

# Severe Meningococcal Infection

## A Review of Epidemiology, Diagnosis, and Management

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### KEYWORDS

- *Neisseria meningitidis* • Meningococcus • Meningococcal infection • Sepsis
- Diagnosis • Antimicrobial therapy

### KEY POINTS

- Severe meningococcal infection manifests as meningitis, primary bloodstream infection, or, less commonly, as a primary localized infection such as within the respiratory tract.
- The low incidence of meningococcal infection in high-income countries challenges the diagnosis during the early phase of disease, before the development of a severe, invasive infection.
- Early (<1 hour after presentation) antimicrobial therapy is paramount to the survival of patients with a severe meningococcal infection, and therapy should not be withheld while awaiting the results of diagnostic studies.
- Proper prevention of infection and measures of control are required for patients suspected of being infected with *Neisseria meningitidis*, and chemoprophylaxis is warranted for exposed close contacts.

Invasive infections caused by *Neisseria meningitidis*, commonly known as meningococcus, are associated with significant morbidity and mortality. Among patients admitted to the intensive care unit, this organism presents as meningitis, primary bloodstream infection (or meningococemia), or localized infection.<sup>1</sup> Although the

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incidence of invasive meningococcal infection in high-income countries may be decreasing because of efficacious vaccination programs, a review of meningococcal sepsis is pertinent to critical care practitioners, as timely recognition and appropriate antimicrobial and supportive therapy can alter the course of this rapidly progressive disease. This article reviews the epidemiology, as well as diagnostic and therapeutic interventions for severe meningococcal infections.

## **PATHOGENESIS**

Invasive meningococcal disease typically develops within 2 weeks of colonization of the pharyngeal mucosa.<sup>2</sup> Several factors promote bacterial invasion into the host cell. Type IV pili provide for a twitching motility that allows the bacterium to penetrate through the mucus layer down to the epithelium.<sup>3</sup> Neisserial pili and opacity proteins then bind to epithelial surface proteins, inducing cytoskeletal rearrangement and phagocytosis of the bacterium.<sup>3,4</sup> Exocytosis then allows *N meningitidis* to enter the bloodstream, where rapid bacterial growth (doubling time of approximately 30 minutes) leads to a high burden of bacteremia and facilitates entry of the organism into other sterile compartments (eg, central nervous system [CNS]).<sup>5</sup> At this point *N meningitidis* also releases its endotoxin, lipo-oligosaccharide, in the form of membrane blebs into the bloodstream, which activates proteins involved in inflammation and thrombosis, subsequently promoting multisystem organ failure.<sup>6-8</sup>

## **EPIDEMIOLOGY**

Humans are the only reservoir for meningococcus, and transmit this organism by way of droplets and close contact.<sup>9</sup> The carrier rate among a randomly selected population of individuals is approximately 10% with a peak of 24% during adolescence, likely attributable to increased social mixing.<sup>10-13</sup> Carrier rates are highest within close-knit populations such as college dormitories and military barracks.<sup>14,15</sup>

Invasive meningococcal disease generally occurs within the first 2 weeks following colonization before the development of immunity, with most patients experiencing either meningitis (approximately 50%) or primary bloodstream infection (approximately 40%).<sup>1,16</sup> Other less commonly observed localized infections associated with *N meningitidis* include pneumonia, pericarditis, endocarditis, supraglottitis, conjunctivitis, urethritis, and otitis media.<sup>1,17-22</sup> Fortunately, the incidence of meningococcal infection in high-income countries is low (from <1 to 5 cases per 100,000 people), with a bimodal distribution peaking in children younger than 4 years and teenagers between 15 and 19 years old.<sup>1,23-26</sup> However, during epidemics in low-income countries throughout the "meningitis belt" in sub-Saharan Africa, the incidence can reach as high as 1000 cases per 100,000 people.<sup>27</sup> Most meningococcal infections are caused by 1 of 5 serogroups (classified according to capsular polysaccharide type), namely serogroups A, B, C, W-135, and Y.<sup>28</sup> Serogroups B, C, and Y are responsible for most infections in North America and Europe, whereas serogroup A continues to be responsible for major epidemics in African countries.<sup>1,28</sup> For example, during a 1996 outbreak of serogroup A meningococcus in Nigeria, there were more than 100,000 suspected infections resulting in 11,711 deaths.<sup>27</sup>

