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High risk and low incidence diseases: Meningococcal disease

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ABSTRACT

Introduction: Meningococcal disease is a serious condition that carries with it a high rate of morbidity and mortality.
Objective: This review highlights the pearls and pitfalls of meningococcal disease, including presentation, diagnosis, and management in the emergency department (ED) based on current evidence.
Discussion: Invasive meningococcal disease is a severe, rapidly progressive infection caused by *Neisseria meningitidis* associated with high morbidity and mortality. Emergency physicians must maintain a high index of suspicion, as early symptoms may mimic a benign viral illness, potentially delaying treatment with serious consequences. This early phase is typically followed by the emergence of more specific features of meningococcal infection, such as meningococcal meningitis, meningococcemia, or a combination of both. Suspected cases warrant immediate implementation of droplet precautions and strict isolation to reduce the risk of healthcare worker exposure and secondary transmission. Prompt treatment, ideally within one hour of clinical suspicion, is essential. Management includes empiric parenteral antibiotics, and in cases of suspected meningitis, adjunctive corticosteroids should be administered prior to or concurrently with the first antibiotic dose. Patients with meningococcemia and shock require aggressive fluid resuscitation, vasopressor support as indicated, and prompt admission to a critical care setting. All close contacts of confirmed cases should receive chemoprophylaxis, regardless of their meningococcal immunization status.
Conclusions: An understanding of meningococcal disease can assist emergency clinicians in diagnosing and managing this potentially deadly disease.

1. Introduction

This article series addresses high risk but uncommon diseases that are encountered in the emergency department (ED). Much of the primary literature evaluating these conditions is not emergency medicine-focused. By their very nature, many of these disease states and clinical presentations have little useful evidence available to guide the emergency physician in diagnosis and management. The format of each article defines the disease or clinical presentation to be reviewed, provides an overview of the extent of what we currently understand, and finally discusses pearls and pitfalls using a question and answer format. This article will discuss meningococcal disease. This condition's high morbidity and mortality, as well as its variable atypical patient presentations and challenging diagnosis, makes it a high risk but uncommon disease.

1.1. Definition

Meningococcal disease encompasses a diverse spectrum of clinical conditions caused by *Neisseria meningitidis* (*N. meningitidis* or the meningococcus) [1,2]. Although the severe forms of invasive meningococcal disease (IMD) commonly manifest as meningitis or bacteremia (meningococcemia), with or without concurrent meningeal involvement, IMD is fundamentally defined as an infection with *N. meningitidis* occurring at a normally sterile site [2]. *N. meningitidis* most commonly exists as a silent nasopharyngeal colonizer but may give rise to localized infections such as purulent conjunctivitis, septic arthritis, and meningococcal pneumonia [1-4]. Less commonly, it may lead to myocarditis, endocarditis, or pericarditis [5]. The infrequency of invasive meningococcal disease, despite high rates of asymptomatic carriage, is largely attributed to the predominance of non-encapsulated strains during colonization. The absence of capsule expression may facilitate immune evasion and enhance persistence within the nasopharynx [6]. Moreover, carriage frequently induces systemic, serogroup-specific bactericidal antibodies, conferring protective immunity and effectively functioning as a natural immunization process [6].

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Currently, invasive meningococcal disease (IMD) remains synonymous with meningitis and/or meningococcemia [7].

It is essential to highlight that even with appropriate treatment, IMD has a mortality rate of approximately 10 %, which can escalate to 80 % in the absence of intervention [8]. Thus, timely recognition is paramount to improving patient survival and clinical outcomes [8]. This is especially important in industrialized nations like the United States, where the low incidence of disease means that physicians may have limited exposure to IMD cases over their careers [8].

1.2. Epidemiology

Meningococcal epidemics have been recognized for over 100 years [5]. The epidemiology of meningococcal disease is characterized by its unpredictability, and it is shaped by both bacterial and environmental factors (e.g., the Santa Ana winds in Baja California), which have been linked to increased disease incidence [7]. The meningococcus capsule determines the serogroup, and of the 12 known serogroups of *N. meningitidis*, 6 (A, B, C, Y, W, and X) are most frequently associated with IMD [9]. However, prevalence varies by geographic region and age group, with the highest rates observed in Africa [7,9]. In Europe, serogroups B and C account for the majority of meningococcal disease cases, while in the Americas, serogroups B, C, and Y are the most prevalent [10]. In Asia and Africa, serogroups A, C, and W135 are the dominant causes of the disease [10]. Serogroups E and Z have also been reported, though they are most commonly observed in immunocompromised patients [11].

Although the incidence of meningococcal disease in the U.S. has historically remained low and overall disease trends have declined since the 1990s, in large part due to widespread vaccination efforts, a significant rise in cases has been observed since 2021, surpassing pre-COVID-19 levels [3,12]. In 2024, a total of 503 confirmed and probable cases were reported in the U.S., representing the highest annual incidence since 2013 [12]. This resurgence has been largely driven by *N. meningitidis* serogroup Y, which has emerged as the predominant cause of recent cases [12]. While meningococcal disease can affect individuals across all age groups, the highest incidence rates occur in infants under 1 year, attributable to immature immune systems and waning maternal antibodies, and in adolescents and young adults aged 16 to 23 years, likely due to increased nasopharyngeal carriage, close-contact behaviors, and social clustering in settings such as college dormitories and military barracks [12]. However, the recent rise in cases has disproportionately impacted adults between the ages of 30 and 60, particularly among African American populations, and individuals with a history of human immunodeficiency virus (HIV) [12].

