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# MICROBIOLOGICAL BASIS OF MENINGOCOCCIC INFECTION AND MODERN DIAGNOSTICS METHODS

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**Abstract**
This literature provides information on the meningitis disease in the last 10 years. That is, the microbiological etiology, epidemiology, clinic presentation of the disease, modern diagnostic methods and preventive measures are described in detail. This article aims to enhance the understanding of meningitis and to highlight the most current updates that describe outbreaks of meningitis and the subsequent investigations. We also described the current diagnosis methods such as such as polymerase chain reaction (PCR) testing, fully automated US FDA-approved molecular assays, CE-marked diagnostic assays as well as classical ones: lumbar puncture and Computer tomography and finally treatment methods of the disease: immediate priorities, before and on arrival to hospital and all necessary antibiotics.

**Keywords**: meningococcal meningitis, fatal septicemia, neck stiffness, photalgia, quantitative Polymerase Chain Reaction (qPCR), meningococcal diagnosis, CSF

Это статья дает информацию о заболеваемости менингитом за последние 10 лет. То есть подробно описаны микробиологическая этиология, эпидемиология, клиника заболевания, современные методы диагностики и меры профилактики. Эта статья призвана улучшить понимание менингита и выделить самые последние обновления, описывающие вспышки менингита и последующие расследования. Мы также описали

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Volume 2, Issue 6, June -2023
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современные методы диагностики, такие как полимеразная цепная реакция (ПЦР), полностью автоматизированные молекулярные анализы, одобренные FDA США, диагностические анализы с маркировкой CE, а также классические: люмбальная пункция и компьютерная томография и, наконец, методы лечения болезнь: неотложные приоритеты, до и по прибытии в больницу и все необходимые антибиотики.

**Ключевые слова**: менингококковый менингит, фатальная септицемия, ригидность затылочных мышц, флуоталгия, количественная полимеразная цепная реакция (КПЦР), менингококковая диагностика, ЦСЖ.

## Introduction

Meningitis is an infection/inflammation of the brain and spinal cord surrounding membranes known as the meninges. Meningococcal meningitis is the term used to describe a bacterial form of meningitis caused by Neisseria meningitidis. This form of meningitis is associated with high morbidity and mortality. Meningococcal meningitis is a medical emergency for which symptoms can range from transient fever to fulminant bacteremia and septic shock [20].

## Etiology

Neisseria meningitides is the organism responsible for meningococcal meningitis and is the second most common causative organism for bacterial meningitis in the United States. This bacterium is an anaerobic, bean, or kidney-shaped gram-negative diplococci. (Picture 1) It grows in chocolate agar and blood agar at room temperature with 5%-10% atmospheric carbon dioxide. Neisseria meningitides are catalase-positive, oxidize glucose and maltose that changes pH, and helps to differentiate from gonococci, which cannot oxidize maltose. The organism grows in selective Thayer-Martin media, which contains antibiotics like vancomycin, colistin, and nystatin by preventing the growth of other gram-negative bacteria, gram-positive bacteria, and yeast. N. meningitidis colonizes mostly in the naso-and oropharynx but can colonize in other body parts like the anal mucosa, conjunctiva, and urogenital tracts. It possesses multiple virulent factors: Pilli, opacity proteins, lipo-oligosaccharides, capsular

Picture 1

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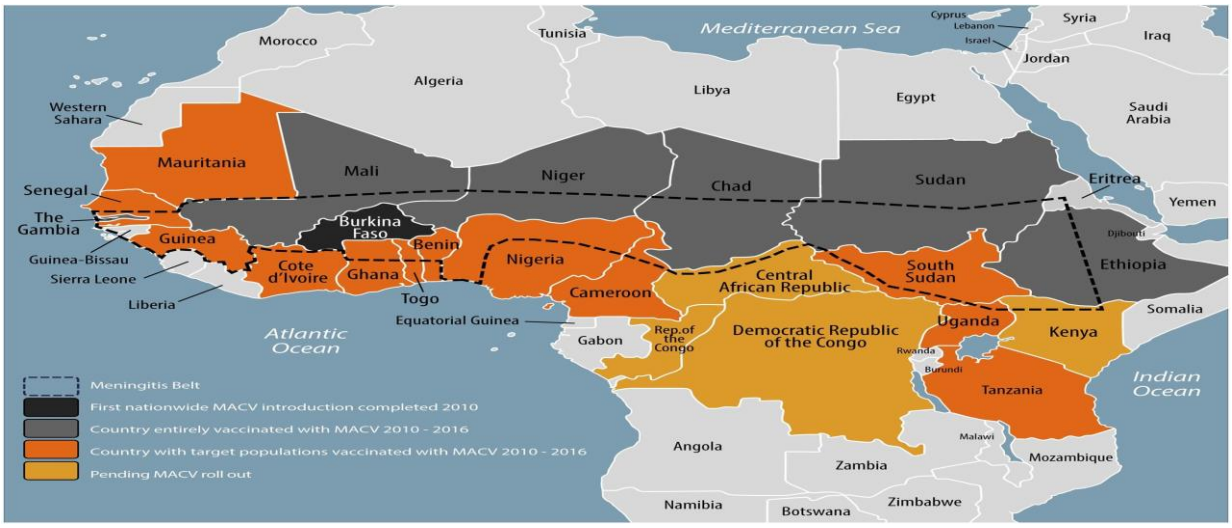
polysaccharide, and factor H binding protein. The polysaccharide capsule protects the bacterium from complement-mediated phagocytosis and lysis[ 11].

