https://doi.org/10.48047/AFJBS.6.2.2024.4493-4501

African Journal of Biological Sciences

Journal homepage: http://www.afjbs.com

Research Paper Open Access

An Overview about Procalcitonin and Bacterial Meningitis

Abdallah Moatasem Nawara [1], Mohammed Mahmoud Mohammed El Saeed [2] , Doaa Metwaly AbdElmonem [3], Walid Mohamed Attiah Hamad [4], Heba Shafeak Abd El Khalik [5]

1 Professor of Internal Medicine, Faculty of Medicine, Zagazig University

2 MBBCH, Faculty of Medicine, Mansoura University

3 Assistant Professor of Clinical Pathology, Faculty of Medicine, Zagazig University

4 Lecturer of Internal Medicine, Faculty of Medicine, Zagazig University

5 Lecturer of Internal Medicine, Faculty of Medicine, Zagazig University

Corresponding author: Mohammed Mahmoud Mohammed El Saeed

Email: dr.mohamedmahmoud25@gmail.com

Article History

Volume 6, Issue 2, Apr-Aug 2024

Received: 5 July 2024

Accepted: 20 July 2024

Published: 25 July 2024

doi:10.48047/AFJBS.6.2.2024.4493-4501

Abstract: Background: Bacterial meningitis is associated with high morbidity and mortality worldwide, with about 1.2 million cases per year resulting in 135,000 deaths.1 The fatality rate can be as high as 70% in patients who are not treated, and one in five survivors may have permanent sequelae in the form of hearing loss, neurologic disability, and/or visual impairment. For these reasons, a rapid diagnostic evaluation with near 100% sensitivity is essential for optimizing outcomes in patients with suspected bacterial meningitis. There are currently gaps in the clinical diagnosis of bacterial meningitis that using PCT serum concentrations may address. One of the limitations to the current gold standard for bacterial meningitis diagnosis (e.g. lumbar puncture) is the likelihood of false negatives when a patient has received antibiotics prior to the lumbar puncture. In instances where a lumbar puncture must be delayed, such as in new onset seizures or history of CNS disease (e.g. CNS mass lesion, stroke, etc.) where a negative CT scan is required prior to lumbar puncture, CSF gram stains and cultures can be less useful in the diagnosis of bacterial meningitis. Another benefit of PCT assays is that results are available much more rapidly than the other diagnostic tests for bacterial meningitis. For example, a CSF culture takes about 72 hours for cultures to return with an identified organism and CRP testing takes about 50 minutes for results to return. In contrast, PCT results are available within 20 minutes from drawing a serum level. Although cost-effectiveness studies have been done showing that a PCT assay is actually a more cost-effective diagnostic tool than both CRP assay and white cell counts, there may still be some hesitation for implementation of the PCT assay in hospitals and labs due to higher costs per test. Also, a serum PCT assay alone cannot provide all the essential information needed in treating bacterial meningitis, such as the identification of the organism present. For this reason, a serum PCT assay cannot replace the standard of care, a CSF analysis, which would mean that the cost of serum PCT assay would be an additional cost on top of the cost of a CSF analysis

Keywords: *Procalcitonin, Bacterial Meningitis*

Introduction

Meningitis is an inflammation of the meninges and subarachnoid space that can also involve the brain cortex and parenchyma owing to the close anatomical relationship between the cerebrospinal fluid (CSF) and the brain. Per definition, bacterial meningitis is an infection of the CSF-filled subarachnoid space. Inflammation of the meninges and subarachnoid space leads to the classic triad of meningitis symptoms — headache, fever and neck stiffness — and to pleocytosis (an increased cell count, particularly of leukocytes) in the CSF (1). Involvement of the brain cortex and parenchyma, because of either direct inflammation or vascular complications, might result in behavioural changes, focal neurological abnormalities and impairment of consciousness¹, which are typically considered symptoms of encephalitis. Acute meningitis can be caused by a wide variety of infectious agents, but can also be a manifestation of non-infectious diseases. Bacterial meningitis is considered the most severe form of this disease; the routes of exposure are mainly respiratory, but can be enteric, as is the case in listerial infection. Meningitis can be acquired spontaneously in the community-acquired bacterial meningitis or in the hospital as a complication of invasive procedures or head trauma (nosocomial bacterial meningitis) (2).