Currently, three types of meningococcal vaccines are available [13]. The quadrivalent MenACWY vaccine provides protection against serogroups A, C, W, and Y, while the MenB vaccine targets serogroup B [13]. More recently, a pentavalent MenABCWY vaccine has been introduced, covering serogroups A, B, C, W, and Y; however, its use is recommended only in situations where both MenACWY and MenB vaccines are indicated during the same visit [13]. In all other circumstances, MenACWY and MenB vaccines should be administered separately [13]. Meningococcal vaccination is recommended as part of routine adolescent immunization, with a primary dose of MenACWY administered at 11 to 12 years of age, followed by a booster at age 16 [13]. For adolescents and young adults, MenB vaccination should be considered through a shared decision-making discussion; individuals who opt for vaccination should receive a two-dose series spaced six months apart [13]. Additional meningococcal vaccination is recommended for individuals at increased risk, including children between 2 and 10 years of age and adults 19 years or older [13]. High-risk groups comprise those with functional or anatomic asplenia, such as those with sickle cell disease; individuals with persistent complement component deficiencies (C5–C9, properdin, factor H, or factor D); those receiving complement inhibitor therapy, including eculizumab (Soliris®) or ravulizumab (Ultomiris®); and persons living with HIV [13]. Vaccination is also recommended for laboratory personnel who are routinely exposed to *Neisseria meningitidis*, travelers to or residents of regions where the disease is endemic or outbreaks are occurring, military recruits, and first-year college students residing in dormitories who are not up to date with their immunization [13]. For at-risk individuals aged 10 years and older, a three-dose primary series is recommended (second dose at 1–2 months, third dose at 6 months), followed by a booster 1 year after series completion and every 2 to 3 years thereafter [13]. During outbreaks, the CDC recommends a MenACWY booster for at-risk individuals if five or more years have elapsed since their last dose [13].

1.3. Pathophysiology

N. meningitidis is an encapsulated Gram-negative diplococcus with the typical morphology of a bean or kidney shape [2]. *N. meningitidis* is a commensal colonizer of the nasopharynx, with humans the sole natural host [2,14,15]. However, it can also be detected in other anatomical sites, including the anal mucosa, conjunctiva, and urogenital tract [16].

The virulence of invasive *N. meningitidis* is driven by several key factors, including its surface adhesion proteins (i.e., pili), protective capsule, iron sequestration mechanisms, and the release of endotoxin (i.e., lipid A from lipooligosaccharide) [14]. Additionally, the bacterium has evolved genetic adaptations, such as horizontal gene exchange, antigenic variation, and molecular mimicry, which allow it to successfully colonize mucosal surfaces, invade the bloodstream, and evade the immune system [14].

The acquisition of *N. meningitidis* typically occurs through exposure to respiratory droplets [14]. The initial attachment of the bacterium to mucosal surfaces of the upper respiratory tract plays a pivotal role in the establishment of both the human carrier state and the potential development of IMD [14]. The adhesive properties of capsulated *N. meningitidis* are mediated by pili, which allow the bacterium to adhere to epithelial cells in mucosal surfaces [14]. Additionally, the twitching motility, generated by pilus retraction, is crucial for the organism's ability to traverse the epithelial mucus layer, move across epithelial surfaces, and form microcolonies [17].

Once *N. meningitidis* enters the bloodstream, its capsule is critical for survival in the extracellular space as it helps the bacterium evade immune detection and resist both antibody and complement-mediated killing, as well as inhibiting phagocytosis [18]. This ability to escape immune surveillance is partly due to molecular mimicry [14]. The main meningococcal capsular polysaccharides, which are associated with invasive disease, are composed of sialic acid derivatives, with *N*-acetylneuraminic acid (Neu5Ac) being one of the most significant [14,19]. Neu5Ac is the most common form of sialic acid in humans and plays a key role in cellular recognition [19]. By incorporating Neu5Ac into its capsule, *N. meningitidis* can effectively avoid immune system detection and invade its host [14].

Unlike other Gram-negative bacteria, the subcapsular envelope of *N. meningitidis* contains an outer membrane that is primarily composed of lipooligosaccharide (LOS), which lacks a repeating O-side chain [20]. One peculiar virulence factor that *N. meningitidis* possesses is its ability to release vast amounts of surface "blebs" containing LOS, which function as an endotoxin [21]. LOS comprises three principal structural components: lipid A, a core oligosaccharide, and heptose residues [22]. These components contribute to *N. meningitidis* pathogenesis by facilitating adhesion to host cells, evading immune detection through host molecular mimicry and antigenic variation, and inducing an innate immune response via its endotoxin [14]. The pathogenicity and toxicity of meningococcal endotoxin are predominantly attributed to its Lipid A component, which binds to key receptors on monocytic and dendritic cells, including LPS-binding protein (LBP), CD14, and Toll-like receptor 4 (TLR4), activating the innate immune response, which in turn initiates a potent inflammatory response [14,23,24]. This activation leads to the release of cytokines such as tissue necrosis factor alpha (TNF-α),

interleukins (i.e., IL-1, IL-6, and IL-8), reactive oxygen species (ROS), and nitric oxide (NO), which ultimately promote endothelial injury, vascular leakage, coagulation activation, and microvascular thrombosis [14,21,25].

The precise site and mechanism by which *N. meningitidis* enters the CSF remains incompletely defined [26]. However, bacterial adhesion to the meninges and meningeal cells is thought to be a critical step in its dissemination within the meningeal spaces, likely via the venous system, a known point of vulnerability in the blood-brain barrier (BBB) [26]. The bacterium may traverse the BBB through several mechanisms, including passive or adhesion-induced transcytosis, paracellular migration via disrupted tight junctions, direct endothelial injury, or leukocyte-facilitated transport within infected phagocytes (the 'Trojan horse' mechanism) [26]. Electron microscopy studies have demonstrated increased permeability of interendothelial tight junctions as venules transition into veins and exit the brain parenchyma [26]. This suggests that postcapillary venules and veins within the subpial and subarachnoid spaces may represent primary sites for bacterial entry into the CSF [26].