Serotypes are classified according to the polysaccharide capsule it contains. Out of 13 serotypes, A, B, C, X, Y, Z, W-135, and L are mostly responsible for human disease[ 24]. Unencapsulated strands found in asymptomatic carriers rarely have been the cause of invasive disease. Lipo-oligosaccharide is similar to lipopolysaccharide of gram-negative bacilli. LOS acts as endotoxin and activates the pro-inflammatory cytokine pathway of the host to cause meningococcal sepsis. LOS interacts with immune cells of the host to initiate the release of inflammatory mediators like TNF-alpha, IL-1, IL-6, and INF-gamma to cause shock [ 25].

In 2011–2015, Burkina Faso reported 20,389 cases of suspected meningitis. A quarter (4,503) of suspected meningitis cases with cerebrospinal fluid specimens were laboratory-confirmed as either S. pneumoniae (57%), N. meningitidis (40%), or H. influenzae (2%). Average adjusted annual national incidence of meningococcal meningitis was 3.8 (range: 2.0–10.2 annually) and was highest among infants aged <1 year (8.4). N. meningitidis serogroup W caused the majority (64%) of meningococcal meningitis among all age groups. Only six confirmed NmA cases were reported in 2011–2015. Five cases were in children who were too young (n = 2) or otherwise not vaccinated (n = 3) during the 2010 MACV mass vaccination campaign; one case had documented MACV receipt, representing the first documented MACV failure (Picture 2)[3].




Picture 2. Bacterial meningitis epidemiology and return of Neisseria meningitidis serogroup A cases in Burkina Faso in the five years following MenAfriVac mass vaccination campaign

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## Epidemiology

The epidemiology of bacterial meningitis varies widely by age (e.g., the higher incidence in neonates and elderly patients) [6]. Streptococcus agalactiae (or Group B Streptococci) and Escherichia coli are the principal etiologies of neonatal meningit [6]. Recent epidemiological studies from Africa and the Netherlands show that between 2006 and 2014 of 1,412 episodes of community-acquired bacterial meningitis demonstrated that Streptococcus pneumoniae, Neisseria meningitidis, and Listeria monocytogenes accounted for 51, 37, and 4% of cases, respectively [30]. S.pneumoniae and N.meningitidis cause up to 90% of cases in infants and children.

There are significant geographical differences in the epidemiology of bacterial meningitis worldwide. Sub-Saharan Africa, a region referred to as the "meningitis belt," has a large proportion of meningitis cases. Epidemic meningococcal group A disease outbreaks have recorded incidence rates up to 100 per 100,000 [28]. The introduction of MenAfriVac (Serum Institute of India Ltd, Hadapsar, Pune, India), a conjugate vaccine against serogroup A N. meningitidis, in sub-Saharan Africa has virtually eliminated Group A meningococcal meningitis outbreaks. However, new epidemics in Burkina Faso, Chad, Mali, Niger, and Togo with other serogroups (W and C) are now occurring A systematic review of bacterial meningitis in Africa found that the most common pathogens were N. meningitidis (n = 2,433; 56%), S. pneumoniae (n = 1,758; 40%), and Haemophilus influenzae (n = 180; 4%) [28].

