THE MANY FACES OF MENINGOCOCCAL DISEASE:
A CASE SERIES AND REVIEW OF
PRESENTATIONS AND TREATMENT OPTIONS

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A Case Series and Review of Presentations and Treatment Options

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Abstract

We present three cases of *Neisseria meningitidis* with varied clinical presentations, including meningococcemia, meningitis, and pneumonia. Our cases suggest an association between concomitant bacterial and viral infections, including group A *streptococcus* and adenovirus, and an increased risk of invasive *Neisseria* infections. Polymerase chain reaction data are a useful adjunct to bacterial cultures for the diagnosis. Our case series exemplify the continued high mortality of *N. meningitides* and highlights the need for more immunogenic vaccines for prevention.
**Introduction**

*Neisseria meningitidis* is a significant cause of morbidity and mortality worldwide and the leading cause of bacterial meningitis in the United States. Meningitis is the most common (80 to 85% of cases) presentation of *N. meningitidis*, but this Gram-negative diplococcus may also cause bacteremia, meningococcemia, or pneumonia. Uncommon presentations include pericarditis, arthritis, and conjunctivitis (1,2). Most cases in the United States are sporadic, although outbreaks are well described (3-5). Infection is transmitted person-to-person via aerosol secretions; up to 10% of healthy adults have nasopharyngeal colonization. Invasive disease occurs when the organism penetrates the mucosa and gains entrance into the bloodstream, leading to systemic meningococcal disease. Risk factors for the development of clinical disease include ages of 18 to 23 years, crowded living conditions such as college dormitories or military barracks (6), tobacco use (7), concomitant respiratory infection (8,9), and terminal complement deficiency (10). We describe three cases of *N. meningitidis* among military members evaluated at our institution over a 1-year period. Our cases exemplify both the potential variable clinical presentation and high risk of mortality.

**Case 1**

An 18-year-old white/Hispanic Marine Corps recruit awoke at 3:30 a.m. with a bilateral lower extremity rash that was palpable and extremely painful. He had no previous medical diagnoses and was taking no medications. One month prior, he had arrived from northern California to the training center, at which time he received a single dose of 1.2 million units of benzathine penicillin for prophylaxis against group A *streptococcus*, as well as pneumococcal (polyvalent pneumovax 23, Merck & Company, Inc.) and meningococcal (Menomune
quadrivalent polysaccharide vaccine, Aventis Pasteur, Inc.) vaccinations. He noted a 3-day history of cough and sore throat, but no headache or fevers. He reported to the medical clinic at 9:00 a.m., 6 hours after the rash began. He was in acute respiratory distress and reported intense myalgias. During the time of presentation, there was an ongoing outbreak of group A streptococcal pneumonia at the same training site (11).

Vital signs showed a temperature of 98.1°F, blood pressure of 79/41 mmHg, pulse of 140 beats/minute, and respiratory rate of 36. Oxygen saturation was 84% on a 12-L oxygen non-rebreather facemask. His skin examination showed a diffuse, palpable purpuric rash consistent with purpura fulminans (Figure 1). Conjunctival petechiae were also noted (Figure 2). Lung examination revealed tachypnea, accessory muscle use, and diffuse respiratory crackles. His heart sounds were normal except for tachycardia; there were no murmurs, rubs, or gallops. Neurological examination was initially unremarkable with normal mental status, no nuchal rigidity, and normal strength throughout.

The differential diagnosis included meningococcemia, toxic shock syndrome, and sepsis. Two liters of normal saline, as well as 2 g of ceftriaxone and 900 mg of clindamycin, were administered. His blood pressure increased to 122/68 mmHg, and he was transferred to our emergency room. On arrival, his systolic blood pressure was 90 mmHg, pulse 118, respiratory rate 36, and oxygen saturation 84% on 15 L of oxygen by facemask; he was intubated. Laboratories on admission included a blood gas with a pH of 6.84, pCO₂ 103, and a pO₂ of 78; the white blood cell count was 20,200 cells/ml with 85% neutrophils, hemoglobin 14.5 g/dl, and platelet count 35,000. Chemistry panel and liver function testing revealed bicarbonate of 18 mEq/L, anion gap of 15, and albumin of 2.1 g/dl; transaminases were normal. A chest radiograph showed patchy to confluent airspace opacities throughout all the visualized lobes;
small biapical pneumothoraces and bilateral chest tubes were present. Cultures were unremarkable. During transfer to the intensive care unit, he became asystolic; the patient died, despite aggressive resuscitation efforts. On autopsy, he had multiple petechiae and small hemorrhages of his intestines, mesentery, renal cortex, adrenals, lungs, skeletal muscle, conjunctiva, myocardium, and epicardium (Figure 3). Skin was noteworthy for a purpuric rash of his face, trunk, and extremities. There was pulmonary edema, evidence of shock to multiple organs, and numerous microthrombi in the heart, lungs, liver, kidney, and brain. There was no purulent meningeal exudate. Polymerase chain reaction on the cerebrospinal fluid (CSF) (Centers for Disease Control and Prevention [CDC], Atlanta, Georgia, USA) was positive for \textit{N. meningitidis} serogroup C. The cause of death was determined as \textit{N. meningitidis} septicemia (meningococcemia).