2. Discussion

2.1. Presentation

The diagnosis of invasive meningococcal disease (IMD) necessitates a heightened index of clinical suspicion given its abrupt onset and rapid progression [7].

2.2. Meningococcal meningitis

The initial phase spans the first 6 to 9 h and is marked by nonspecific symptoms that often resemble a flu-like illness [7]. After this early phase, patients may progress to more classical symptoms associated with bacterial meningitis, although no single presenting symptom can reliably distinguish it from other neurologic or infectious conditions [27,28]. Headache is the most common symptom of bacterial meningitis, but other frequently observed features include photophobia, petechiae or purpura, fever, nuchal rigidity, and altered mental status [7,27]. Although symptoms such as nausea, vomiting, and myalgia are often present in central nervous system (CNS) infections, they are considered nonspecific and offer limited diagnostic utility [27,29]. The classic triad of fever, neck stiffness, and altered mental status is observed in only 44–66 % of patients with meningococcal meningitis, highlighting the necessity of maintaining a high index of suspicion even in the absence of these hallmark features [29,30]. However, when headache is added to the triad, 2 out of the 4 symptoms have been found to be present in 95 % of cases [29].

2.3. Meningococcemia

In the case of meningococcemia, fever accompanied by early signs of sepsis and rash is concerning for IMD [8]. Cutaneous manifestations of meningococcemia often begin with petechiae and erythema, which may evolve into purpura fulminans and progress to painful necrotic lesions accompanied by bullae and vesicle formation, which reflects an underlying coagulopathy (Fig. 1) [8,27,31]. Purpura fulminans represents the most severe and often fatal complication of invasive meningococcal disease, with mortality rates approaching 50 % but can be as high as 80 % [5,8,21]. It arises from a massive release of proinflammatory mediators, precipitating septic shock, disseminated intravascular coagulation, and acute adrenal hemorrhage (Waterhouse–Friderichsen syndrome), ultimately culminating in multiorgan failure [5].

IMD is not limited to severe septicemia and meningitis; meningococci can also be isolated from other normally sterile sites, including synovial, pericardial, and pleural fluids [7]. These less common presentations may be underreported, as they often occur alongside or are masked by the more typical forms of the disease [7]. Vascular compromise may occur, which can present as abnormal skin discoloration, cold extremities, and limb pain, particularly in the legs [31]. Special consideration should be given to those with sickle cell disease; immunocompromised states such as HIV, solid organ transplantation, or rheumatological disease, as these patients may be on immunosuppressive therapies; and those with terminal complement pathway (C5–9) deficiencies, as they are at an increased risk [7,27].

2.4. ED evaluation

Initial ED evaluation should focus on patient hemodynamics to identify early indicators of sepsis, such as tachycardia and hypotension. A thorough skin examination is essential in the evaluation of suspected IMD, with particular attention to identifying characteristic rashes. A diffuse petechial rash involving the palms and soles is classically associated with *N. meningitidis* infection, while the presence of a non-blanching hemorrhagic rash is considered pathognomonic for IMD and reflects an underlying coagulopathy [8,27]. The Kernig and Brudzinski signs demonstrate poor sensitivity, but they possess relatively high specificity in the diagnosis of meningitis [32]. Jolt accentuation is another commonly cited physical examination finding; however, recent studies have shown it to be unreliable for either confirming or excluding meningitis [27]. More advanced focal neurological deficits (e.g., motor

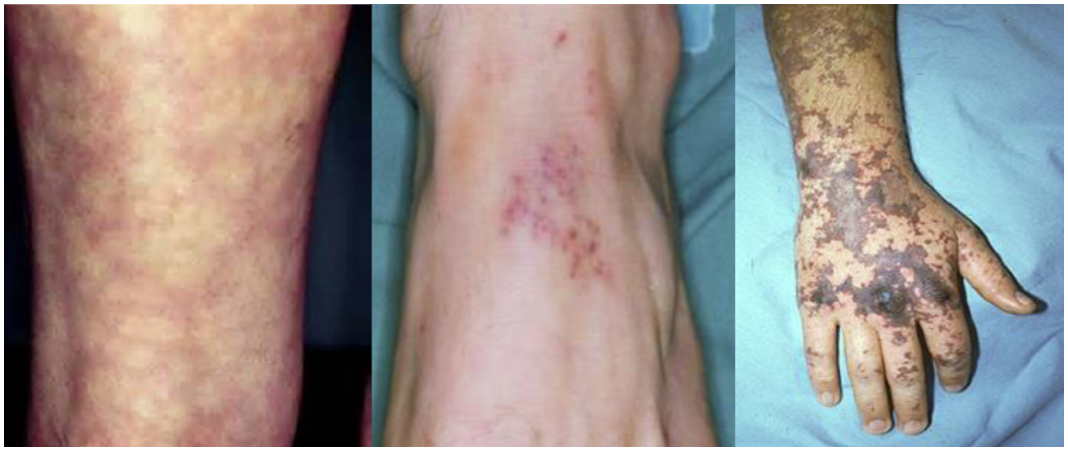

Fig. 1. Mottling, petechiae, and purpura. Reproduced under Creative Commons Attribution-NonCommercial-NoDerivs 3.0 (New Zealand).

weakness, aphasia) indicate involvement of the brain parenchyma and the presence of encephalitis [33].

Lumbar puncture (LP) for CSF analysis remains the key diagnostic test in suspected bacterial meningitis [27]. Adjunctive evaluations should include a complete blood count, metabolic and coagulation panels, C-reactive protein, serum procalcitonin, lactate, and blood cultures [27]. Serum polymerase chain reaction (PCR) demonstrates greater sensitivity than blood cultures, though its utility may be limited by availability and timing of collection [34].