## Pathophysiology

The pathophysiology of N.meningitidis involves a series of sequential steps. The process begins when the bacterium colonizes the nasopharynx. The only known reservoir for N.meningitidis is the upper respiratory tract, although only a few will develop invasive disease. The bacterium incubates for a period to 1 to 10 days and then further penetrates the submucosa. In 10 to 20% of cases, the bacterium invades the bloodstream. Once present in the plasma, host defenses, which include bactericidal antibodies, complement, and phagocytic cells, may prevail and eliminate bacteria. In cases, where host defenses fail to clear bacteria, the patient enters the bacteremic phase. Bacteria may now invade

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meninges and other local sites, which can rapidly lead to meningitis and fatal septicemia [13].

Monogenic disorders underlying Neisseria meningitidis infection. Nm is transmitted via droplets and selectively colonises the human nasopharynx. In susceptible hosts, meningococci can invade and cross the nasopharyngeal mucosal epithelium to gain access to the blood stream. Once inside the bloodstream the meningococci grow in number and are disseminated throughout the host.

Uncontrolled growth in the blood, leads to high titres of Nm and septicaemia. In other patients, there is less Nm replication in the blood, but meningococci breach the blood brain barrier (BBB), multiply uncontrollably in the cerebrospinal fluid and infect the meninges, leading to meningitis. The genes highlighted in red are monogenic disorders almost exclusively associated with IMD. Highlighted in orange, are monogenic disorders associated with bacterial infections and, though not exclusive to Nm infection, has been observed in cases of IMD. SPLUNC1, highlighted in yellow, has recently been demonstrated as a monogenic disorder associated with IMD though its pathogen exclusivity is unknown. Image created with biorender [14].

When meningococci invade the bloodstream, endotoxin is released from the bacteria. This triggers an inflammatory response, with release of inflammatory mediators, which is directed against the endothelial surface lining the blood vessels. One of the main functions of the endothelium is regulation of vascular permeability, and disturbance of this function causes the endothelial lining to become 'leaky', allowing increased passage of protein and water from the intravascular to extra-vascular compartments, causing a '**capillary leak syndrome**'. The patient becomes hypovolaemic due to reduction in circulating volume, thus reducing cardiac output.

In compensation for reduced circulating volume, heart rate and contractility increase, and perfusion to skin and the splanchnic circulation is reduced. Therefore signs of hypovolaemia in sepsis include:

- **Tachycardia**
- **Tachypnoea**
- **Cool peripheries**
- **Reduced urine output**

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- **Irritability or lethargy.**

Note that in the early phases of septic shock blood pressure is maintained by these compensatory mechanisms. This means that early in shock, children are alert as blood flow to the brain is being maintained at the cost of the other organs.

## Clinical Presentation

The illness could be age-related and nonspecific. In adults, 44% of cases present with the classic triad of symptoms: Fever, stiff neck, and altered mental status. There are four general symptoms, namely fever, headache, neck stiffness, and altered mental status; at least two of which are diagnosed in meningitis cases Positive Kernig and Brudzinski's signs of meningeal irritation might be present in patients. Moreover, nausea, vomiting, cardiorespiratory arrest, focal CNS signs, photalgia, and seizures might occur as well Among all the symptoms in newborns and infants fever, poor feeding, vomiting, lethargy, diarrhea, and sometimes apnea are the most common ones, due to temperature instability and the bulging fontanel in newborns [10]. In children, photalgia and mental disorder might be present as well. Sometimes in pediatric patients with pneumococcal meningitis seizure is the only symptom. In Neisseria-caused meningitis, rash and petechiae are also present (more than 50%). In elderly and immunocompromised patients, due to age- or immunodeficiency associated conditions, signs might be masked, patients can be presented with lethargy and mental disorder (as the common early signs), headaches, photalgia, seizures, rash, nausea, vomiting, meningeal irritation, stiff neck and positive Kernig and Brudzinski upon physical examination . Sequelae of ABM can be listed as follows: Neurological (increased ICP, seizures, extra-axial fluid collection, ventriculitis, cranial nerve palsies, hemi/quadriparesis, hearing loss, hydrocephalus), systemic (peripheral circulatory failure, disseminated intravascular coagulation, syndrome of inappropriate secretion of antidiuretic hormone, arthritis) and sequelae mental retardation, seizures, sensorineural hearing loss, visual impairment, behavioral problems, motor deficits, hydrocephalus, and learning disabilities [32].

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## DIAGNOSIS

### Microbiological Diagnosis

Recently, the UK Standards for Microbiology Investigation issued an update on the investigation of cerebrospinal fluid and this forms the cornerstone for laboratory diagnosi [26].