Despite the existence of antibiotic therapies, acute bacterial meningitis causes substantial morbidity and mortality, both in high-income and low-income countries. Bacterial meningitis is an emergency situation and individuals with suspected disease require immediate evaluation and treatment. In this Primer, we provide an overview of community-acquired bacterial meningitis, focusing on the epidemiology, disease mechanisms, diagnosis, screening, prevention and management (3).

Viral meningitis is the most common type of aseptic meningitis and usually affects young children. Enteroviruses (EVs) are the most common causative agents of viral meningitis, with an estimated 75,000 new cases annually in the United States. Here, we provide an overview of viral meningitis and its most common causative agents and their pathogenesis. We also discuss epidemiological aspects, diagnosis, and clinical manifestations of the disease (4).

Epidemiology:

Bacterial meningitis was previously more common in pediatric patients. However, as vaccines are developed and utilized, the prevalence of acute bacterial meningitis has decreased and the epidemiology of causative microorganisms has changed. Vaccinations have increased the median age of patients infected. In 2006 there were 72,000 meningitis-related hospitalizations in the United States. The majority of these cases were due to viral infection (54.6%). Bacterial infections accounted for 21.8% of cases, and 7.3% were due to fungi and parasite infections, while 17.2% were due to an unspecified cause. There was an 8% in-hospital mortality rate for patients with bacterial meningitis, and it rose substantially for patients older than 45 (5).

The annual incidence of meningitis in the United States decreased from 2.00 cases per 100,000 populations in 1998–1999 to 1.38 cases per 100,000 populations in 2006–2007 while the median age of patients increased from 30.3 years in 1998–1999 to 41.9 years in 2006–2007. As per CDC data, rates of meningococcal disease have been declining in the United States since the late 1990s. In 2017, there were about 350 total cases of meningococcal disease reported (incidence rate of 0.11 cases per 100,000 persons) (6). In Africa, epidemics of meningococcal disease occur in a well-defined region — the meningitis belt (7).

Bacterial meningitis is caused by a bacterial infection of the meninges, resulting in inflammation. The infection is either community-acquired or nosocomial. Community-acquired bacterial meningitis is the result of the invasion of the bacteria into the meninges from bacteremia or direct extension from local infection. The most common bacterial culprit varies by age. Group B Streptococcus is common in infants less than 2 months of age while *Streptococcus pneumoniae* is the most common in all other age groups, with the exception of 11 - 17 year old, where *Neisseria meningitidis* is still the most common cause (8).

Listeria monocytogenes and gram-negative bacteria such as *Escherichia coli*, *Klebsiella*, *Enterobacter*, *Pseudomonas aeruginosa* are other less common causes. *Haemophilus influenzae* is still occasionally encountered in nonvaccinated individuals. Nosocomial infections are caused

by *S. pneumoniae*, *Staphylococcus aureus*, *Staphylococcus albus*, and gram-negative bacilli. As per Thigpen et al., out of the 1670 cases reported in the U.S. during 2003–2007, *S. pneumoniae* was the predominant infective species (58.0%), followed by GBS (18.1%), *N. meningitidis* (13.9%), *H. influenzae* (6.7%), and *L. monocytogenes* (3.4%). Infectious meningitis may also be caused by viruses, fungi, and protozoa. Meningitis may also be non-infectious in etiology and can be caused by cancer, medications, or inflammatory conditions (9).

Aseptic is differentiated from bacterial meningitis if there is meningeal inflammation without signs of bacterial growth in cultures. These cases are often viral, and enterovirus is the most common pathogen in immunocompetent individuals. The most common etiology in U.S. adults hospitalized for meningitis is enterovirus (50.9%), followed by unknown etiology (18.7%), bacterial (13.9%), herpes simplex virus (HSV; 8.3%), noninfectious (3.5%), fungal (2.7%), arboviruses (1.1%), and other viruses (0.8%).⁵ Enterovirus and mosquito-borne viruses, such as St. Louis encephalitis and West Nile virus, often present in the summer and early fall. HSV and varicella zoster virus can cause meningitis and encephalitis (10).

