculous meningitis (TB meningitis) is characterized by WBC counts between 102 and 5 × 102 per microliter, predominantly lymphocytes, protein levels ≥1.0 g/L, a CSF-to-serum glucose ratio ≤0.5, and negative culture results, as Mycobacterium tuberculosis requires specialized media and prolonged incubation times for growth. Emerging diagnostic approaches aim to overcome the limitations of traditional methods by leveraging novel biomarkers and advanced detection techniques, particularly in resource-constrained settings.

Gram Smear

Gram staining of cerebrospinal fluid (CSF) specimens is a routine procedure once the specimen reaches the laboratory. This technique serves as an initial microbiological diagnostic tool that allows targeted empirical therapy to commence, especially if bacteria are detected. The sensitivity of Gram staining is significantly influenced by the bacterial concentration in the sample, with detection rates ranging from 25% to 97%. Positive results are more likely in cases of meningitis caused by *Streptococcus pneumoniae* compared to infections caused by *Neisseria meningitidis* or *Listeria monocytogenes*. However, prior administration of antimicrobial agents before CSF collection significantly decreases the likelihood of a positive Gram smear result [28], [29].

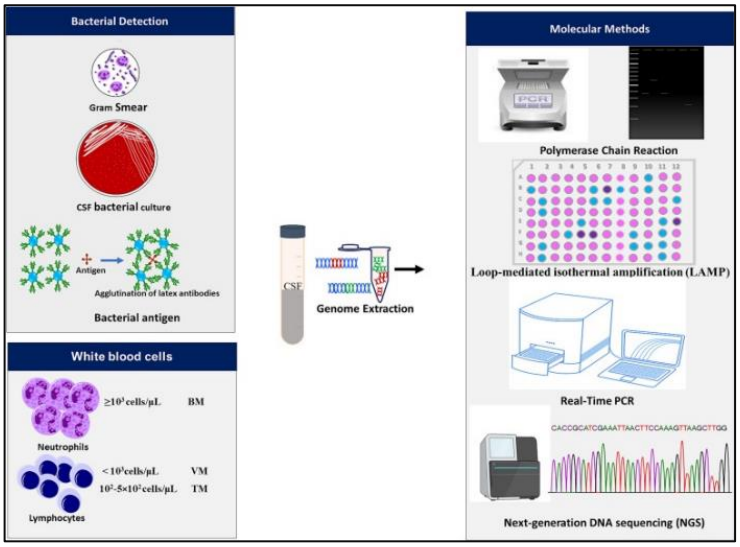

Figure 1: Meningitis Detection Techniques.

CSF Protein

The concentration of CSF protein is typically elevated in meningitis caused by both bacterial and viral infections due to an increase in blood-brain barrier (BBB) permeability as a response to inflammation. Protein levels are notably higher in bacterial meningitis compared to viral meningitis (≥1 g/L vs. <1 g/L). However, in cases of viral meningitis caused by herpes simplex virus (HSV) or varicella-zoster virus (VZV), protein levels may reach values comparable to those observed in bacterial meningitis (≥1 g/L) [28], [30].

CSF Glucose

CSF glucose levels generally decrease in bacterial meningitis but remain within normal ranges in viral meningitis. In contrast, elevated levels may occur in cases of cryptococcal or tuberculosis meningitis. The CSF glucose concentration correlates with blood glucose levels, maintaining a normal CSF-to-blood glucose ratio of approximately 0.6. A ratio of ≤0.5 has demonstrated a sensitivity of 100% and a specificity of 57% for diagnosing bacterial meningitis. Notably, this ratio remains unchanged following antimicrobial therapy. However, in hyperglycemic patients, the diagnostic utility of this ratio may be limited [28], [31].

Lactate Levels

CSF lactate levels can serve as a valuable biomarker for distinguishing bacterial meningitis from non-bacterial cases. A cutoff level of ≥35 mg/dL (3.9 mmol/L) has shown sensitivity and specificity of 93% and 99%, respectively, for bacterial meningitis. Unlike serum lactate, CSF lactate is not directly proportional to systemic levels. Elevated CSF lactate can also occur in other central nervous system (CNS) conditions such as viral encephalitis or seizures, limiting its specificity to bacterial infections [28], [32].