Newer molecular biology techniques, including multilocus sequence typing and multilocus enzyme electrophoresis, have facilitated identification of hyperinvasive strains of *N meningitidis* that contribute little to colonization rates, but account for the majority of invasive disease.<sup>29,30</sup> A study that included more than 600 meningococcal isolates demonstrated that multilocus sequence type 11 (ST-11) comprised 30% of invasive versus 3% of noninvasive isolates.<sup>31</sup> In addition to the virulence of

individual strains, host defense mechanisms also regulate the probability of developing an invasive meningococcal infection (**Box 1**). Humoral immunity via specific antibodies is likely the most important host defense mechanism. Evidence in support of this hypothesis stems from the timing of the epidemiologic peak in the rate of meningococcal infection among infants (ie, during the period between passive maternal immunization and active immunity acquired from meningococcal carriage),<sup>32</sup> and the decreased incidence of serogroup C following the widespread use of serogroup C vaccines.<sup>33</sup> A functional spleen also confers protection against invasive meningococcus disease, and patients with functional or anatomic asplenia are at significantly increased risk.<sup>34</sup> Additional risk factors for the development of a severe meningococcal infection include environmental exposure to *N meningitidis*, such as among health care workers<sup>35</sup> or household contacts of infected cases,<sup>36</sup> and other immune system deficits such as late complement deficiencies or infection with the human immunodeficiency virus (HIV).<sup>37,38</sup>

Although the incidence of meningococcal infections is decreasing in high-income countries, infection with *N meningitidis* is associated with a high case fatality rate of approximately 7% to 11%,<sup>1,23</sup> with an increase in the risk for death in those patients older than 50 years and in those who manifest purpura fulminans.<sup>1,39–42</sup> Perhaps somewhat contrary to clinical intuition, nonfocal meningococcemia is associated with a higher case fatality rate than meningococcal meningitis, even when the latter is associated with bacteremia.<sup>40</sup> Among those that survive this severe infection the morbidity is high, because of tissue loss and amputation from disseminated intravascular coagulation and purpura fulminans and neurologic deficits in those with meningitis. A review of 258 cases of adult meningococcal meningitis found that 8% of patients suffered from hearing loss at hospital discharge and an additional 3% had other cranial nerve palsies.<sup>39</sup> In addition to these focal neurologic deficits, follow-up examination of the 76 adult patients with meningococcal meningitis in the European Dexamethasone Study (EDS)<sup>43</sup> and Dutch Meningitis Cohort<sup>42</sup> found cognitive impairment among 21 patients (28%) compared with only 5 of the healthy controls (6%).<sup>44</sup>

**Box 1****Risk factors for invasive meningococcal disease**

## 1. Environmental

- Contact with an incident case (household, health care provider)
- Crowded living quarters (college dormitory, military barracks)
- Employment in a microbiology laboratory that handles *N meningitidis*
- Smoking

## 2. Host-related

- Lack of immunity to *N meningitidis*
- Asplenia
- Late complement deficiency: C<sub>5-9</sub>, properdin, complement factor H
- HIV
- Hypogammaglobulinemia