Cross-sectional imaging with computed tomography (CT) lacks sensitivity and specificity in diagnosing meningitis but may aid in excluding alternative intracranial pathologies [8,27]. The primary objective of pre-LP imaging is to identify patients at risk of brain herniation [35]. According to the Infectious Diseases Society of America (IDSA) guidelines, CT should precede LP in patients with altered mental status, focal neurologic deficits, immunocompromised states, a history of CNS disease, recent-onset seizures (within one week), papilledema, or recent head trauma [36,37]. If imaging is necessary, it must not cause delays in antibiotic administration.

2.5. ED management

Hemodynamic support is necessary in those with evidence of meningococcemia, which may include fluid resuscitation and vasopressors [37]. Parenteral antimicrobial therapy, typically with a third-generation cephalosporin such as ceftriaxone or cefotaxime, should be administered as rapidly as possible—preferably within one hour of recognizing IMD [37]. In suspected cases of meningitis where LP cannot be promptly performed, antibiotic therapy, along with adjunctive dexamethasone, must not be delayed and should precede any neuroimaging to minimize treatment delays and optimize patient outcomes [38,39]. Additionally, strict isolation and droplet precautions should be instituted to reduce the risk of healthcare worker exposure and prevent secondary transmission [8]. Early escalation of care to the intensive care unit (ICU) is an integral component of management due to the risk of hemodynamic compromise [8]. Finally, the identification of close contacts for targeted chemoprophylaxis is an essential aspect of comprehensive care in the context of IMD [37].

3. Pearls and pitfalls

3.1. When should the clinician consider meningococcal disease based on the history and examination?

Meningitis and meningococcemia are the most common manifestations of IMD, which may present either independently or in combination [21]. Meningococcemia is associated with a high mortality rate, ranging from 10 to 80 %, compared to 5–18 % for meningococcal meningitis [8,21]. In patients with a sudden onset of fever, early signs of sepsis, rapid disease progression, and rash, clinicians should consider *N. meningitidis* infection [8,27]. The initial 6–9 h of IMD are typically characterized by nonspecific symptoms including fever, chills, muscle aches, nausea, and vomiting, which resemble a flu-like illness [7,8]. This early phase is typically followed by the emergence of more specific features of meningococcal infection, such as those associated with meningitis (e.g., headache, neck stiffness, photophobia, altered mental status) [8,21,40]. However, in approximately 40–70 % of patients with meningococcal disease, the nonspecific symptoms will progress to sepsis due to meningococcemia, characterized by the pathognomonic hemorrhagic petechial or purpuric rash and signs of circulatory collapse resulting in shock with multi-organ failure, which is associated with poor outcomes [8,40].

A non-blanching hemorrhagic rash (i.e., petechiae, purpura) accompanied by fever and signs of sepsis is concerning for meningococcemia. This rash is most prominent in the extremities but may occur anywhere in the body [8,21]. Petechiae or purpura are observed in approximately 50–60 % of patients with meningococcemia, while 20–30 % of children may initially present without any rash, and thus it is crucial to note that a significant number of patients with meningococcemia may not exhibit a rash [21,41].

In the case of meningitis, the classic triad of fever, neck stiffness, and altered mentation is present in 44–66 % of cases, underscoring the importance of maintaining clinical vigilance even in the absence of this hallmark presentation [29,30]. The prevalence rates for fever, neck rigidity, and altered mentation have been reported as 78 %, 73–83 %, and 79–80 %, respectively [27,29]. Headache is the most frequently observed symptom in bacterial meningitis (84–87 % of cases), but when included in the triad, two of the four symptoms have been found to be present in 95 % of cases [27,29]. The detection of at least one of these symptoms exhibits a sensitivity ranging from 99 to 100 % [29]. Conversely, the absence of all four symptoms rules out meningitis [42].

Elevated intracranial pressure (ICP) can be suggested by fluctuating or deteriorating levels of consciousness (e.g., Glasgow Coma Scale ≤8), normal or elevated blood pressure accompanied by a slow or normal heart rate, unequal or dilated pupils that poorly react to light, focal neurologic signs, abnormal posturing, seizures, and papilledema [8].

The Kernig and Brudzinski signs, while highly specific, exhibit poor sensitivity [27]. A 2014 study in ED patients found the Kernig sign to have a sensitivity of 2 % and a specificity of 97 %, while the Brudzinski sign demonstrated a sensitivity of 2 % and a specificity of 98 % [32]. Jolt accentuation, which involves having the patient in a seated position and horizontally rotating their head 2–3 times per second, with a positive result indicated by worsening of the patient's headache, was once thought to outperform the Kernig and Brudzinski signs [27]. However, more recent studies have shown it to be less reliable, with a sensitivity of 21 % and a specificity of 82 % [27]. All three of these physical examination signs have low diagnostic value and are insufficient to rule out meningitis [27].

3.2. What is the EM-focused differential diagnosis for fever with rash?

Fever accompanied by a rash has a broad differential diagnosis, encompassing both common and life-threatening conditions [43]. In the ED, clinical evaluation should prioritize the identification of high-risk or 'can't miss' etiologies that carry the potential for significant morbidity and mortality—many of which can be suspected through a careful history and detailed physical examination [43]. Life-threatening causes of fevers with a rash include meningococcal disease, staphylococcal scalded skin syndrome, toxic shock syndrome (TSS), Steven-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS), acute rheumatic fevers, Ebola virus, and Rocky Mountain spotted fever [43,44]. In the pediatric population, Kawasaki disease and measles should be considered (Table 1) [43,44].

3.3. What are the clues on laboratory testing for meningococcal disease?

Culture techniques remain the diagnostic gold standard for meningococcal disease, though their clinical applicability is often limited by delayed turnaround times [45]. In cases of suspected meningitis, CSF analysis is necessary, as no alternative test can provide equivalent diagnostic accuracy, though several other tests may serve as adjuncts and offer supportive information [27].