Case 2

A 22-year-old active-duty female developed fevers, headaches, confusion, and a rash on her bilateral lower extremities. She had no significant past medical history and was taking only progesterone injections for contraception. She received routine vaccinations, including meningococcal immunizations (Menomune quadrivalent polysaccharide vaccine) in 1999 and January 2003. Her symptoms developed over 3 days while on vacation to visit her family, and she reported no ill contacts. On examination, she was mildly confused and had a temperature of 103°F with a normal blood pressure. Neurologic evaluation demonstrated nuchal rigidity without cranial nerve deficits. Skin examination revealed a palpable erythematous, petechial rash on her bilateral extremities extending to the thighs. Heart and lung examinations were unremarkable.
Laboratory values were significant for a white blood cell count of 13,200 cells/ml, with 79% neutrophils and 19% band forms; other peripheral values were normal. CSF was cloudy with a white blood count of 2,320, 96% neutrophils, protein 581 mg/dl, and glucose 23 mg/dl. The patient was initially treated with ceftriaxone, vancomycin, and dexamethasone. Dilantin was also administered for seizure prophylaxis. Latex agglutination for *N. meningitidis* in the CSF was positive, but the culture and Gram stain were negative. One of two blood cultures grew *N. meningitidis* serogroup B sensitive to ceftriaxone and penicillin. The patient defervesced, and her mental status cleared over a 3-day period. She completed a 14-day course of ceftriaxone. A CH50 level was normal, and she had no personal or family history of *Neisseria* infection. The patient had complete resolution of all symptoms without neurologic deficits.

Case 3

A 32-year-old white/Hispanic male in his 20th day of military recruit training presented with a fever of 103°F and enuresis. Three weeks earlier, he had arrived from Texas; at that time, he received an injection of benzathine penicillin for group A *streptococcus* prophylaxis, as well as meningococcal and pneumococcal vaccinations. He had no known medical problems and was HIV negative. His enuresis was judged secondary to not getting out of bed at night to void; a urinalysis was unremarkable. The patient had a concurrent cough, fevers, and upper respiratory symptoms for which a chest radiograph was ordered but not obtained by the patient. On a follow-up visit 4 days later, his cough was improved, and his vital signs were within normal limits.

Two days later, he collapsed during a training exercise from acute respiratory distress and developed pulseless ventricular fibrillation. His temperature was 105°F. Attempts at resuscitation were unsuccessful. No laboratory tests were obtained prior to death. At autopsy, a
multilobar acute pneumonia was noted without other significant findings; there was no evidence of cardiac or central nervous system (CNS) disease. Multiple samples of lung tissue were positive for *N. meningitidis* by culture, PCR evaluation (sequence confirmed), and immunohistochemistry analysis; the organism was not groupable (Naval Health Research Center, San Diego, California; Walter Reed Army Institute of Research, Silver Spring, Maryland; and the CDC). Blood and CSF were negative for evidence of *N. meningitidis* by culture and PCR, but brain tissue was weakly PCR positive. Lung tissue and blood were also positive for adenovirus type 4 by PCR, using universal and adenovirus serotype 4-specific primers. The case occurred during an adenoviral outbreak at the recruit camp. Lung tissue was also culture and PCR positive for *Haemophilus influenzae*. The cause of death was determined to be cardiopulmonary arrest secondary to multilobar pneumonia caused by *N. meningitidis* with concomitant adenovirus and *H. influenza* infections.

**Discussion**

*N. meningitidis* has a variety of clinical presentations, including meningococcemia with purpura fulminans, meningitis, and pneumonia. All of our cases occurred in young military members, and two cases occurred during outbreaks of respiratory infections (group A *streptococcus* and adenovirus type 4), suggesting that concomitant viral and bacterial infections increase the risk of invasive disease. Our two fatal cases demonstrate the significant mortality of meningococcal disease despite medical advances. All patients had previously received the meningococcal quadrivalent polysaccharide vaccine.