Gold standard culture methods for meningococcal diagnosis are too slow and frequently compromised by prior antibiotic treatment. The development and application of sensitive quantitative Polymerase Chain Reaction (qPCR) assays has significantly improved laboratory detection rates and has reduced the time required to confirm invasive meningococcal disease [31].

Typically, molecular testing protocols follow a two stage process (i) confirmation of infection using specific qPCR detection of N.meningitidis ctrA gene (capsule transport gene) (ii) identification of meningococcal serogroup by qPCR analysis of specific conserved regions within N.meningitidis capsular biosynthesis (cps) locus. A positive qPCR result for a normally sterile site specimen e.g., blood and/or CSF is regarded as definitive for meningococcal diagnosis· Despite concerns regarding detection of carriage strains, molecular testing of respiratory specimens in clinical context is increasingly recognised as a valuable adjunct NICE acknowledge the proven clinical utility of molecular assays (qPCR) for meningococcal diagnosis, but also note that such assays are not available in most NHS hospitals due to resource limitations [23] Currently, qPCR remains the preserve of a limited number of centralised reference laboratories who possess the necessary infrastructure, equipment and technical skills to routinely deliver an effective service. The time required to transport samples to centralised laboratories ultimately means that molecular detection of meningococci has little or no impact on patient management, whereby such testing merely confirms an initial clinical diagnosis and provides epidemiological data on circulating strains [5]. Recently, the Regional Virus Laboratory at the Royal Victoria Hospital has developed a Loop-Mediated Isothermal Amplification (LAMP) molecular assay, comprising a high activity strand displacing enzyme, nucleotides and $Mg^{2+}$ and a minimum of four or a maximum of six primers targeting a total of six or eight specific regions on target sequence, resulting in an assay with stringent specificity. This assay offers performance equivalent to reference laboratory qPCR testing and this LAMP

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technology has opened up the ability to perform rapid detection of N. meningitidis in any health care setting in less than 60 minutes [16]. Compared to qPCR, LAMP offers several advantages including simplified methodology, quicker reaction time and lower instrument costs combined with visual detection of positive reactions. LAMP is also highly resilient to inhibition and is capable of being applied to crude specimen preps which increases their potential for use in resource limited environments [12].

Testing of respiratory specimens (i.e. nose, throat or nasopharyngeal swabs) to detect meningococci using conventional culture methods is often discouraged, unless the objective is to detect meningococcal carriage. Indeed, throat and nasopharyngeal swab cultures have been used for decades to recover both pathogenic capsular strains and non-pathogenic non-capsular strains in carriage studies. However, there is growing evidence that direct molecular testing of respiratory specimens is useful for diagnosis of meningococcal disease in children. Carriage rates are very low in young children and employment of the sensitive LAMP assay to specifically detect capsular strains has shown very high positive and negative predictive values in a recent clinical study. Rapid molecular testing of non-invasive respiratory specimens could help clinicians to identify the many children with meningococcal disease who are not diagnosed when they first present to healthcare. In addition to improving diagnosis of disease, molecular testing of respiratory swabs has also been useful to detect carriage in adolescents. Currently a meningococcal carriage study is being undertaken of undergraduate students in Belfast, employing direct molecular testing of self-collected throat swabs using real-time PCR and LAMP to identify carriers of serogroups B, W and Y [7].

Common diagnostic laboratory & imaging tests

CT and MRI may be considered as adjunctive diagnostics tests but are generally nonspecific and show meningeal enhancement. Imaging may be helpful in cases of focal neurologic deficits, particularly when a tuberculoma or cryptococcoma is suspected . In the absence of trauma, altered mental status or focal neurologic deficit, imaging increases healthcare costs and has minimal yield in providing a definitive diagnosis. PET has even greater expense with no ability to provide a definitive etiologic diagnosis in a person with meningitis.

**ISSN (E):** 2980-4612
Volume 2, Issue 6, June -2023
**Website:** intentresearch.org/index.php/irsj/index

Standard diagnostic testing of CSF includes: white blood cell (WBC) count with differential, total protein, and CSF/blood glucose (or CSF glucose itself), used in conjunction with patient history and epidemiology to support potential diagnoses. Total protein and WBC counts reflect inflammation in the CSF while decreased glucose CSF/blood ratio is a sign of glucose consumption by an active infection. These common laboratory tests cannot be the lone laboratory method of diagnosis and while overlap in their values among different diagnoses does occur, general trends emerge and are useful as they help the clinician to focus on particular possible diagnoses [21].