Data from Refs. <sup>14,15,34–38,102–104</sup>

## CLINICAL FEATURES

Most patients infected with *N meningitidis* present with acute illness; however, there are rare reports of chronic meningococemia characterized by fever, rash, and arthralgias.<sup>16</sup> Early symptoms reported by patients with meningococcal meningitis and/or meningococemia are outlined in **Table 1**. These symptoms are often nonspecific (eg, fever, headache, malaise) and challenge the early diagnosis of a meningococcal infection. Furthermore the classic triad of fever, meningismus, and altered mental status is observed in only one-third of patients with meningococcal meningitis at presentation.<sup>39</sup> Although the characteristic petechial rash is a more specific finding, it is observed in only 45% to 65% of cases at presentation.<sup>39,40</sup> In an effort to delineate additional clinical features to facilitate early diagnosis, a recent retrospective study of children with meningococcal infection revealed that leg pain, cold extremities, and abnormal skin color preceded, or were concurrent with, the classic signs of rash, meningismus, and altered mental status<sup>45</sup>; however, the sensitivity and specificity of these signs have yet to be validated in a prospective study. Other classic signs of meningismus such as those described by Kernig and Brudzinski have high specificity (>90%) but low sensitivity (10%), and thus cannot be used to rule out meningitis.<sup>46</sup> Although accentuation of a headache provoked by horizontal rotating of the head at a frequency of 2 to 3 Hz (ie, jolt accentuation) has been cited as a more useful test for ruling out meningitis, the sensitivity reported in the original study (100%)<sup>47</sup> was not replicated in a more recent study where the test performed poorly, with a sensitivity of only 6%.<sup>46</sup> Finally, although up to one-quarter of patients with meningococcal meningitis have focal neurologic deficits (eg, aphasia, cranial neuropathies), these are also late findings, and their absence cannot be used to rule out a diagnosis of meningitis.<sup>39</sup>

Although many of the initial clinical features of meningococcal infections are nonspecific, the clinical course of a patient with a severe meningococcal infection is well characterized by rapidly progressive disease, which may progress to multisystem organ failure and death. Severe cases are also marked by a petechial rash, and may be complicated by extremity amputation secondary to purpura fulminans, disseminated intravascular coagulation (DIC), and thromboses. This distinctive petechial rash occurs as a result of endotoxin-induced damage to endothelial cells and attendant thrombosis, necrosis, and eventually dermal hemorrhage, ultimately resulting in purpura fulminans.<sup>48</sup> Although the petechial rash is a characteristic finding in patients

**Table 1**  
Clinical features of invasive meningococcal disease at presentation

Finding at Presentation	Frequency (%)
Fever	92–93
Headache	45–81
Nausea/vomiting	53–77
Rash	45–78
Neck stiffness	35–71
Leg pain	37–65
Altered level of consciousness	27–45
Photophobia	28–30
Abnormal skin color	19

Data from Refs.<sup>40,42,45,105</sup>

with severe disease, a similar rash may also be observed in other febrile conditions such as Rocky Mountain spotted fever, severe DIC (due to other causes), thrombotic thrombocytopenic purpura, Henoch-Schönlein purpura, and other vasculitides.

Altered mental status is common among patients with an invasive meningococcal infection, and is often a result of the interaction of multiple factors such as meningeal inflammation, sedative medications, and metabolic derangements. However, intracranial hypertension, stroke (ischemic or hemorrhagic), seizures, and vasculitic brain infarction may complicate severe meningococcal infection.<sup>49–51</sup> Refractory hypotension is also common and is generally a consequence of vasodilation from septic shock; nonetheless, pericarditis and cardiac tamponade may result from primary meningococcal infection of the pericardium, disseminated meningococcal disease with malignant spread to the pericardium, or an immune-mediated reactive phenomenon.<sup>17</sup> *N meningitidis* accounts for up to one-fifth of cases of purulent pericarditis.<sup>17</sup> Therefore, examination for features of cardiac tamponade and an echocardiogram may aid in the management of patients with hypotension and severe meningococcal infection. Adrenal insufficiency from adrenal hemorrhage (Waterhouse-Friderichsen syndrome) may manifest with refractory hypotension, metabolic acidosis, and hyperkalemia, and may require treatment with supplemental mineralocorticoids.

Multiple clinical and laboratory features have been studied for the prognostication of invasive meningococcal infection. The main prognostic scoring systems for invasive meningococcal disease have generally been developed and validated in children, and thus should not be extrapolated to predict outcomes in adults. Therefore, aside from general risk prediction models such as the APACHE (Acute Physiology and Chronic Health Evaluation)<sup>52</sup> and SOFA (Sequential Organ Failure Assessment)<sup>53</sup> scores, well-validated prognostic models specific to meningococcal disease are not currently available.