CSF Bacterial Culture

CSF bacterial culture is considered the gold standard for diagnosing meningitis, with a sensitivity ranging from 60% to 90% in patients who have not received antibiotics. However, the sensitivity significantly decreases following antimicrobial therapy. Concurrent blood cultures are recommended for all patients with suspected bacterial meningitis, as they may yield bacterial growth even when Gram smears and CSF cultures are negative [28], [29].

Bacterial Antigen

Bacterial antigen testing is commonly utilized for detecting *Streptococcus pneumoniae* in CSF, with sensitivity ranging from 67% to 100% and specificity reaching 95%. Pneumococcal antigen testing is particularly advantageous as it can be completed within minutes of the sample's arrival at the microbiology laboratory, offering a faster alternative to other detection methods [28], [29].

Molecular Methods

Molecular diagnostic methods address many limitations associated with traditional bacterial culture techniques by targeting specific genes and bypassing the need for viable pathogens. Among these methods, polymerase chain reaction (PCR) and its variants—real-time PCR (RT-PCR), qualitative PCR (qPCR), and quantitative PCR—are widely used for meningitis diagnosis. PCR was the first molecular technique introduced for detecting single pathogens. Advanced PCR-based assays allow the detection of multiple microorganisms in a single test using minimal clinical specimens, reducing time and costs. Additionally, certain PCR methods are designed to identify bacterial capsular antigens, aiding in burden estimation and vaccination planning.

Loop-mediated isothermal amplification (LAMP) is another molecular technique that amplifies specific DNA sequences without requiring thermocyclers. The DNA polymerase used in LAMP functions at a constant temperature, enabling the process to be conducted in a water bath. LAMP exhibits high specificity and minimal interference from background DNA. The sensitivity and specificity of molecular methods depend on the targeted genes and sample type. For PCR-based assays, CSF samples demonstrate higher sensitivity and specificity compared to blood or oropharyngeal specimens. Despite their advantages, molecular methods are cost-intensive, requiring specialized equipment, reagents, and expertise. Next-

generation sequencing (NGS) has gained traction in clinical microbiology, offering advanced diagnostic capabilities. Selective whole-genome amplification (SWGA), an isothermal amplification technique, has been used to analyze DNA molecular profiles and vaccine antigens for *Neisseria meningitidis* in specimens with low bacterial loads. NGS has enhanced the diagnosis of CNS infections, providing actionable data in several cases. When compared to bacterial culture, the sensitivity and specificity of metagenomic NGS for detecting *S. pneumoniae* meningitis have been reported as 73.1% and 88.1%, respectively [33], [34], [35], [36], [37].

Diagnostic Efficacy of Molecular Methods for Meningitis Diagnosis

The diagnostic utility of molecular techniques in meningitis is well-documented, encompassing a range of pathogens and targets. For bacterial identification, broad-range bacterial polymerase chain reaction (BRB-PCR) targeting 16S rRNA achieved sensitivities of 59% and 100%, with specificities of 97% and 98.2% respectively [38], [39]. Real-time PCR for *Haemophilus influenzae* demonstrates highly variable sensitivity and specificity depending on the gene targeted. Markers such as *bexA* and *licA* exhibited sensitivities between 95% and 100%, with specificities up to 100% [40]-[44]. For *Neisseria meningitidis*, genes such as *ctrA* and *sodC* showed sensitivities ranging from 71.6% to 99.6% and specificities up to 100% [45]-[46]. Similarly, assays for *Streptococcus pneumoniae* using genes like *lytA* and *GntR-family SP2020* reached sensitivity and specificity levels of 100% in certain instances [50]-[51]. Loop-mediated isothermal amplification (LAMP) methods also present robust diagnostic capabilities, with sensitivity and specificity values as high as 100% for targets like the *Hib capsule* of *H. influenzae* and *lytA* of *S. pneumoniae* [54]. However, markers like *cfb* for *Streptococcus agalactiae* lacked conclusive sensitivity and specificity data [52]. These findings emphasize the variability in molecular method performance based on pathogen and genetic marker selection.