3.4. Cerebrospinal fluid

CSF analysis usually includes gram staining, culture, cell count, protein count, and glucose; findings characteristic of bacterial meningitis typically include a polymorphonuclear pleocytosis, reduced glucose concentration (hypoglycorrhachia), and elevated protein levels [46].

CSF Gram stain sensitivity for detecting *N. meningitidis* is variable and may be significantly reduced if the LP is performed after the

Table 1
Common, non-life threatening diagnoses and "can't miss," life-threatening diagnoses.

Type of disease	Diagnoses
Common, Non-life threatening	Viral exanthema Roseola Parvovirus Coxsackievirus (hand, foot, and mouth disease) Varicella Measles Epstein-Barr Virus/Cytomegalovirus Eczema herpeticum Scarlet fever Lyme disease Erythema multiforme Henoch-Schönlein purpura Cellulitis/erysipelas
Life threatening, "can't miss"	Staphylococcal scalded skin syndrome Meningococcal disease (*Neisseria meningitidis*) Toxic shock syndrome Steven-Johnson syndrome/toxic epidermal necrolysis Kawasaki disease Drug reaction with eosinophilia and systemic symptoms (DRESS) Acute rheumatic fever Rocky Mountain spotted fever

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initiation of antimicrobial therapy [44]. Reported sensitivity for CSF Gram stain in acute bacterial meningitis ranges from 60 % to 90 %, while specificity is 97 % to 100 % [38,39].

CSF culture remains the diagnostic gold standard in meningococcal disease, providing definitive identification of the pathogen along with antimicrobial susceptibility profiles [27,45]. However, similar to Gram stain, the diagnostic yield is significantly diminished when LP is delayed until after the initiation of antibiotic therapy [46]. Notably, CSF sterilization can occur within as little as two hours following antimicrobial administration in cases of meningococcal infection [47].

CSF cell counts in meningococcal disease will typically present with an elevated white blood cell (WBC) count, with a predominance of neutrophils, often in the range of 10 to 10,000 cells/μl but usually >100 [27,48,49]. However, low or normal CSF WBC counts do occur, especially early in the disease, in immunodeficient states, and in those with septic shock and systemic complications [27,46]. Nearly all patients with bacterial meningitis have an elevated CSF protein level, with a mean value of 135 mg/dL [39,50]. The CSF to serum glucose ratio has also been evaluated for use in acute bacterial meningitis [27]. The normal CSF to serum glucose ratio is >0.67, but in acute bacterial meningitis, this value is often decreased. Ultimately, this varies depending on the type of pathogen, the time since onset of infection, and the presence of dextrose in any intravenous fluid administered [51]. One study found that using a cutoff point of <0.36 yielded a sensitivity of 95 % [52].

CSF nucleic acid amplification testing, particularly PCR, is increasingly utilized in the diagnosis of bacterial meningitis due to its high sensitivity (87–100 %) and specificity (98–100 %), even when performed several days after the initiation of antibiotic therapy [27,37]. Another useful adjunct is the measurement of CSF lactate levels. Lactate, a byproduct of anaerobic metabolism, accumulates in the CSF in response to bacterial proliferation, cerebral edema, vascular inflammation, and cerebral ischemia [27,50]. Due to its limited ability to cross the blood-brain barrier, CSF lactate concentration is largely independent of serum levels [27,53]. Normal CSF lactate concentrations are <35 mg/dL [27,50]. A threshold of >35.1 mg/dL has demonstrated a sensitivity of 93 % and specificity of 97 % for diagnosing bacterial meningitis when measured prior to antibiotic administration; however, its diagnostic accuracy diminishes following antimicrobial exposure [27,50,54]. Elevated CSF lactate may also occur in fungal or viral infections, as well as in cases of seizure activity, cerebral ischemia, or hemorrhage [27,53,55]. Table 2 outlines the distinguishing features of CSF analysis across bacterial, viral, tuberculous, and fungal etiologies of meningitis.

3.5. Blood tests

A CBC has limited diagnostic specificity [27]. While a systemic inflammatory response may be reflected by leukocytosis with neutrophilic predominance, this finding is nonspecific and may be absent, particularly in the early stages of illness or in immunocompromised or elderly patients [27]. Similarly, liver function tests and coagulation profiles may aid in distinguishing infectious purpura, such as that seen in meningococcemia, from noninfectious hematologic conditions like thrombotic thrombocytopenic purpura [27]. However, in the context of meningitis, these tests do not reliably differentiate between bacterial, viral, or alternative etiologies and offer limited diagnostic utility beyond their supportive role in assessing systemic involvement [27].

CRP is an acute-phase reactant synthesized in response to infectious and inflammatory stimuli [27]. While CRP may aid in the differentiation between bacterial and viral meningitis, its diagnostic accuracy is moderate; levels exceeding 37 mg/L have demonstrated a sensitivity of approximately 85 % and a specificity of 84 % [27,56]. However, its utility is limited in immunocompromised and elderly populations due to impaired acute-phase responses and diminished CRP synthesis [27]. In contrast, PCT serves as a more specific biomarker of bacterial infection [57]. Undetectable in healthy individuals and largely unaffected by viral illnesses, PCT levels begin to rise within four hours of bacterial infection onset, peak at around six hours, and remain elevated beyond 24 h [27,58]. In distinguishing bacterial from viral meningitis, serum PCT concentrations greater than 0.25–0.5 ng/mL have been reported to yield sensitivities ranging from 90 to 95 % and specificities between 98 and 100 % [50,56,58].