## DIAGNOSIS

*N meningitidis* should be suspected as a pathogen in any patient presenting with signs and symptoms of meningitis, a febrile illness with a petechial rash, a nonspecific febrile illness in patients with risk factors such as splenectomy, or high-risk groups in the setting of an outbreak. Because of the invasive and fulminant nature of this disease, the need for early treatment often mandates the concomitant administration of antimicrobials with diagnostic testing. Case series have indicated that typically, less than one-third of adult patients with bacterial meningitis receive antibiotics before the full diagnostic workup.<sup>39,42</sup> However, delaying antimicrobial therapy while awaiting the results of diagnostic tests is associated with worse outcomes for patients with invasive meningococcal disease, and should be avoided.<sup>54</sup>

Given that blood cultures are positive in only half of the patients with meningococcal meningitis,<sup>39</sup> patients with suspected meningitis require an analysis of the cerebrospinal fluid (CSF) obtained via lumbar puncture (LP). However, this test is also the most controversial of those performed in patients suspected of having meningitis. It is infrequently performed in a timely manner because of coagulopathy of sepsis and DIC, as well as the perceived risk of cerebral herniation associated with drainage of CSF in patients with meningitis. The risk of cerebral herniation from lumbar puncture among all patients with bacterial meningitis is roughly 1 in 20,<sup>55</sup> and nearly one-third of deaths in children with meningitis are thought to represent a herniation event.<sup>56</sup> Therefore, as a result of this valid concern, a computed tomography (CT) scan of the brain is often obtained to assess for evidence of intracranial mass effect before performing an LP. However, CT scans are unnecessary for all patients and a more

appropriate approach is to individualize the decision to perform a CT scan based on the patient's risk profile. A prospective observational study by Hasbun and colleagues<sup>57</sup> found that the CT scan was normal in 93 of 96 patients without any baseline clinical risk factors for an intracranial mass (negative predictive value of 97%). The baseline clinical predictors for an abnormal finding on the CT scan included age 60 years and older, immunocompromise, history of CNS disease, history of a seizure within 1 week before presentation, altered mental status, and a focal neurologic finding.<sup>57</sup> The 3 patients without any of the aforementioned risk factors found to have an abnormal CT scan underwent LP, none of whom experienced an episode of cerebral herniation. Therefore, the Infectious Diseases Society of America (IDSA) supports the use of a CT scan of the brain before LP in patients with immune impairment, a history of CNS disease, altered mental status, papilledema, focal neurologic deficits, or seizures.<sup>58</sup> The IDSA recommends that patients without these risk factors generally do not require a CT scan before LP.<sup>58</sup>

The CSF in patients with meningococcal meningitis has a similar appearance to that in patients with other forms of bacterial meningitis. The median leukocyte count is 1200/ $\mu$ L with a neutrophilic predominance; the median protein concentration is 1.5 g/L, and 75% have a glucose level of less than 2.2 mmol/L.<sup>59</sup> When CSF is obtained before the initiation of antibiotics, the Gram stain is positive in about 90% of samples, and the culture has a sensitivity of greater than 90% (Table 2).<sup>39</sup> However, appropriate antibiotic therapy has been shown to sterilize the CSF in as little as 15 minutes, and one study found that the CSF culture was negative among all patients in whom the LP was performed 2 or more hours after antimicrobial administration.<sup>60</sup> Newer microbial identification techniques such as those that use the polymerase chain reaction (PCR) may improve the yield of CSF analysis. Several studies report the sensitivity for a PCR-based CSF analysis that approaches 100%.<sup>61–63</sup> PCR-based techniques also do not depend on the presence of viable bacteria, and may help in patients for whom there was a delay in obtaining the CSF sample.<sup>61</sup> In addition, the results of PCR-based tests are available after a few hours of testing, whereas traditional culture methods often require days of incubation. Unfortunately, PCR-based bacterial identification is unable to test antimicrobial sensitivity as is currently performed by traditional culture methods. Nonetheless, rapid microbial identification despite a delay in CSF sampling makes PCR-based analysis an attractive addition to the workup of patients with suspected meningitis.