Acute Phase Proteins (APPs): Diagnostic Biomarkers of Inflammation and Infection

Acute phase proteins (APPs) are critical biomarkers of inflammation and infection, as their expression is triggered by the host's immunological response to microbial pathogens. Biomarkers are defined as biological molecules in bodily fluids or tissues that signify normal or pathological conditions [60]. The acute phase reaction (APR), an immediate and nonspecific host defense mechanism, encompasses physiological responses such as fever, leukocytosis, hormonal changes, and muscle protein breakdown, aimed at minimizing tissue injury and facilitating repair. APR is orchestrated by the release of pro-inflammatory cytokines, including tumor necrosis factor-alpha (TNF-α), interleukin-1 (IL-1), and interleukin-6 (IL-6), which stimulate hepatic production of APPs [63]. Elevated levels of APPs, including alterations in cerebrospinal fluid (CSF) protein, often result from disruptions in endothelial cell tight junctions during central nervous system infections [64]. Studies have reported significant changes in cytokines and APP concentrations as diagnostic markers for meningitis. For instance, TNF-α, IL-1, and IL-6 levels are pivotal in identifying inflammatory responses. The upregulation of these markers in CSF and blood underscores their utility in diagnosing CNS infections.

Diagnostic Efficacy of Immunologic Biomarkers for Meningitis

The diagnostic performance of various immunologic biomarkers in meningitis has been extensively studied. Procalcitonin (PCT) thresholds as low as 0.16 ng/mL in serum yielded sensitivity and specificity rates of 100% and 95.7%, respectively, when tested via fluorescence immune chromatographic methods [70]. In CSF, PCT levels of 0.74 ng/mL demonstrated a sensitivity of 94.7% and specificity of 100% using chemiluminescence immunoassay [69]. For C-reactive protein (CRP), sensitivities ranged from 50.9% to 100% depending on the concentration cutoff and the assay employed. For instance, CRP levels of 0.62 mg/dL in CSF showed sensitivity and specificity rates of 87% and 95%, respectively [73]. Additional biomarkers such as phosphatidylcholine derivatives, ferritin, and calprotectin also displayed high diagnostic accuracy. For instance, ferritin concentrations of 7.5 μg/L in CSF achieved 100% sensitivity and specificity using latex particle immunoassay (LPIA) [78]. Similarly, phosphatidylcholine species such as PC.aa.C32.1, measured by mass spectrometry, exhibited sensitivities and specificities above 90% at cutoffs

as low as 0.22 μM [75]. Cytokines like interleukin-6 (IL-6) and interleukin-8 (IL-8) have emerged as pivotal markers. IL-6 levels of 38.2 pg/mL in CSF demonstrated 100% sensitivity and 91% specificity using flow cytometry, while IL-6 levels detected through chemiluminescent enzyme immune assays achieved sensitivity and specificity rates of 84.6% and 85.7%, respectively [86]-[87]. These biomarkers collectively enhance the diagnostic landscape of meningitis, enabling precise differentiation of inflammatory states.

C-reactive Protein (CRP)

C-reactive protein (CRP) is an acute-phase protein (APP) produced predominantly by the liver in response to inflammation, such as tissue injury or irritation [89]. It is recognized as a highly sensitive marker for identifying infectious conditions [72]. Numerous studies have demonstrated the utility of CRP in differentiating bacterial from viral meningitis [90], [91]. In cases of culture-positive bacterial meningitis, CRP tests have shown a 100% positivity rate in initial lumbar puncture (LP) cerebrospinal fluid (CSF) samples, compared to only 6% in patients with aseptic meningitis [92]. A CSF CRP cutoff of 0.62 mg/dL has demonstrated 87% sensitivity and 95% specificity in diagnosing and distinguishing various forms of meningitis in pediatric populations [73]. Similarly, a cutoff of 0.18 mg/dL in CSF has been associated with 80% sensitivity and 92.3% specificity for differentiating bacterial and viral meningitis in children. In serum, a CRP cutoff of 29.9 mg/dL achieved 60% sensitivity and 100% specificity for the same differentiation in pediatric cases [71].