Pathogenesis:

Bacterial invasion

The current assumption is that high-grade bacteremia precedes meningitis and that bacteria invade from the blood stream to the central nervous system (CNS). Alternatively, direct accesses to the CNS through dural defects or local infections are potential entrance routes. In the clinical setting, such defects should be identified by CCT or MRI scans (11).

The anatomical site of bacterial invasion from the bloodstream remains unidentified. Experimental evidence suggests that the choroid plexus may be a site of invasion. Meningococci are found in the choroid plexus as well as in the meninges and pneumococci infiltrate the leptomeningeal blood vessels in meningitis. These data suggest that several highly vascularized sites are potential entry locations. In order to cross the blood—brain or the blood—CSF barrier and to overcome sophisticated structures such as tight junctions, meningeal pathogens must carry effective molecular tools (12).

Streptococcal proteins such as CbpA interact with glycoconjugate receptors of phosphorylcholine with platelet activating factor (PAF) on the eukaryotic cells and promote endocytosis and crossing the blood—brain barrier. Meningococci's PilC1 adhesin interacts with CD46 and the outer membrane protein connects to vitronectin and integrins. Bacteria causing meningitis in newborns, most importantly group B streptococcal (GBS) and *E. coli*, are also well equipped with adhesive proteins allowing them to invade the CNS. Detailed knowledge of how bacteria activate and invade cells may allow to block these interactions and therefore to prevent disease progression (13).

⎫ Inflammatory response

Inflammatory activation of endothelial cells seems to be a prerequisite for bacterial invasion but also results in the regulation of adhesion molecules as ICAM-1. Subsequently, these molecules promote the multistep process of leukocyte invasion. Leukocytes, in particular the presence of granulocytes in the CSF, are the diagnostic hallmark of meningitis. Early inflammatory response and bacterial invasion seem to progress in parallel and products of activated leukocytes such as MMPs contribute to early damage of the blood—brain and blood—CSF barrier. Once bacteria have entered the subarachnoidal space, they replicate, undergo autolysis and cause further inflammation (14).

Several cell types seem to be involved and as mentioned endothelial cells, perivascular macrophages and mast cells may play a crucial role. Heat killed bacteria and pathogen-associated molecular patterns (PAMP) of meningitis pathogens as lipoprotein (LP), lipoteichoic acid (LTA), peptidoglycan (PG), and lipopolysaccarid (LPS) cause meningitis indistinguishable from living bacteria. Immune pattern recognition molecules as CD14 and LBP function as sensors in identifying PAMPs. Pneumococcal PG and LP are recognized by TLR2 whereas LPS, and interestingly the pneumococcal toxin pneumolysin, signal through TLR4. TLR signals are conveyed by

the intracellular adapter protein MyD88 downstream to a multitude of inflammatory signaling cascades including NFkB and MAP kinases leading to a rapid inflammatory response in meningitis (15).

Neuronal damage

Up to 50% of survivors of bacterial meningitis suffer from disabling neuropsychological deficits. Clinically as well as experimentally, the hippocampus seems to be the most vulnerable area of the brain. Neuronal loss translates into hippocampal atrophy and has been reported on MRI scans in survivors of bacterial meningitis (16).

The predisposition of the hippocampus for neuronal damage remains unclear. The extracellular fluid around brain cells is contiguous with the CSF and the proximity to the ventricular system allows diffusion between these compartments that could deliver soluble bacterial and inflammatory toxic mediators. Neuronal damage in meningitis is clearly multi-factorial, involving bacterial toxins, cytotoxic products of immune competent cells, and indirect pathology secondary to intracranial complications (17).

Procalcitonin (PCT) has developed into a promising new biomarker for the early detection of systemic bacterial infections. PCT is a 116-amino acid residue first explained by Le Moullec et al. in 1984; its diagnostic significance was not recognized until 1993. In 1993, Assicot et al. demonstrated a positive correlation between high serum levels of PCT and patients with positive findings for bacterial infection and sepsis (e.g., positive blood cultures). Further, they demonstrated that PCT did not elevate in viral infections and that serum levels of PCT would decrease following the administration of appropriate antibiotic therapies (18).