Meningococcus can also be isolated from a biopsy of skin lesions. Although the sensitivity of this test is poor (34%–47%), skin cultures are positive up to 13 hours following the administration of antibiotics, and the Gram stain can identify *N meningitidis* up to 45 hours after antimicrobial treatment.<sup>64,65</sup> Moreover, one study reported that a definitive diagnosis of *N meningitidis* infection was made via the results of skin culture in 12% of patients for whom blood and CSF cultures were negative.<sup>64</sup>

**Table 2**

**Sensitivity of microbiologic testing in meningococcal sepsis and meningitis**

Clinical Syndrome	Sensitivity (%)				
	Blood Culture	Skin Culture	CSF Culture	CSF Gram Stain	Skin Gram Stain
Sepsis	93	34–47	59	N/A	80
Meningitis	57		94	89	

*Abbreviations:* CSF, cerebrospinal fluid; N/A, no data available.

*Data from Refs.*<sup>39,76,106</sup>

Although skin culture will not add to the diagnostic workup in all patients with meningococcal disease, the results of this study suggest that skin culture may add considerably to the workup of patients from whom the CSF sample was obtained several hours following antimicrobial administration.

Given the severity of invasive disease, clinicians should maintain a low threshold for diagnosing meningococcal infections. A complete set of investigations should include blood and CSF cultures with or without PCR-based analysis. A CT scan of the brain may be required in select patients with risk factors for intracranial mass effect before obtaining CSF via an LP; however, this does not need to be performed in all patients suspected of having meningitis. PCR-based microbial techniques may improve the sensitivity of CSF cultures in the future; however, this methodology is not routinely used in all microbiology laboratories.

### ANTIMICROBIAL MANAGEMENT

Given the short doubling time and fulminant course induced by *N meningitidis*, the most important therapy provided to patients suspected of having a severe meningococcal infection is early, appropriate intravenous antimicrobial therapy.<sup>66</sup> Most guidelines and expert opinion support the administration of antimicrobials within 1 hour of presentation. Anyone thought to have a severe meningococcal infection should have blood cultures drawn, LP performed, and appropriate intravenous antibiotics administered within 1 hour of presentation. Patients who require a CT scan of the brain before an LP should receive antibiotics after blood cultures are drawn and before the CT scan. Unfortunately, case series have suggested that as little as 15% of patients with invasive meningococcal disease receive antibiotics within 1 hour of presentation to hospital.<sup>67</sup> As patients with meningococcal infection generally present with a nonspecific syndrome of sepsis or meningitis, the initial antimicrobial regimen is typically broad, with coverage for other common community-acquired causes of sepsis and CNS infection, most notably *Streptococcus pneumoniae* and *Haemophilus influenzae*. There is a broad differential diagnosis for CNS infections that may require other investigations and management, but a detailed description of this is beyond the scope of this review. The principle of antibiotic selection and administration is that high doses of intravenous agents that penetrate the blood-brain barrier should be used to cover the likely pathogens. A typical regimen for patients presenting with a syndrome of community-acquired meningitis includes ceftriaxone at a dose of 2 g every 12 hours to cover *N meningitidis*, *S pneumoniae*, and *H influenzae*, and vancomycin at a dose of 15 mg/kg to cover for potential  $\beta$ -lactam-resistant strains of *S pneumoniae*. A clinical suspicion of herpes simplex virus or *Listeria monocytogenes* infection mandates the addition of acyclovir or ampicillin to this regimen, respectively.

On recovery of meningococcus from blood or CSF cultures, penicillin G at a dose of 4 million units every 4 hours is an acceptable alternative to ceftriaxone.<sup>58</sup> However, this depends on the reported sensitivity of the given strain of *N meningitidis*, as penicillin resistance (via alteration of penicillin binding proteins) is an increasingly common finding.<sup>68</sup> The number of meningococcal isolates with intermediate susceptibility to penicillin (minimum inhibitory concentration [MIC] 0.12–0.25  $\mu\text{g}/\text{mL}$ ) ranges from 5% to 41%.<sup>68–70</sup> On the other hand, complete resistance to penicillin (MIC > 0.5  $\mu\text{g}/\text{mL}$ ) is rare,<sup>71</sup> and meningococcus seems uniformly susceptible to third-generation cephalosporins.<sup>69,70</sup> Despite the severity of invasive meningococcal infections, treatment with intravenous antibiotics for 7 days is all that is required to affect a clinical cure with highly susceptible strains.<sup>58</sup>