More specific technologies have been, or are under development to enable more confident diagnosis of the major etiologic agents of meningitis . One example of a technology that could potentially be applied broadly to meningitis is that of a PCR multiplex panel. These panels allow for detection of multiple different pathogens that might cause a particular syndrome with one test – ideally in rapid, easy to use and accurate manner. Panels have successfully been trialed for use in respiratory illnesses and blood cultures [27], a panel developed for sepsis has been trialed in patients with meningitis, and another multiplex PCR panel has been developed for use in meningitis (although not yet thoroughly studied) [4]. Technologies such as multiplex PCR are exciting, but in the case of meningitis, not yet ready to aide clinicians.

**Neuroimaging: Why computed tomography before lumbar puncture is not usually required?**

In many patients with meningitis, performing a lumbar puncture (LP) and starting empirical treatment are unnecessarily delayed while waiting for computed tomography (CT) of the head. CT prior to LP should not be performed for most patients for several reasons. First, and most importantly, if a patient is not pretreated with antibiotics, the sequence of CT followed by LP followed by antibiotics causes an unacceptable delay in starting treatment and increases the likelihood of an unfavourable outcome. Second, the yield of CT is low in patients who do not have clinical features of raised intracranial pressure (ICP), with 97% having a normal result. Third, if a patient is pretreated with antibiotics prior to CT and LP, the yield of CSF culture will be significantly decreased, although a diagnosis can often still be obtained through polymerase chain reaction (PCR) testing [15].

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Volume 2, Issue 6, June -2023
**Website:** intentresearch.org/index.php/irsj/index

**CSF analysis**

CSF analysis is of vital importance in suspected meningitis as clinical characteristics alone are unable to distinguish meningitis from other diagnoses, and bacterial from non-bacterial aetiologies. For the majority of patients who do not require CT prior to LP and do not have another clinical contraindication to LP, CSF analysis should be performed within 1 h of the presumptive diagnosis of meningitis without awaiting further investigations, such as platelet count or coagulation studies. Clinical contraindications to LP include anticoagulation, clinical evidence of disseminated intravascular coagulation and local infection or loss of skin integrity at the puncture site. LP is safe in patients taking aspirin, but safety is less well established for those taking other anti-platelet agents, such as clopidogrel or ticagrelor, or for those on dual anti-platelet therapy; deferring LP is recommended in these circumstances [17].

**Cerebrospinal fluid polymerase chain reaction**

Cerebrospinal fluid polymerase chain reaction (PCR), using pathogen specific nucleic acid sequences, can detect both bacteria and viruses with high sensitivity. Polymerase chain reaction is the 'gold standard' for diagnosis of viral meningitis. Polymerase chain reaction is increasingly relied upon in bacterial meningitis. It has far greater sensitivity than culture in invasive meningococcal disease [17]. Cerebrospinal fluid PCR is particularly valuable in patients who receive antibiotics before LP. Polymerase chain reaction for 16S ribosomal RNA (present in almost all bacteria) enables a broad screen for bacteria, but has lower sensitivity than pathogen specific PCR [18].

Brain imaging

Brain imaging is neither obligatory in the management of meningitis, nor a prerequisite to LP. Performing neuroimaging before LP is associated with delays in commencing antibiotics, which in turn can lead to an increase in mortality [22]. An urgent CT scan should be performed if there are clinical signs of brain shift. Clinical features indicative of a brain shift include focal neurological signs and reduced Glasgow Coma Score (GCS). The 2016 UK meningitis guidelines recommend an LP be performed without prior neuroimaging if the GCS is >12.Patients with a GCS ≤12 should be considered for critical care, intubation assessment and neuroimaging. Imaging, particularly when contrast is used, may

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Volume 2, Issue 6, June -2023
**Website:** intentresearch.org/index.php/irsj/index

exhibit meningeal enhancement in meningitis. When brain shift is identified liaison with critical care and neurosurgical teams are essential.

ADOPTION BARRIERS

Cost remains a significant barrier for many new molecular diagnostics both in high-income and low/middle-income countries. Excluding reference laboratories, most local hospital microbiology labs are costs to a healthcare system, not a revenue generator. An integrated health system approach needs to be considered for decision making. A new relatively expensive assay may cost more for a microbiology laboratory budget, yet accrue significant cost savings in avoidance of other unnecessary procedures/testing, decreased pharmaceutical costs for empiric treatments and shorter duration of hospitalization. A second, ironic barrier to adoption is the standard Good Clinical Lab Practice of every laboratory internally validating a new assay. For fully automated US FDA-approved molecular assays, this slows adoption for relatively rare diseases where validation takes significant time and effort. Third, as new molecular tests become available, how best to utilize such testing in a cost-effective manner in high- and low-income settings needs to be explored [9]. Lastly, the patchwork of individual country regulatory requirements, which are often unclear or unknown in low- and middle-income countries, creates a substantial disincentive for manufacturers to bring new FDA-approved and/or CE-marked diagnostic assays to markets where there is minimal financial return. These barriers unfortunately impact vulnerable patients with deadly diseases, foremost.