PCT should not be used as the sole determinant for antimicrobial therapy. The results of a PCT assay should be placed in the context of the clinical scenario considering the possible site of infection, the likelihood of bacterial infection, the severity of illness, and other pertinent clinical data (19).

It is well-documented that early diagnosis of a bacterial infection can decrease mortality and morbidity among all patients. Efficient diagnosis of bacterial infections allows clinicians to initiate antibiotic therapy when deemed appropriate, thus preventing the misuse and overuse of antibiotics. As antibiotic resistance continues to rise, it has become increasingly important for clinicians to determine different algorithms and laboratory tests that help sustain current antibiotic parameters (20).

Unfortunately, most first-line tests for determining infection, such as blood cultures and C-reactive protein, lack the efficiency and specificity needed to treat patients promptly. Therefore, procalcitonin (PCT) serum assays have been developed to provide healthcare providers with an earlier detection method to determine the origin of a systemic inflammatory response (e.g., bacterial versus non-bacterial). Early detection, in turn, limits the development of antibacterial resistance and patient exposure to antibiotics when they are no longer warranted (21).

The prognostic value of PCT has also shown clinical significance by providing clinicians with a positive correlation between disease severity and elevated PCT serum levels, especially within septic patients. Although PCT assays have shown great promise, the cost-effectiveness of these tests continues to be debated. Current research has shown that these tests are already being overused because there are currently no adequate guidelines for when these tests should and should not be obtained. Therefore, the clinical significance of these tests needs to be more thoroughly researched on a large scale and through randomized clinical trials so that guidelines can be implemented to ensure the practice of cost-effective medicine (22).

Quality Control and Lab Safety:

For non-waived tests, laboratory regulations require, at the minimum, analysis of at least two levels of control materials once every 24 hours. If necessary, laboratories can assay QC samples more frequently to ensure accurate results. Quality control samples should be assayed after calibration or maintenance of an analyzer to verify the correct method performance. To minimize QC when performing tests for which manufacturers' recommendations are less than those required by the regulatory agency (such as once per month), the labs can develop an individualized quality control plan (IQCP) that involves performing a risk assessment of potential sources of error in all phases of testing and putting in place a QC plan to reduce the likelihood of errors.

Westgard multi-rules are used to evaluate the quality control runs. In case of a rule violation, proper corrective and preventive action should be taken before patient testing (23).

The laboratory must participate in the external quality control or proficiency testing (PT) program because it is a regulatory requirement published by the Centers for Medicare and Medicaid Services (CMS) in the Clinical Laboratory Improvement Amendments (CLIA) regulations. It is helpful to ensure the accuracy and reliability of the laboratory concerning other laboratories performing the same or comparable assays. Required participation and scored results are monitored by CMS and voluntary accreditation organizations. The PT plan should be included as an aspect of the quality assessment (QA) plan and the overall quality program of the laboratory (24).

Consider all specimens, control materials, and calibrator materials as potentially infectious. Exercise the normal precautions required for handling all laboratory reagents. Disposal of all waste material should be in accordance with local guidelines. Wear gloves, a lab coat, and safety glasses when handling human blood specimens. Place all plastic tips, sample cups, and gloves that come into contact with blood in a biohazard waste container. Discard all disposable glassware into sharps waste containers. Protect all work surfaces with disposable absorbent bench top paper, discarded into biohazard waste containers weekly or whenever blood contamination occurs. Wipe all work surfaces weekly (25).

Enhancing Healthcare Team Outcomes:

As bacterial drug resistance continues to rise across the globe, it has become of utmost importance to enhance antibiotic stewardship. Procalcitonin (PCT) provides healthcare providers with a more specific marker for determining the presence of bacterial infections when compared to current measures. Therefore, PCT assays can be utilized to determine if antibiotics need to be initiated, discontinued, or changed based on changing serum levels, thus decreasing the overall use or misuse of antibiotics. Moreover, the assays have also been useful as a prognostic indicator for patients in the critical care setting. However, further research needs to be performed to determine if PCT assays are adequate for this purpose (26).