## SUPPORTIVE CARE

In addition to early, appropriate antimicrobial therapy, other adjunctive therapeutic strategies may improve patient outcomes. These approaches include prompt resuscitation,<sup>72</sup> dexamethasone for those with a presenting syndrome of undifferentiated meningitis,<sup>73</sup> systemic mineralocorticoid replacement for those with adrenal insufficiency in the setting of the Waterhouse-Friderichsen syndrome, and the consideration of other adjunctive immunotherapy.

The neurologic morbidity reported among survivors of bacterial meningitis is thought to be due to inflammation in the subarachnoid space, therefore supplemental corticosteroids have been extensively investigated as a means of decreasing CNS inflammation and improving patient outcomes. As this has been the subject of several randomized trials, the overall effect of adjunctive corticosteroids in patients with bacterial meningitis is best represented by 2 recent meta-analyses.<sup>73,74</sup> On pooling data from 4041 participants (adults and children) in 24 randomized trials, Brouwer and colleagues<sup>73</sup> did not find that corticosteroids reduced the risk of death in patients with bacterial meningitis (pooled risk ratio [RR] 0.92, 95% confidence interval [CI] 0.82–1.04). However, they did find a mortality benefit among patients infected with *S pneumoniae* (RR 0.84, 95% CI 0.72–0.98), an effect consistent with conclusions from one of the main randomized trials.<sup>43</sup> In addition, adults treated with adjunctive corticosteroids demonstrated a reduced risk for hearing loss (RR 0.74, 95% CI 0.56–0.98) and short-term neurologic sequelae (RR 0.72, 95% CI 0.51–1.01).<sup>73</sup> Van de Beek and colleagues<sup>74,75</sup> examined the effect of corticosteroids among patients with bacterial meningitis by pooling individual patient data from 5 randomized trials included in a previous Cochrane review. These investigators also found that dexamethasone did not decrease the odds of death in all patients with bacterial meningitis (pooled odds ratio [OR] 0.97, 95% CI 0.79–1.19), yet did find a decrease in the odds of contracting hearing loss (OR 0.77, 95% CI 0.60–0.99). As the conclusions from individual randomized trials are discordant and the results of these 2 recent meta-analyses are marked by considerable between-study heterogeneity, the empiric use of dexamethasone in patients with bacterial meningitis remains controversial. A reasonable approach as recommended by the IDSA is to administer intravenous dexamethasone (0.15 mg/kg) concomitant with the antibiotic infusion, and continue with a dose every 6 hours until a pathogen is recovered from blood or CSF cultures. Only if meningitis is due to *S pneumoniae* should treatment with dexamethasone continue for 4 days. Of course, patients with meningitis may also require supplemental mineralocorticoids to treat adrenal insufficiency in the setting of the Waterhouse-Friderichsen syndrome; however, this is targeted at treatment of circulatory collapse rather than decreasing subarachnoid inflammation.

Other immunotherapies have been investigated in patients with severe meningococcal infection; however, the target population has largely been children. Levin and colleagues<sup>76</sup> conducted a randomized trial of recombinant bactericidal permeability-increasing protein (BPI), an endotoxin-neutralizing protein, in 395 children with suspected meningococcal infection at high risk for death. Although there was a reduction in the need for transfusions in the group that received recombinant BPI, this drug did not confer a survival benefit to high-risk children with meningococcal infection (OR for mortality in the placebo group 1.31, 95% CI 0.62–2.74). However, there was a trend toward improved mortality among patients who survived to receive the study drug infusion for the prespecified 24-hour period (2.2% for BPI vs 6.2% for placebo,  $P = .07$ ). The effect of a human immunoglobulin M antibody to the lipid-A moiety of bacterial endotoxin (HA-1A) has also been examined in patients with meningococcal septic



shock. However, the potential mortality benefit failed to reach statistical significance among children with presumed *N meningitidis* infection (OR 0.59, 95% CI 0.31–1.05).<sup>77</sup> Nonspecific polyclonal immune globulin has shown promise in septic shock, but because of the lack of data its use in meningococcal infections cannot yet be recommended.<sup>78</sup>