Vieusseux first described meningococcal disease in 1805, and the causative organism was identified in 1887 (12-14). Worldwide, *N. meningitidis* accounts for 500,000 infections and 50,000 deaths annually (15). Within the United States, the annual incidence is 0.9 to 1.5 cases
per 100,000, and 98% of cases are sporadic (12). Disease incidence is highest among infants after maternal antibodies wane and in young adults ages 15 to 23 years. Although the disease is most common in young children, case-fatality rates are highest in the teenage years. Infection occurs when virulent *N. meningitidis* organisms are acquired during close contact with a colonized host; the bacterium must hematogenously disseminate, while the host lacks immunity to that specific serogroup.

Risk factors for disease development include concurrent respiratory infection, which may decrease the integrity of the mucosal barrier (7,8). Respiratory illness may also increase the risk of *N. meningitidis* transmission due to increased cough and secretions (12). Crowded living conditions, such as college dormitories and military barracks, have been associated with a heightened disease incidence (12, 16). Among military members, military recruits have the highest risk due to crowding and arrival from diverse locations throughout the United States (6). Other risk factors include tobacco smoke and indoor fire exposure, which likely interfere with mucosal integrity; all of our cases were in non-smoke environments.

Immunodeficiencies, including terminal complement deficiency, properdin deficiency, asplenia, and HIV infection predispose to meningococcal disease (9, 17). Of patients with a single meningococcal infection, 5 to 10% are found to be complement C5-C9 deficient, whereas those with multiple episodes have a 30% prevalence of deficiency (18). All patients in this case series were HIV seronegative and had normal splenic function; only one could be tested (case 2) for complement deficiency and had a normal level. None of the cases had family or personal histories remarkable for *Neisseria* infections or meningitis.

Other potential host factors that may play a role in susceptibility and severity of the infection include alterations of plasminogen activator inhibitor type 1, Toll-like receptor 4,
Fcγ-receptors, tumor necrosis factor α, and mannose-binding lectin (15, 19-21). Bacterial factors are also important determinants of disease. Serogroup C is an independent predictor of death, and certain subgroups are known to be more virulent than others. A recent study of an outbreak in western Canada revealed that the circulating virulent strain was infrequently identified in the at-risk population during the outbreak (22).

Clinical disease manifests as meningitis in 80 to 85% cases, and *N. meningitidis* is currently the most common cause of bacterial meningitis in the United States. Classic findings include headache, fevers, and a petechial rash that begins on the lower extremities with a predilection for areas of pressure. Blood cultures are positive in 50 to 70% of patients, and culture of petechial skin lesions have a sensitivity of nearly 70% (1). Other presentations include bacteremia without sepsis, or meningococcemia, which may occur with or without meningitis. Early signs of meningococcemia include a petechial or purpuric rash, rigors, severe pain in the extremities, and rapid evolution of the illness (23). Meningococcemia, accounting for 10 to 20% of disease, may progress to septicemia, multiorgan system, and adrenal insufficiency (the Waterhouse-Friderichsen syndrome). Our case of meningococcemia presented with purpura fulminans, shock, and death within 8 hours of symptom development. Although there was no clinical evidence of CNS involvement, the diagnosis was confirmed by a positive PCR of the CSF.

Pneumonia occurs in 5 to 15% of cases, but is often unrecognized due to a lack of familiarity with this entity among providers. In addition, isolation of *Neisseria* from respiratory samples may represent pharyngeal colonization versus active infection, since 10% of healthy adults may be carriers (12). Clinical presentation is typically cough, chills, and chest pain; a previous or concurrent upper respiratory infection is common (12). Serogroup Y has a greater
predilection to respiratory involvement (24). Multilobar disease occurs in 40%, and mortality is reportedly rare (25). One of our cases had a multilobar pneumonia due to *N. meningitidis* that was established with autopsy lung tissue showing invasive disease. Concurrently, 6 military recruits at the same training center presented with radiographically confirmed pneumonias and grew *N. meningitidis* from sputum samples; all recruits received a single dose of oral levofloxacin 500 mg for prophylaxis, and no further cases were noted. Other less common presentations of *N. meningitidis* include pericarditis, arthritis, conjunctivitis, pharyngitis, and genital infections (1, 26-28).