Furthermore, CRP levels in serum, with cutoffs of 10 mg/dL and 20 mg/dL, demonstrated sensitivities of 89% and 74% and specificities of 60% and 78%, respectively, in diagnosing bacterial meningitis in children [65]. Patients with bacterial meningitis exhibited significantly elevated CSF CRP levels (exceeding 100 mg/L) compared to controls and patients with viral meningitis [93]. Among adults, serum CRP with a cutoff of ≥90 mg/L provided 67.5% sensitivity and 86.3% specificity for acute meningitis diagnosis [69]. A meta-analysis revealed that negative CRP results in either CSF or serum can effectively exclude bacterial meningitis with a high degree of certainty [94]. Moreover, serum CRP has been identified as a more reliable screening biomarker for differential diagnostic purposes [95]. Notably, CSF CRP levels are significantly elevated in patients with bacterial meningitis caused by Gram-negative pathogens compared to those with Gram-positive bacterial meningitis [96]. This marked increase, alongside the trend of a heightened CSF-to-blood CRP ratio, underscores the role of Gram-negative bacterial lipopolysaccharides (LPS) in augmenting blood-brain barrier (BBB) permeability, a feature absent in Gram-positive pathogens [97].

Procalcitonin (PCT)

Procalcitonin (PCT), a protein comprising 116 amino acids and serving as a precursor peptide to calcitonin, is synthesized in extrathyroidal tissues during microbial infections [27], [100]. Inflammatory mediators, including tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6), induce the overexpression of the CALC-1 gene in parenchymal tissues, leading to elevated serum PCT levels [68], [101]. Intriguingly, viral infections do not elicit a similar PCT response, enabling its differentiation between viral and bacterial meningitis [102], [103]. PCT concentrations are measurable in both plasma and CSF [104]. The mechanism underlying increased PCT in CSF during meningitis involves cytokine-induced PCT release from leukocytes or cerebral vascular endothelial cells [64]. Studies have consistently shown significantly elevated mean CSF and serum PCT levels in bacterial meningitis compared to control groups. In culture-positive patients, these levels are notably higher than in culture-negative cases [68], [105]. Variations in bacterial species, prior antibiotic treatments, and patient age can differentially affect proinflammatory and anti-inflammatory cytokines, leading to discrepancies in serum PCT levels [64]. The comparative efficacy of serum versus CSF PCT for meningitis diagnosis has been debated, with Shen et al. reporting higher diagnostic accuracy for serum PCT based on receiver operating characteristic (ROC) curves (0.96 for serum PCT vs. 0.9 for CSF PCT). Additionally, the sensitivity of CSF PCT has been observed to surpass that of plasma PCT in diagnosing bacterial meningitis [106]. Reported sensitivities for serum or CSF PCT range between 87.5% and 100%, with specificities from 66% to 100% across studies [24], [107].

At admission, serum PCT cutoffs of 2 ng/mL and 10 ng/mL exhibited sensitivities of 100% and 86% and specificities of 63% and 82%, respectively, for bacterial meningitis [65]. A serum PCT cutoff of 0.5 ng/mL demonstrated 95.45% sensitivity and 84.61% specificity [66], while a cutoff of 2 ng/mL showed 100% sensitivity and 66% specificity for early diagnosis [67]. Serum and CSF PCT levels exceeding 0.5 ng/mL were reliable biomarkers for bacterial central nervous system (CNS) infections, with serum exhibiting 90% sensitivity and 100% specificity and CSF showing 55% sensitivity and 100% specificity [64]. CSF PCT levels above 0.9 ng/mL were associated with 92% sensitivity and 68% specificity in distinguishing bacterial meningitis cases from those without infection [68]. The integration of PCT measurement into standard immunological profiles highlights its suitability as a marker for acute conditions, applicable to patients with positive or negative bacterial CSF cultures [108]. PCT has been described as an ideal biomarker due to its precision in early bacterial infection detection and its utility in guiding clinical decisions [105]. For serum PCT, a cutoff of 5.91 ng/mL provided 24.14% sensitivity and 94.44% specificity, while CSF PCT with a cutoff of 0.085 ng/mL yielded 55.17% sensitivity and 95.83% specificity [109]. Notably, PCT levels rise more rapidly than CRP levels during inflammatory episodes, within 6 hours versus 12–24 hours, respectively [69]. Consequently, PCT assessment is regarded as a valuable tool for the early identification of acute meningitis in emergency clinical settings.