Plasmapheresis is theoretically able to remove endogenous and exogenous inflammatory mediators while simultaneously replacing both prothrombotic and antithrombotic factors known to be dysregulated in patients with septic shock and/or purpura fulminans.<sup>79–81</sup> Stegmayr and colleagues<sup>80</sup> retrospectively examined outcomes associated with the use of plasmapheresis among patients with sepsis and multisystem organ failure. These investigators found that patients who received a median of 2 plasmapheresis treatments had a mortality of 18%, compared with a mortality of 67% to 80% among a similar cohort of historical controls. With regard to the use of plasmapheresis in patients with sepsis caused by meningococcus, several small case series describe reversal of coagulopathy and a possible survival advantage.<sup>82–84</sup> However, higher-grade evidence is required before the use of this therapy can be recommended for routine care among patients with severe meningococcal infection.

Protein C supplementation has been extensively investigated in patients with severe meningococcal infection. De Kleijn and colleagues<sup>85</sup> performed a phase I dose-finding randomized clinical trial evaluating the use of protein C concentrate in 40 children with purpura fulminans caused by *N meningitidis*. Although the study was not powered to detect meaningful differences in mortality, they were able to demonstrate that the use of protein C concentrate in patients with severe meningococcal infections produced dose-related increases in protein C and activated protein C levels, and did not result in any additional adverse reactions in comparison with placebo. In addition to this small phase I pediatric study, the active version of protein C (activated protein C) has been the subject of 2 large randomized trials among adult patients with septic shock.<sup>86,87</sup> Although the original PROWESS (Recombinant Human Activated Protein C Worldwide Evaluation in Severe Sepsis) study found a significant mortality benefit associated with the use of activated protein C in adult patients with septic shock (number needed to treat to prevent 1 death = 16),<sup>86</sup> the more recent PROWESS-SHOCK trial showed that this drug confers no survival benefit to adult patients with septic shock, but increased their tendency to bleed.<sup>87</sup> Neither trial included a subgroup analysis among patients with meningococcal infections; however, because of the results of the PROWESS-SHOCK trial, this drug has been withdrawn from the market and is no longer available for use.<sup>87</sup>

Before the development and use of activated protein C, patients with severe meningococcal infection complicated by purpura fulminans or DIC may have been treated with intravenous unfractionated heparin.<sup>88</sup> Now that activated protein C is no longer available for clinical use, clinicians may be tempted to prescribe intravenous heparin for patients with thrombotic complications of severe DIC. The rationale underlying the use of heparin in this setting is its ability to decrease the prothrombotic state that is responsible for the morbidity (eg, digital infarction and amputation) and mortality in patients with purpura fulminans or DIC. However, despite this sound pathophysiologic rationale, prospective controlled studies have failed to demonstrate a survival benefit associated with the use of intravenous heparin in patients with a severe meningococcal infection.<sup>89,90</sup> On the other hand a large, retrospective, propensity-matched cohort study recently demonstrated that early (<48 hours after admission) intravenous unfractionated heparin reduced the hazard for death in patients with septic shock attributable to any infectious source (hazard ratio for 28-day mortality 0.85, 95% CI 0.73–1.00;  $P = .05$ ).<sup>91</sup> Of note, this survival benefit was not accompanied by any

increased risk of bleeding or requirement for blood products. Although the results of this retrospective study suggest that systemic heparin may be beneficial for patients with septic shock, the recently published randomized, double-blind, placebo-controlled HETRASE study did not demonstrate any clinical benefit associated with intravenous heparin in critically ill patients with sepsis.<sup>92</sup> Unfortunately, few participants in the HETRASE study had septic shock (10% in the intervention and control groups), and the dose of heparin did not produce any significant differences in the median activated partial thromboplastin time between the treatment and control groups. Therefore, although activated protein C is no longer available for use in patients with purpura fulminans and/or DIC, the current literature does not support its replacement with intravenous heparin.