## Treatment

### Immediate priorities, before and on arrival to hospital

In bacterial meningitis, prompt treatment is life-saving. For patients who present to primary care with suspected meningococcal disease, pre-hospital treatment with parenteral benzylpenicillin or ceftriaxone has been advocated. Intuitively, the benefits of early antibiotic administration seem clear [2]. However, evidence that this practice improves outcomes is lacking; observational studies have reported that pretreated patients have worse outcomes, although this may be because those who were pretreated had more severe disease than those who were not. An alternative hypothesis for this finding is that rapid bacteriolysis following antibiotic administration may precipitate shock due to the release of

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Volume 2, Issue 6, June -2023
**Website:** intentresearch.org/index.php/irsj/index

meningococcal endotoxins; this could be deleterious if it occurs in the community, rather than in the hospital where there is greater access to fluid resuscitation and inotropic support. This theory is also unproven. Given this lack of evidence, the role of pre-hospital antibiotics remains unclear; they should be given to patients who present to rural or remote practices and face a prolonged transport time to a secondary care facility.

On arrival at hospital, the patient should be placed in droplet precautions to prevent potential nosocomial transmission of meningococcal infection and resuscitated as required. Blood and, ideally, CSF cultures should be quickly obtained, following which dexamethasone and antibiotics should be given, aiming for administration within 1 h of admission. The importance of timely therapy has been demonstrated in multiple studies, with one study showing an increase in mortality of 13% and another showing an increase in mortality and disability of 30%for every hour that treatment is delayed [19].

If a patient exhibits signs of airway, breathing or circulatory difficulties (eg in coexisting sepsis), management should initially focus on stabilisation of these systems. All patients should be reviewed by a senior clinician. The Royal College of Physicians recommends consultant review for all acute medical patients within 14 hours of admission. Urgency of review should be assessed using the National Early Warning Score. The GCS should be recorded for its prognostic value, and to enable changes to be monitored. Presence of a rash and use of preadmission antibiotics should also be recorded.

If the patient presents with sepsis, they should be managed according to the sepsis guidelines. If the infective focus of sepsis is meningitis, then the antibiotic treatment should follow the guidelines for meningitis. For example, piperacillin / tazobactam is not recommended for use in sepsis secondary to meningitis, because of its poor penetration of the blood brain barrier. A recent large open-label trial showed no benefit of prehospital antibiotics in sepsis [1]. Previous trials for meningitis have also been inconclusive. Consequently, the benefit of prehospital antibiotics for suspected meningitis is unclear. Management of other aspects of sepsis, eg circulation, should follow the sepsis guidelines [8].

In suspected bacterial meningitis, dexamethasone should be started either shortly before or simultaneously with antibiotics at 10 mg intravenously (IV) 6-hourly. Up until 12 hours after antibiotic initiation, dexamethasone can still be

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Volume 2, Issue 6, June -2023
**Website:** intentresearch.org/index.php/irsj/index

started, but the impact of this on mortality has not been studied. If pneumococcal meningitis is probable, dexamethasone should continue for 4 days. In suspected tuberculous meningitis, dexamethasone provision should follow the recommended guidelines[29] Once another cause of meningitis is probable, dexamethasone should be stopped.

There is no specific treatment for viral meningitis. Treatment with aciclovir has only been of proven benefit in herpes encephalitis, not meningitis. Only if the patient has encephalitic features, such as impairment of consciousness, focal neurological signs, inflammation of brain parenchyma in the region of the temporal lobe on cranial imaging, should aciclovir be considered.

## Conclusion

In this article, we've used the previous articles in the last decade all about Neisseria meningitidis, it's etiology, epidemiology, pathophysiology, clinical presentation of the bacterial meningitis, and most importantly you can see here modern diagnostic methods of the disease such as polymerase chain reaction (PCR) testing, fully automated US FDA-approved molecular assays, CE-marked diagnostic assays as well as classical ones: lumbar puncture and Computer tomography and finally management of the disease: immediate priorities, before and on arrival to hospital and all necessary antibiotics.

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