PCT assays have utility in several clinical scenarios; current research suggests that PCT levels are most useful in acute exacerbations of chronic obstructive pulmonary disease (COPD) to determine when and if antibiotics should be initiated. The current European Respiratory Society and American Thoracic Society guidelines state that using antibiotics in the setting of COPD exacerbations is controversial because research showing improvement in clinical outcomes is inadequate. Therefore, they recommend further effectiveness studies and the use of biomarkers to determine when antibiotics are clinically appropriate. A biomarker, such as PCT, can be used to determine if antibiotics are appropriate in an acute COPD exacerbation; this improves antibiotic stewardship and reduces morbidity associated with unnecessary antibiotic use (27).

Overall, PCT levels provide a promising laboratory measurement for identifying bacterial infections. However, the utility of this test is limited by the clinical setting and patient population. Therefore, further research must be conducted before implementing PCT guidelines for everyday clinical practice (28).

Procalcitonin and Bacterial Meningitis

Bacterial meningitis is associated with high morbidity and mortality worldwide, with about 1.2 million cases per year resulting in 135,000 deaths.¹ The fatality rate can be as high as 70% in patients who are not treated, and one in five survivors may have permanent sequelae in the form of hearing loss, neurologic disability, and/or visual impairment. For these reasons, a rapid diagnostic evaluation with near 100% sensitivity is essential for optimizing outcomes in patients with suspected bacterial meningitis (29).

According to the 2004 guidelines for management of community-acquired bacterial meningitis, the Infectious Disease Society of America (IDSA) recommends that on suspicion of acute bacterial meningitis, blood cultures and a lumbar puncture are performed immediately, prior to initiating antibiotics but without significantly delaying time to antibiotics, to determine whether the cerebral spinal fluid (CSF) is consistent with the clinical diagnosis. The 2004 guidelines do not recommend routine use of procalcitonin (PCT) due to the lack of widespread ability to measure levels in clinical laboratories (30).

In contrast, the 2017 IDSA guidelines for the management of healthcare-associated meningitis do recommend collecting CSF PCT and serum PCT levels, in addition to CSF lactate levels to aid in the diagnosis and management of bacterial meningitis. However, these are weak recommendations given the low level of evidence that exists about CSF and serum PCT use in bacterial meningitis. The purpose of this article is to provide a focused review of PCT, its application to bacterial meningitis, select literature published to date, and considerations for its use (31).

PCT is a naturally occurring peptide synthesized by thyroid C cells as pre-procalcitonin which is later cleaved into its active component, PCT, by endopeptidases. Under normal physiological conditions, serum concentration of PCT is less than 0.10 ng/mL. During bacterial infections, the production of PCT is significantly increased through overexpression of the *CALC-1* gene in response to bacterial endotoxins and inflammatory cytokines, including IL-6, TNF-alpha, and IL-1-beta.⁵ In contrast, viral infections lead to the release of cytokines, such as IFN-gamma, which down regulates PCT. Multiple studies evaluating the application of PCT to bacterial meningitis used a cutoff value of 0.5 ng/mL for diagnosis in both adult and pediatric populations, with higher levels correlating to higher bacterial burden and increased mortality (32).

There are currently gaps in the clinical diagnosis of bacterial meningitis that using PCT serum concentrations may address. One of the limitations to the current gold standard for bacterial meningitis diagnosis (e.g. lumbar puncture) is the likelihood of false negatives when a patient has received antibiotics prior to the lumbar puncture. In instances where a lumbar puncture must be delayed, such as in new onset seizures or history of CNS disease (e.g. CNS mass lesion, stroke, etc.) where a negative CT scan is required prior to lumbar puncture, CSF gram stains and cultures can be less useful in the diagnosis of bacterial meningitis. Another benefit of PCT assays is that results are available much more rapidly than the other diagnostic tests for bacterial meningitis. For example, a CSF culture takes about 72 hours for cultures to return with an identified organism and CRP testing takes about 50 minutes for results to return. In contrast, PCT results are available within 20 minutes from drawing a serum level (33).