Although blood cultures have a relatively slow turnaround time, which limits their immediate utility in the ED setting, they remain an essential component of the diagnostic evaluation and should be obtained —ideally prior to the initiation of antimicrobial therapy—as they provide critical data for guiding downstream treatment [27]. In the case of meningococcal disease, serum PCR testing offers superior sensitivity compared to blood cultures, particularly in patients who have received empiric antibiotics before sample collection [34]. However, the utility of serum PCR is often constrained by limited availability [27]. Serum lactate levels, while commonly elevated in systemic illness, lack specificity; elevations may occur in both bacterial and viral infections as well as in various noninfectious inflammatory conditions [27].

3.6. What is the management of meningococcal disease in the ED, and what are potential pitfalls?

Optimal management of invasive meningococcal disease relies on early recognition, with immediate attention directed toward hemodynamic stabilization and initiating antibiotics [8]. Additionally, in suspected cases of IMD, strict isolation and droplet precautions should be instituted to reduce the risk of healthcare worker exposure and prevent secondary transmission [8].

Delaying antibiotic therapy until the LP is completed is the most common error in the ED management of meningitis [59]. Empiric treatment should begin without delay, preferably within one hour of recognizing IMD and typically includes a third-generation cephalosporin, such as ceftriaxone (2 g intravenous [IV] every 12 h for adults; 50 mg/kg IV every 12 h for children older than 1 month), or cefotaxime (2 g IV every 4–6 h for adults; 50 mg/kg IV every 6 h for children older than 1 month) [8,37]. These agents are favored for their proven efficacy and convenient dosing schedules. Penicillin G (4 million units IV every 4 h for both adults and children older than 1 month) remains an alternative [8]. In patients with severe beta-lactam allergies,

Table 2
CSF features of meningitis.

Parameter	Normal	Bacterial	Viral	Tuberculous	Fungal
Opening pressure	12–20 cm H_2O	Raised	Normal or mildly raised	Raised	Raised
Appearance	Clear	Turbid, cloudy, or purulent	Clear	Clear or cloudy	Clear or cloudy
CSF WCC (cells/μL)	<5	Elevated (>100)	Elevated (5–1000)	Elevated (5–500)	Elevated (5–500)
Predominant cell type	–	Neutrophils	Lymphocytes	Lymphocytes	Lymphocytes
CSF protein (g/L)	<0.4	Elevated	Mildly elevated	Markedly elevated	Elevated
CSF glucose (mmol/L)	2.6–4.5	Very low	Normal or slightly low	Very low	Low
CSF/Plasma glucose ratio	>0.66	Very low	Normal or slightly low	Very low	Low

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chloramphenicol (50 mg/kg IV every 6 h for both adults and children older than 1 month) may be used, although due to its toxicity profile, close therapeutic monitoring is required [8]. Meropenem (2 g IV every 8 h for adults; 40 mg/kg IV every 8 h for children older than 1 month) represents an alternative, particularly in cases of cephalosporin-resistant bacterial meningitis or when multidrug-resistant pathogens are suspected [8,60].

Given that the causative organism is often not immediately identified in the ED, empirical coverage is necessary. In regions where penicillin-resistant *Streptococcus pneumoniae* is prevalent—which includes most developed countries—vancomycin (20 mg/kg IV every 8 h for adults; 20 mg/kg IV every 6 h for children older than 1 month) should be added when ceftriaxone resistance exceeds 1 % [8,61].

Immunocompromised patients—including those with HIV/AIDS, solid organ transplants, or those receiving immunosuppressive therapy, as well as neonates, individuals over the age of 50, and pregnant women —require expanded empirical coverage due to their increased risk for atypical and opportunistic pathogens [27]. Empiric antimicrobial regimens in these individuals should include agents active against *Listeria monocytogenes,* and in some cases, *Pseudomonas aeruginosa* [27]. Ampicillin remains the treatment of choice for L. *monocytogenes*, whereas cefepime (2 g IV every 8–12 h for adults; 2 g IV every 12 h for children older than 1 month) or an antipseudomonal carbapenem such as meropenem (2 g IV every 8 h for adults; 40 mg/kg IV every 8 h for children older than 1 month) should be used to cover *P. aeruginosa* [8,27]. Importantly, meropenem also demonstrates activity against L. *monocytogenes*, obviating the need for additional ampicillin when this agent is employed [61]. In cases of suspected viral infection with clinical signs of acute encephalitis, including focal neurological deficits indicative of brain parenchymal involvement, empiric treatment with acyclovir should be initiated [27,48]. Patients with suspected cryptococcal meningitis require treatment with amphotericin B liposomal and flucytosine, but due to the toxicity profile of these medications, they should only be initiated in consultation with an infectious disease specialist [27,62]. Table 3 provides a summary of the antimicrobial agents discussed above for empiric and targeted management of IMD.

The management of sepsis or septic shock necessitates prompt intravenous fluid resuscitation and, when indicated, vasopressor support – most commonly with norepinephrine [37]. In patients exhibiting signs of disseminated intravascular coagulation, treatment may involve aggressive hydration, blood product transfusions, platelet replacement, and, in select cases, coagulation factor administration [63,64].

3.7. Adjunctive therapies

Corticosteroids reduce inflammation by downregulating pro-inflammatory genes, limiting leukocyte recruitment, stabilizing lysosomal membranes, and temporarily restoring the BBB integrity, as well as interacting with DNA recognition sites to activate the transcription of anti-inflammatory genes [65]. One proposed mechanism by which *N. meningitidis* crosses the BBB involves its adhesion to endothelial cells, which triggers intracellular signaling pathways that disrupt intercellular tight junctions, thereby permitting paracellular migration of the bacteria into the CNS [26]. Animal studies have shown that dexamethasone upregulates tight junction proteins (i.e., ZO-1 and occludin) thus reinforcing the BBB via tightening endothelial tight junctions [66].