A Gram stain of the blood or CSF showing Gram-negative diplococci suggest the diagnosis; bacterial culture PCR is confirmatory. Cultures may be negative after administration of antibiotics and therefore lack sensitivity in clinical cases. Latex agglutination is used most often in meningitis diagnosis, but false-negative results limit large-scale application. PCR may be useful in cases in which cultures are negative, since it does not require live organisms and may provide a more rapid diagnosis than cultures (29). Serogroup-specific (30) PCR primers are also available. PCR or latex agglutination may also be useful postmortem to determine the cause of death, as in two of our cases.

Antibiotic therapy should be immediately instituted with intravenous penicillin G or ceftriaxone. Early or preadmission administration of penicillin has been shown to reduce mortality (2). Strains showing relative resistance to penicillin have been noted, emphasizing the importance of using high-dose penicillin G therapy (4 million units every 4 hours) (31). Chloramphenicol is still utilized in developing countries, although resistant isolates are described (32). Adjunctive steroids are somewhat controversial in *N. meningitidis* meningitis; their use in *H. influenzae* and *Streptococcus pneumoniae* is better defined. Steroids are not indicated for
meningococcemia without meningitis. Use of activated protein C (drotrecogin alfa) is better studied, and levels of protein C in meningococcemia are correlated to outcome. Several studies have suggested activated protein C improves morbidity and mortality, and use of this product should be considered for meningococcemia (33-40). The use of other immunomodulating agents to alter cytokine and endotoxin levels requires further investigation. Mortality rates continue to be high (up to 10%), despite antimicrobial therapy and intensive unit care. Poor prognostic findings include petechiae present for less than 12 hours before presentation, hypotension, absence of meningitis, and low white blood cell count (41). Those with septicemia have mortality rates of 30 to 50% frequently, with death occurring early in the course of the illness (1, 2).

Preventive strategies include the use of the quadrivalent polysaccharide vaccine in high-risk groups, including college freshmen residing in dormitories, military members aboard ship or at training centers, and travelers to areas including sub-Saharan Africa and pilgrimages to Saudi Arabia. The vaccine is 85% or more efficacious against serogroups A, C, Y, and W-135 (42). According to data from 2000 to 2002, the most common serogroups causing clinical disease in the United States are B (40%), Y (29%), and C (24%); most cases are vaccine preventable (43). Unfortunately, the B capsule is poorly immunogenic, and a vaccine is not currently available for this serogroup. Disease may still develop despite vaccination, as seen in our cases. Also, multiple vaccinations may cause tolerance to the polysaccharide antigen. A novel meningococcal group C conjugate vaccine offers the potential advantages of improved T cell-mediated immune response, herd immunity of unvaccinated persons, and an increased duration of protection; it has been shown to decrease both clinical cases and fatalities in the United Kingdom. (44, 45).
Close contacts of a case of meningococcal disease should receive chemoprophylaxis with a fluoroquinolone, such as ciprofloxacin or levofloxacin, rifampin, or ceftriaxone. Disease occurrence due to failed prophylaxis from rifampin-resistant strains is described, but is rare (31). Index cases treated with penicillin should also be treated with a fluoroquinolone or rifampin to assure eradication of the carrier state. This is not needed for those treated with ceftriaxone. Our three cases led to the immediate prophylaxis using levofloxacin 500 mg oral tablet of persons sharing berthing areas; there were no secondary cases.

In summary, meningococcal disease has a variety of presentations, including meningitis, meningococcemia with purpura fulminans, and pneumonia. Cases may occur in all age groups, however, young adults who reside in crowded living conditions are at particular risk. Molecular techniques are a useful adjunct to bacterial cultures when commercially available. Our case series highlights the need for better preventive strategies, including novel vaccines with improved immunogenicity.

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Figure 1: Rash of purpura fulminans on lower extremity.
Figure 2: Palpebral conjunctival petechiae.
Figure 3: Petechiae of the epicardium on postmortem examination.
**Abstract**

We present three cases of *Neisseria meningitidis* with varied clinical presentations, including meningococcemia, meningitis, and pneumonia. Our cases suggest an association between concomitant bacterial and viral infections, including group A streptococcus and adenovirus, and an increased risk of invasive *Neisseria* infections. Polymerase chain reaction data are a useful adjunct to bacterial cultures for the diagnosis. Our case series exemplify the continued high mortality of *N. meningitides* and highlights the need for more immunogenic vaccines for prevention.