Procalcitonin may also be useful in monitoring treatment of acute bacterial meningitis. In a prospective study published by Alavi and colleagues, serum PCT was measured in patients with acute bacterial meningitis prior to the start of treatment and after 24 and 72 hours of treatment to determine if PCT can be monitored to predict response to treatment. This study found that serum PCT levels decreased as treatment duration increased in patients who were improving. There was a significant difference between PCT levels prior to treatment and 24 and 72 hours after treatment. At 24 and 72 hours after treatment, PCT levels changed by 0.044 ± 0.08 ($p=0.025$) and 1.74 ± 2.92 ($p=0.013$), respectively, from the PCT level at diagnosis (34).

Additionally, they found that PCT levels were high and remained high in patients who were not improving. Another prospective study done by Viallon and colleagues also looked at the change in PCT levels from admission to 72 hours after the start of treatment. This study found that PCT concentrations rapidly decreased within the first 24 hours of treatment as seen by a statistically significant change. These studies indicate that PCT could be used to assess response to antibiotic therapy. However, some studies contradict these findings and suggest that PCT does not have a benefit in diagnosing meningitis (35).

As mentioned previously, in order to limit morbidity and mortality associated with bacterial meningitis, there is a need for rapid diagnosis with near 100% sensitivity and specificity. In a study published by Makoo and colleagues, the sensitivity and specificity of serum and CSF procalcitonin in 50 patients with acute meningitis was compared to the sensitivity and specificity of CSF gram stain and culture. This study concluded that serum PCT had a sensitivity of 100% and a specificity of 87.9% and CSF PCT had a sensitivity of 84.2% and a specificity of 93.5% as compared to the CSF gram stain and CSF culture which both had a sensitivity of 42.1% and a specificity of 100%. The authors concluded that due to its 100% sensitivity, that serum PCT can be used as a powerful screening test in differentiating bacterial meningitis from aseptic meningitis (36).

There are limitations to a PCT assay, which has prevented it from becoming a standard of care diagnostic test for bacterial meningitis. One of these limitations is that serum PCT is not specific to bacterial meningitis and

can be elevated in various bacterial infections, including pneumonia, acute otitis media, and sepsis. Additionally, there is limited capacity of PCT to distinguish between acute febrile bacterial infections in the central nervous system like meningitis or brain abscesses. PCT levels decrease with antibiotic use, and therefore, this may give misleading results or false negatives in patients who have recently received antibiotics. Furthermore, a PCT assay costs about $10-$40 per use, while a CRP assay costs only about $1-$10 per use (33). Although cost-effectiveness studies have been done showing that a PCT assay is actually a more cost-effective diagnostic tool than both CRP assay and white cell counts, there may still be some hesitation for implementation of the PCT assay in hospitals and labs due to higher costs per test. Also, a serum PCT assay alone cannot provide all the essential information needed in treating bacterial meningitis, such as the identification of the organism present. For this reason, a serum PCT assay cannot replace the standard of care, a CSF analysis, which would mean that the cost of serum PCT assay would be an additional cost on top of the cost of a CSF analysis (37).
Despite some limitations, there is evidence to support use of serum PCT levels to aid in the diagnosis of bacterial meningitis. There is no indication that a PCT assay could replace the current standard of practice; however, there is evidence to suggest that the addition of a PCT assay to the current gold standard diagnostic tools can lead to a more rapid diagnosis of bacterial meningitis, lower cost, and better outcomes. The brevity in which PCT levels return could help to limit unnecessary antibiotic use and hospital admissions, and therefore reduce overall cost.⁸ Additionally, in scenarios where a CT scan of the head is required prior to a lumbar puncture, such as in a patient with elevated intracranial pressure, the IDSA recommends collecting blood cultures immediately and then initiating empiric antimicrobial therapy and dexamethasone as soon as possible. In these scenarios, serum PCT, serum lactate and other biomarkers act as guiding tools for differentiating between viral and bacterial etiologies since antibiotics administered prior to a lumbar puncture may diminish the yield of CSF cultures and CSF gram stains. The role of PCT has yet to be fully explained, but it can at least be considered as a part of standard care in patients with suspected meningitis (31).