In the case of bacterial meningitis due to *Streptococcus pneumoniae* and *Haemophilus influenzae,* high-dose corticosteroids are the only adjunctive therapy that has been shown to have mortality benefits and decrease the incidence of hearing loss and other neurological sequelae when given at the same time as the first dose of antibiotics [8,61]. However, the benefit of adjunctive dexamethasone in meningococcal meningitis remains uncertain. While some studies suggest it does not significantly improve clinical outcomes, others have reported trends toward improved outcomes with corticosteroid therapy in this population [65,67]. Currently, the most widely recommended guideline-based

Table 3
Antimicrobial regimens.

Indication/Pathogen	Antibiotic/Antiviral	Adult dose	Pediatric dose (>1 month)	Notes/Considerations
Empiric treatment of IMD	Ceftriaxone	2 g IV every 12 h	50 mg/kg IV every 12 h	Preferred empiric agent; broad-spectrum, convenient dosing
	Cefotaxime	2 g IV every 4–6 h	50 mg/kg IV every 6 h	Equivalent to ceftriaxone
	Penicillin G	4 million units IV every 4 h	Same as adult dose	Alternative for penicillin-sensitive strains
	Chloramphenicol	50 mg/kg IV every 6 h	50 mg/kg IV every 6 h	For beta-lactam allergy; requires toxicity monitoring
	Meropenem	2 g IV every 8 h	40 mg/kg IV every 8 h	Covers MDR pathogens and L. *monocytogenes*
Suspected resistant *S. pneumoniae*	Vancomycin	20 mg/kg IV every 8 h	20 mg/kg IV every 6 h	Add if cephalosporin resistance >1 %; monitor trough levels
Listeria monocytogenes	Ampicillin	2 g IV every 4 h	100–200 mg/kg/day in divided doses	Drug of choice for *Listeria*
	Meropenem	2 g IV every 8 h	40 mg/kg IV every 8 h	Covers L. *monocytogenes*, eliminates need for ampicillin
Pseudomonas aeruginosa	Cefepime	2 g IV every 8–12 h	2 g IV every 12 h	Preferred in immunocompromised hosts
	Meropenem	2 g IV every 8 h	40 mg/kg IV every 8 h	Antipseudomonal activity; dual *Listeria* coverage
Suspected viral encephalitis	Acyclovir	10 mg/kg IV every 8 h	10 mg/kg IV every 8 h	Initiate if focal neurologic signs or suspicion for HSV
Cryptococcal meningitis	Liposomal Amphotericin B	3–4 mg/kg IV once daily	3–4 mg/kg IV once daily	Start under infectious disease supervision
	Flucytosine	25 mg/kg PO four times daily	25 mg/kg PO four times daily	Used in combination with amphotericin; monitor renal/hepatic function

regimen includes administering dexamethasone at 0.15 mg/kg (up to a maximum of 10 mg) IV every 6 h at the same time as the first dose of IV antibiotics as part of initial empiric treatment [8,27,37,39,68]. The timing of dexamethasone administration is important; it should be given up to 15–20 min before or concurrently with the first dose of antibiotics [27]. Administering corticosteroids after the initiation of antibiotics may fail to attenuate the inflammatory cytokine surge triggered by bacterial lysis, thereby missing the critical window to prevent neurological complications such as cerebral edema, raised ICP, and sensorineural hearing loss [69]. This diminished therapeutic effect may be further compounded by corticosteroid-induced upregulation of tight junction proteins and their subsequent reinforcement of the BBB, potentially impairing antibiotic penetration into the CSF and increasing the risk of treatment failure [70]. Although corticosteroids may adversely affect outcomes in infections such as *Listeria monocytogenes* or *Cryptococcus neoformans*, empiric administration in immunocompetent patients with suspected bacterial meningitis is generally recommended [27,68,71]. This recommendation is due to the difficulty in identifying a causative pathogen within the first hour of presentation and the relative rarity of these atypical infections [27,71]. Approximately 75–80 % of acute bacterial meningitis cases are caused by one of three primary meningeal pathogens – *Streptococcus pneumoniae*, *Neisseria meningitidis*, and *Haemophilus influenzae* – for which adjunctive corticosteroid therapy is considered safe [71]. Therefore, the potential benefit of treating bacterial meningitis outweighs the risk of inadvertently treating a patient with listerial or cryptococcal meningitis [27]. There is insufficient evidence to support the routine use of dexamethasone in reducing complication rates in the treatment of meningitis in older adults (above age 60) [72]. Adjuvant dexamethasone therapy should be avoided in specific populations, including children younger than 6 weeks, immunocompromised or debilitated individuals, patients with nosocomial or CSF shunt–associated meningitis, and those with comorbidities such as diabetes mellitus or chronic alcoholism [71,73]. High-dose corticosteroid therapy is contraindicated in cases of meningococcal septicemia with shock in the absence of meningitis, as evidence suggests it may worsen outcomes in adults with septic shock [74].

Lastly, although mild ICP elevation frequently accompanies meningococcal meningitis, significantly raised ICP is uncommon [8]. The underlying mechanism involves meningeal inflammation and capillary leak, which contribute to cerebral edema [8]. Therapeutic hypothermia is believed to reduce cerebral oxygen demand, thus decreasing the effect of hypoperfusion on edema whereas osmotic agents – such as hypertonic saline, mannitol, glycerol, and sorbitol – are theorized to reduce ICP by creating an osmotic gradient that shifts fluid from the extracellular space into the intravascular space [27,75,76]. However, the effectiveness of osmotic agents relies on an intact BBB, which is typically compromised in bacterial meningitis [75,76]. Studies evaluating these adjunctive therapies in bacterial meningitis have shown no clinical benefit, and in some cases, were terminated early due to concerns over increased mortality [75,76]. As a result, current guidelines do not recommend their routine use [27]. Some experts suggest that adjusting mean arterial pressure (MAP) to support cerebral perfusion and elevating the head of the bed to 30 degrees may be beneficial [28]. In certain cases, CSF drainage – either through serial LPs or placement of a lumbar drain by a neurosurgical specialist – has been considered, although evidence supporting these interventions is limited [28].