Phosphatidylcholine

Phosphatidylcholines (PCs) represent a class of phospholipids characterized by two fatty acid chains and a choline head group linked to glycerol phosphoric acid. Due to their bipolar properties, PCs are integral components of the lipid bilayer in eukaryotic cell membranes. In addition to their structural role, PCs are found in free form within bodily fluids such as cerebrospinal fluid (CSF) and serum. PCs play a crucial role in regulating phospholipase activity, which subsequently induces mediators that activate various cell-signaling pathways. Both PCs and phospholipases are synthesized in response to cellular damage and inflammation. Within the central nervous system (CNS), PCs are pivotal for signal transduction and maintaining acetylcholine levels. Elevated levels of free PCs in the CSF often result from cell membrane damage, and phagocyte-mediated elimination of PC residues may contribute to meningitis-associated CNS inflammation [110], [111]. Consequently, PC levels can serve as indicators of CNS inflammation caused by microbial pathogens. Among the various PC molecules, PC ae C44:6, a key component of cell membranes, has emerged as a sensitive biomarker for distinguishing bacterial meningitis from viral infections and other non-infectious CNS disorders. Mass spectrometry analysis of 221 CSF samples revealed that PC ae C44:6, at a threshold of >5 nM, can differentiate bacterial meningitis with 97% sensitivity and 87% specificity [112]. Furthermore, other PCs such as PC.aa.C32.1 (0.22 μM), PC.ae.C40.6 (0.02 μM), PC.ae.C36.5 (0.02 μM), PC.ae.C38.4 (0.11 μM), and PC.aa.C32.2 (0.01 μM) have demonstrated diagnostic sensitivities of 91%, 91%, 91%, 75%, and 94%, and specificities of 82%, 74%, 74%, 85%, and 68%, respectively, for bacterial meningitis [75]. Further investigations into the diagnostic accuracy of PCs across diverse patient populations and settings are warranted to enhance their clinical applicability in distinguishing meningitis types.

Leucine-Rich α-2 Glycoprotein (LRG)

Leucine-rich α-2 glycoprotein (LRG) is a glycoprotein characterized by a repeated leucine-rich motif [82], [113]. It is secreted by both neutrophils and liver cells [114]. Although its exact biological role remains unclear, LRG production increases significantly during acute inflammatory responses. Elevated serum levels of LRG have been reported in various conditions, including ulcerative colitis [115], rheumatoid arthritis [116], appendicitis [117], and Kawasaki disease [118]. Beyond its secretion by neutrophils and liver cells, LRG is also produced by astrocytes in the brain [82]. Notably, elevated levels of LRG in CSF have been implicated in early CNS disease responses. Studies indicate that LRG levels are significantly higher in bacterial meningitis cases (median: 374.5 ng/mL) compared to control groups (median: 103.3 ng/mL) ($p = 0.014$) [82]. Pathogen-specific analyses have shown that the highest CSF LRG levels occur in infections caused by *Streptococcus agalactiae* (mean: 3063.5 ng/mL), followed by *Haemophilus influenzae* type B (median: 269.0 ng/mL) and *Streptococcus pneumoniae* (median: 259.5 ng/mL) [82]. At a cutoff value of

110.0 ng/mL, CSF LRG levels exhibited sensitivity and specificity of 96% and 100%, respectively, for identifying bacterial meningitis in children [83]. Similarly, this threshold provided sensitivity and specificity of 96% and 75%, respectively, for differentiating bacterial meningitis from aseptic cases. Furthermore, at a cutoff of 139.9 ng/mL, CSF LRG levels demonstrated sensitivity and specificity of 88% and 75%, respectively, for distinguishing definite bacterial meningitis from probable cases [83]. Despite these promising findings, the diagnostic efficacy of LRG, particularly in adult populations, remains underexplored. Comprehensive studies are needed to validate its diagnostic utility across diverse clinical scenarios.