References

1. Alderson, M., Welsch, J., Regan, K., et al. (2021). "Vaccines to Prevent Meningitis: Historical Perspectives and Future Directions. Microorganisms 2021, 9, 771." Bacterial Meningitis: Epidemiology and Vaccination 25: 31.
2. Arshad, A., Dayal, S., Gadhe, R., et al. (2020). "Analysis of tuberculosis meningitis pathogenesis, diagnosis, and treatment." Journal of clinical medicine 9(9): 2962.
3. Azzini, A. M., Dorizzi, R. M., Sette, P., et al. (2020). "A 2020 review on the role of procalcitonin in different clinical settings: an update conducted with the tools of the evidence based laboratory medicine." Annals of translational medicine 8(9).
4. Barichello, T., Rocha Catalão, C. H., Rohlwink, U. K., et al. (2023). "Bacterial meningitis in Africa." Frontiers in neurology 14: 822575.
5. Brink, M., Welinder-Olsson, C. and Hagberg, L. (2015). "Time window for positive cerebrospinal fluid broad-range bacterial PCR and Streptococcus pneumoniae immunochromatographic test in acute bacterial meningitis." Infect Dis (Lond) 47(12): 869-877.
6. Burke, J. R., Downey, C. and Almoudaris, A. M. (2022). "Failure to rescue deteriorating patients: a systematic review of root causes and improvement strategies." Journal of Patient Safety 18(1): e140-e155.
7. Bystritsky,R. J. and Chow, F. C. (2022). "Infectious meningitis and encephalitis." Neurologic Clinics 40(1): 77-91.
8. Carter, E. and McGill, F. (2022). "The management of acute meningitis: an update." Clin Med (Lond) 22(5): 396-400.
9. Cleland, D. and Eranki, A. (2023). "Procalcitonin." StatPearls.
10. Collins, C. D., Brockhaus, K., Sim, T., et al. (2019). "Analysis to determine cost-effectiveness of procalcitonin-guided antibiotic use in adult patients with suspected bacterial infection and sepsis." American Journal of Health-System Pharmacy 76(16): 1219-1225.

11. Dias, S. P., Brouwer, M. C. and van de Beek, D. (2020). "Sex-based differences in the response to dexamethasone in bacterial meningitis: Analysis of the European dexamethasone in adulthood bacterial meningitis study." British Journal of Clinical Pharmacology 86(2): 386-391.