3.8. Chemoprophylaxis of close contacts

All individuals who have had close contact with a patient diagnosed with IMD should receive prophylactic antibiotic therapy, regardless of their prior immunization status against meningococcus [8]. Close contact is defined as prolonged proximity to the patient – typically more than 4 h within the preceding 7 days – and includes household members, college roommates, military recruits in shared living spaces, individuals in daycare settings, and healthcare workers with unprotected exposure to respiratory secretions, such as during intubation or cardiopulmonary resuscitation without appropriate respiratory protection [37,63]. Recommended prophylactic regimens include rifampin (5 mg/kg orally every 12 h for 2 days for infants under 1 month; 10 mg/kg, maximum 600 mg, every 12 h for 2 days for individuals older than 1 month), ceftriaxone (125 mg intramuscularly as a single dose for those under 15 years; 250 mg intramuscularly as a single dose for those 15 years and older), or ciprofloxacin (20 mg/kg, maximum 500 mg, orally as a single dose, for individuals over 1 month of age) [8].

3.9. What are the major complications?

Even with appropriate treatment, IMD has significant mortality [8]. Immediate complications among patients with meningococcal disease include spreading purpura culminating in purpura fulminans with septic shock and multiorgan failure, seizures, hydrocephalus, cerebral venous sinus thrombosis, and subdural empyema [37]. Post-infection sequelae affect 11–19 % of survivors of IMD [77]. Among these, hearing loss and amputations are observed in 3 % of cases [78]. Other long-term complications of IMD include chronic pain, skin scarring, arthritis, and neurologic impairment, which can range from hearing and visual deficits to motor dysfunction and seizures [5,63]. Some survivors experience post-infection inflammatory syndrome [8]. Additionally, up to one-third of survivors of meningococcal disease experience psychological disorders such as post-traumatic stress disorder, anxiety, and depression [8].

In the pediatric population, IMD poses a significant diagnostic challenge due to its diverse and often non-specific clinical presentation [79]. A narrative review of 184 pediatric IMD cases and case series reported that the most common symptoms were fever (78.1 %), vomiting (36.5 %), rash (30.7 %), headache (24.1 %), and petechiae (14.6 %) [79]. Atypical presentations with gastrointestinal symptoms were also observed, particularly in cases caused by serogroup W [79]. The same review identified the most frequent complications as death (14.6 %), multiorgan failure (6.4 %), disseminated intravascular coagulation (DIC) or coagulopathy (5.3 %), amputation (5.3 %), seizures (3.5 %), chronic meningococcemia (2.9 %), and adrenal hemorrhage consistent with Waterhouse–Friderichsen syndrome (2.3 %) [79]. Thus, emergency clinicians should maintain a high index of suspicion for IMD in any unwell neonate, infant, child, or adolescent as it is not uncommon to be initially misdiagnosed due to non-specific signs and symptoms [79]. In particular, IMD should be strongly considered in pediatric patients presenting with fever and petechiae, as morbidity and mortality remains high in cases of severe meningococcemia, even with early intervention [80].

Table 4 provides pearls for evaluating and managing IMD.

4. Conclusion

IMD is a severe, rapidly progressive infection caused by *N. meningitidis*, associated with high morbidity and mortality. Suspected cases warrant immediate implementation of droplet precautions and strict isolation to reduce the risk of healthcare worker exposure and secondary transmission. Timely initiation of treatment, ideally within one hour of suspicion, is critical and includes administration of corticosteroids before or with the first dose of empiric parenteral antibiotics, typically a third-generation cephalosporin such as ceftriaxone or cefotaxime. Patients with meningococcemia and shock require aggressive fluid resuscitation, vasopressor support as indicated, and prompt admission to a critical care setting. All close contacts of confirmed cases should receive chemoprophylaxis, regardless of their meningococcal immunization status.

Table 4
Summary of pearls for IMD.

- The clinical presentation of IMD varies, but its most severe forms include meningococcemia, meningitis, or a combination of both.
- Meningococcal disease can affect individuals across all age groups; the highest incidence rates are observed in children under 1 year of age and in adolescents and young adults aged 16 to 23 years.
- Meningococcemia carries a markedly higher mortality rate, ranging from 20 % to 80 %, compared to 5 % to 18 % for meningococcal meningitis.
- The initial phase is marked by non-specific symptoms that often resemble a flu-like illness, but the presence of a non-blanching rash, fever, and signs of sepsis should prompt suspicion of IMD and immediate initiation of parenteral antibiotic therapy.
- The Kerning, Brudzinski, and jolt accentuation tests have low sensitivity and should not be used to rule out meningitis.
- All suspected cases of IMD require strict isolation and droplet precautions to prevent secondary transmission.
- Parenteral antibiotics should ideally be started within one hour of recognizing IMD and should precede all neuroimaging studies and even the LP if there are expected delays.
- Delaying antibiotic therapy until the LP is completed is the most common error in the ED management of meningitis.
- Dexamethasone should be administered at the same time as the first dose of parenteral antibiotics as part of initial empiric treatment but should be avoided in specific patient populations.
- All individuals who have had close contact with a patient diagnosed with IMD should receive prophylactic antibiotic therapy, regardless of their prior immunization status against meningococcus.

CRediT authorship contribution statement

Mounir Contreras Cejin: Writing – review & editing, Writing – original draft, Visualization, Validation, Resources, Conceptualization. **Alex Koyfman:** Writing – review & editing, Visualization, Validation, Supervision, Resources, Conceptualization. **Brit Long:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Resources, Conceptualization.

Declaration of competing interest

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