Ferritin

Ferritin, an acute-phase protein (APP), exhibits a significant increase in serum levels in response to infections that breach the blood-brain barrier [119]. However, ferritin concentrations in CSF are independent of its serum levels [91]. Inflammatory processes significantly influence CSF ferritin levels, with bacterial meningitis eliciting a more robust inflammatory response compared to viral meningitis. Pro-inflammatory cytokines such as tumor necrosis factor (TNF), interleukin-6 (IL-6), and interferon-gamma (IFN-γ) are known to elevate ferritin levels in both CSF and blood. Baseline ferritin levels in healthy individuals are typically low, ranging from 7 to 140 ng/mL in serum and 2 to 4.6 ng/mL in CSF [76]. In children with bacterial meningitis, a CSF ferritin cutoff of 20 ng/mL demonstrated sensitivity and specificity of 100% and 98.3%, respectively, compared to 95.7% sensitivity and 98.3% specificity at a cutoff of 30 ng/mL [15]. Similarly, a cutoff of 15.6 ng/mL yielded sensitivity and specificity of 96.2% and 96.6%, respectively, for distinguishing bacterial meningitis from viral cases in children [77]. Post-antibiotic treatment, CSF ferritin levels progressively decreased, requiring 14 to 20 days to fall below 15.6 ng/mL. Elevated ferritin levels were observed in both bacterial and viral meningitis patients compared to controls, with bacterial meningitis cases showing significantly higher concentrations. A CSF ferritin cutoff of 7.5 mg/mL was identified as the most effective for detecting bacterial meningitis, with sensitivity and specificity of 100% and 78%, respectively, for differentiating bacterial from viral meningitis [78]. Thus, CSF ferritin represents a valuable biomarker for the early diagnosis of bacterial meningitis, particularly in cases where prior antibiotic treatment precludes organism isolation. However, larger-scale studies are essential to substantiate its diagnostic reliability across varied clinical contexts.

Other Biomarkers:

Beta-2-microglobulin, a low molecular weight protein, is present in all nucleated cells as part of the class I major histocompatibility complex and serves as an indicator of cell turnover and inflammation. Elevated levels of this protein in cerebrospinal fluid (CSF) have demonstrated diagnostic utility in central nervous system (CNS) infections, although its specificity varies across conditions. Vitamin D-binding protein (VDBP), secreted by the liver and present in plasma, primarily transports vitamin D metabolites but also plays a role in immune regulation. Elevated CSF VDBP levels have shown potential as a biomarker for bacterial and tuberculosis meningitis, though their reliability as standalone markers remains limited. Matrix metalloproteinases (MMPs), proteolytic enzymes involved in tissue repair and immune defense, are upregulated in bacterial meningitis, with MMP-9 levels correlating with disease severity. Concurrently, tissue inhibitors of metalloproteinases (TIMPs) modulate MMP activity, offering insight into inflammation. Additionally, calprotectin and lactoferrin, inflammatory biomarkers secreted by immune cells, have demonstrated some utility in distinguishing bacterial from aseptic meningitis, though their clinical application is less frequent. Presepsin, a marker of bacterial infections, shows promise in screening for meningitis and tracking sepsis progression, with sensitivity and specificity varying by bacterial type. Pro-inflammatory cytokines, such as IL-6, are critical in diagnosing bacterial meningitis, with levels significantly higher in bacterial compared to viral infections. IL-6 has exhibited high sensitivity and specificity at defined cutoff levels, making it a valuable diagnostic tool, particularly in the early stages of infection. These biomarkers collectively enhance the understanding of CNS infections and their pathophysiology, though their diagnostic efficacy often depends on the context of use and complementary testing.