## PREVENTION OF MENINGOCOCCAL INFECTIONS

Close contacts of index cases of severe meningococcal disease are at increased risk for subsequent development of disease, and further cases may be reduced by attention to prevention of infection and measures of control.<sup>93</sup> Patients with suspected *N meningitidis* infection should be placed on contact and droplet isolation until at least 24 hours after the initiation of appropriate antibiotic therapy.<sup>94</sup> The local public health authority should also be contacted to facilitate chemoprophylaxis among all identifiable close contacts. Although the process of identifying all potential close contacts is laborious and time consuming, chemoprophylaxis has been shown to decrease the risk of invasive disease by up to 89% in household contacts.<sup>95</sup> Therefore, it is important that chemoprophylaxis with an appropriate antibiotic be initiated within 24 hours of contact with an infected patient.<sup>93</sup> On the other hand, administration of prophylactic antibiotics is not recommended more than 2 weeks after a potential exposure to *N meningitidis*, because of the very low risk of invasive infection.<sup>93</sup> A list of different chemoprophylaxis regimens shown to be effective in reducing invasive disease is provided in **Box 2**.

Although vaccines are generally not provided to patients during an episode of critical illness, their provision to otherwise healthy outpatients provides an additional effective means of preventing the spread of infections with *N meningitidis*.<sup>96,97</sup> Multiple vaccines against meningococcus have been developed, with differences pertaining to the serogroups included (ie, A, C, W-135, and/or Y), and the presence or absence of conjugation to diphtheria or the tetanus toxoid to improve immunogenicity. Within Canada and the United Kingdom, infants typically receive the meningococcal C conjugate vaccine,<sup>33,98</sup> whereas vaccination programs in the United States provide the quadrivalent conjugate vaccine (serogroups A, C, W-135, and Y) to teenagers. Finally, administration of the quadrivalent vaccine is also recommended for patients at high risk of experiencing a meningococcal infection caused by immune deficits,

### Box 2

#### Chemoprophylaxis regimens for exposure to *N meningitidis*

- Rifampin, 600 mg every 12 hours for 2 days
- Ciprofloxacin, 500 mg single dose
- Ceftriaxone, 250 mg intramuscular single dose

Data from Zalmanovici Trestioreanu A, Fraser A, Gafter-Gvili A, et al. Antibiotics for preventing meningococcal infections. *Cochrane Database Syst Rev* 2011;8:CD004785.

such as those with asplenia or terminal complement defects. Serogroup B accounts for one-third to two-thirds of invasive meningococcal infections in high-income countries.<sup>1,23,25</sup> However, owing to the similarity of the serogroup B capsular polysaccharide to human neural cell adhesion molecule,<sup>99</sup> serogroup B capsular vaccines have proved to be poorly immunogenic. More recent work has focused on development of outer membrane protein–based serogroup B vaccines, which have been successful in phase II studies and may be licensed for use in the near future, further reducing the burden of meningococcal disease.<sup>100,101</sup>

## SUMMARY

Although vaccines have reduced the incidence of infection with specific serogroups of *N meningitidis*, this organism continues to be responsible for considerable morbidity and mortality among those who become infected. Before the development of a severe infection, early symptoms associated with meningococcus are generally nonspecific, however, *N meningitidis* should be suspected as a potential pathogen in any patient who presents with a syndrome of meningitis, or fever and a petechial rash. Identification of meningococcus typically requires analysis of CSF obtained via LP, and although antibacterial therapy is known to quickly sterilize CSF, the rapidly progressive nature of a severe meningococcal infection mandates administering antibacterial therapy before performing an LP. This precept holds especially true for those patients who require correction of coagulopathy or a CT scan of the brain before LP is performed. Isolation of patients with suspected meningococcal infection for 24 hours after initiation of antibacterial therapy and chemoprophylaxis of close contacts are 2 important means of preventing the spread of this deadly infection.

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