12. Duan, S., Gu, X., Fan, G., et al. (2021). "C-reactive protein or procalcitonin combined with rhinorrhea for discrimination of viral from bacterial infections in hospitalized adults in non-intensive care units with lower respiratory tract infections." BMC Pulm Med 21(1): 308.
13. Dubot-Pérès, A., Mayxay, M., Phetsouvanh, R., et al. (2019). "Management of central nervous system infections, Vientiane, Laos, 2003–2011." Emerging Infectious Diseases 25(5): 898.
14. Dujari, S., Gummidipundi, S., He, Z., et al. (2021). "Administration of Dexamethasone for Bacterial Meningitis: An Unreliable Quality Measure." Neurohospitalist 11(2): 101-106.
15. Duong, M. T. (2022). "Neuroimaging Patterns of Intracranial Infections." Central Nervous System Infections, An Issue of Neuroimaging Clinics of North America 33(1): 11.
16. Duong, M. T., Rudie, J. D. and Mohan, S. (2023). "Neuroimaging Patterns of Intracranial Infections: Meningitis, Cerebritis, and Their Complications." Neuroimaging Clinics 33(1): 11-41.
17. EUCAST, M. (2018). Antimicrobial wild type distributions of microorganisms, European Committee on Antimicrobial Susceptibility Testing Vaxjo, Sweden.
18. Farber, J. M., Zwietering, M., Wiedmann, M., et al. (2021). "Alternative approaches to the risk management of Listeria monocytogenes in low risk foods." Food Control 123: 107601.
19. Farmen, K., Tofiño-Vian, M. and Iovino, F. (2021). "Neuronal damage and neuroinflammation, a bridge between bacterial meningitis and neurodegenerative diseases." Frontiers in Cellular Neuroscience: 193.
20. Gillet, Y., Grimprel, E., Haas, H., et al. (2023). "Antibiotic treatment of neuro-meningeal infections." Infect Dis Now 53(8s): 104788.
21. Glimåker, M., Johansson, B., Bell, M., et al. (2013). "Early lumbar puncture in adult bacterial meningitis—rationale for revised guidelines." Scandinavian journal of infectious diseases 45(9): 657-663.
22. Glimåker, M., Sjölin, J., Åkesson, S., et al. (2018). "Lumbar puncture performed promptly or after neuroimaging in acute bacterial meningitis in adults: a prospective national cohort study evaluating different guidelines." Clinical infectious diseases 66(3): 321-328.
23. Gregorino, C., Heilmann, E., Molitor, A., et al. (2020). "Role of procalcitonin use in the management of sepsis." Journal of thoracic disease 12(Suppl 1): S5.
24. Hasbun, R. (2022). "Progress and challenges in bacterial meningitis: a review." Jama 328(21): 2147-2154.
25. Hase, R., Hosokawa, N., Yaegashi, M., et al. (2014). "Bacterial meningitis in the absence of cerebrospinal fluid pleocytosis: a case report and review of the literature." Canadian Journal of Infectious Diseases and Medical Microbiology 25: 249-251.
26. Health, M. o. (2011). Immunisation handbook 2017, Ministry of Health Wellington.
27. Hegen, H., Auer, M. and Deisenhammer, F. (2014). "Serum glucose adjusted cut-off values for normal cerebrospinal fluid/serum glucose ratio: implications for clinical practice." Clinical Chemistry and Laboratory Medicine (CCLM) 52(9): 1335-1340.
28. Hu, Y., Jiang, L. and Peng, H.-l. (2015). "Clinical analysis of 134 children with nervous system damage caused by enterovirus 71 infection." The Pediatric infectious disease journal 34(7): 718-723.
29. Huynh, H.-H., Bœuf, A., Pfannkuche, J., et al. (2021). "Harmonization status of procalcitonin measurements: what do comparison studies and EQA schemes tell us?" Clinical Chemistry and Laboratory Medicine (CCLM) 59(10): 1610-1622.
30. Hviid, A. and Melbye, M. (2007). "The epidemiology of viral meningitis hospitalization in childhood." Epidemiology: 695-701.
31. Ivaska, L., Herberg, J. and Sadarangani, M. (2024). "Distinguishing community-acquired bacterial and viral meningitis: Microbes and biomarkers." Journal of Infection.
32. Kadambari, S., Braccio, S., Ribeiro, S., et al. (2019). "Enterovirus and parechovirus meningitis in infants younger than 90 days old in the UK and Republic of Ireland: a British Paediatric Surveillance Unit study." Archives of Disease in Childhood 104(6): 552-557.

33. Kaewpoowat, Q., Salazar, L., Aguilera, E., et al. (2016). "Herpes simplex and varicella zoster CNS infections: clinical presentations, treatments and outcomes." Infection 44: 337-345.

34. Kim, H., Roh, Y.-H. and Yoon, S.-H. (2021). "Blood procalcitonin level as a diagnostic marker of pediatric bacterial meningitis: a systematic review and meta-analysis." Diagnostics 11(5): 846.
35. Kim, K. S. (2019). "Investigating bacterial penetration of the blood–brain barrier for the pathogenesis, prevention, and therapy of bacterial meningitis." ACS Infectious Diseases 6(1): 34-42.
36. Kip, M. M. A., van Oers, J. A., Shajiei, A., et al. (2018). "Cost-effectiveness of procalcitonin testing to guide antibiotic treatment duration in critically ill patients: results from a randomised controlled multicentre trial in the Netherlands." Crit Care 22(1): 293.
37. Kohil, A., Jemmieh, S., Smatti, M. K., et al. (2021). "Viral meningitis: an overview." Arch Virol 166(2): 335-345.