Conclusion:

Bacterial meningitis remains a critical public health concern, characterized by significant morbidity and mortality, particularly in regions with limited healthcare infrastructure. Timely and accurate diagnosis is pivotal to improving outcomes, as delays in treatment often result in severe complications, including neurological sequelae and, in some cases, death. This review highlights the utility of immunologic and biochemical markers in enhancing the diagnostic accuracy of bacterial meningitis. Elevated CSF protein and lactate levels, decreased CSF-to-serum glucose ratios, and the presence of bacterial antigens are key indicators distinguishing bacterial from viral meningitis. While traditional methods, such as Gram staining and CSF culture, remain integral to diagnosis, they are hampered by limitations, including reduced sensitivity in pre-treated patients and prolonged result times. The adoption of molecular diagnostic methods, such as PCR and NGS, represents a significant advancement in meningitis diagnosis. These technologies enable rapid and precise identification of pathogens, even in cases with low bacterial loads, thus facilitating early and targeted therapy. However, their high costs and need for specialized equipment limit widespread application in low-resource settings. Emerging biomarkers, such as CSF lactate and bacterial antigens, also demonstrate potential in improving diagnostic accuracy and speed, but further validation is needed to establish their clinical utility. Ultimately, integrating traditional and molecular diagnostic approaches offers the most comprehensive strategy for addressing the challenges of bacterial meningitis diagnosis. Efforts should focus on increasing accessibility to advanced diagnostics, particularly in resource-limited settings, to ensure equitable care. Future research should aim to refine biomarkers, optimize molecular techniques, and develop cost-effective solutions that bridge the gap between diagnostic efficacy and resource availability.

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التهاب السحايا البكتيري: لمحة عن المؤشرات المناعية والكيميائية الحيوية للتشخيص

الملخص:

الخلفية : التهاب السحايا البكتيري هو عدوى شديدة في الجهاز العصبي المركزي (CNS) تتميز بمعدلات وفيات ومراضة مرتفعة، خاصة في البيئات ذات الموارد المحدودة. تتداخل الأعراض السريرية في كثير من الأحيان مع أمراض أخرى، مما يستلزم طرق تشخيص دقيقة.

الهدف :تستعرض هذه الدراسة المؤشرات المناعية والكيميائية الحيوية للتشخيص المبكر والدقيق لالتهاب السحايا البكتيري، مع التركيز على التمييز بينه وبين التهاب السحايا الفيروسي.

الطرق :تم إجراء تحليل شامل للاختبارات التشخيصية، بما في ذلك فحص السائل الدماغي الشوكي(CSF) ، وصبغة جرام، والطرق الجزيئية مثل تفاعل البوليميراز المتسلسل (PCR) وتسلسل الجيل التالي .(NGS) تم أيضًا تقييم المؤشرات الحيوية مثل البروتين والجلوكوز واللاكتيت والمستضدات البكتيرية لمدى حساسيتها وخصوصيتها في تشخيص التهاب السحايا.

النتائج :يتميز التهاب السحايا البكتيري بارتفاع عدد خلايا الدم البيضاء في السائل الدماغي الشوكي، وزيادة مستويات البروتين، وانخفاض نسب الجلوكوز، وارتفاع تركيزات اللاكتيت. تُظهر صبغة جرام حساسية متغيرة (25%-97%)، في حين يظل زرع البكتيريا هو المعيار الذهبي للتشخيص على الرغم من محدودياته في البيئات ذات الموارد المحدودة وبعد إعطاء المضادات الحيوية. تعزز التقنيات الجزيئية مثل PCR و NGS بشكل كبير الحساسية والخصوصية، حيث يظهر PCR دقة شبه مثالية للجراثيم المستهدفة. كما أظهرت المؤشرات الحيوية الناشئة مثل لاكتات السائل الدماغي الشوكي حساسية بنسبة 93% وخصوصية بنسبة 99% عند حد ≤35 مجم/ديسيلتر.

الخلاصة :يعد التشخيص المبكر لالتهاب السحايا البكتيري أمرًا بالغ الأهمية لبدء العلاج الفعال وتقليل المضاعفات. تظهر المؤشرات المناعية والكيميائية الحيوية، جنبًا إلى جنب مع التشخيصات الجزيئية المتقدمة، وعدًا في التغلب على قيود الطرق التقليدية. يمكن أن يؤدي دمج هذه الأساليب إلى تحسين نتائج المرضى، خاصة في البيئات التي تعاني من نقص الموارد.

الكلمات المفتاحية :التهاب السحايا البكتيري، السائل الدماغي الشوكي، المؤشرات الحيوية، تفاعل البوليميراز المتسلسل، تسلسل الجيل التالي، التشخيص.