EUROPEAN JOURNAL OF BIOMEDICAL AND PHARMACEUTICAL SCIENCES
http://www.ejbps.com

ISSN 2349-8870
Volume: 7
Issue: 2
366-379
Year: 2020

FULMINANT MENINGOCOCCEMIA

***Dr. Madleen Jawad Sobhe Abu Aser and Dr. Amjad Alanqar**

***Corresponding Author: Dr. Madleen Jawad Sobhe Abu Aser**

Email id: hamsat22-7@hotmail.com

Article Received on 20/12/2019 **Article Revised on 10/01/2020** **Article Accepted on 31/01/2020**

ABSTRACT

Meningococcemia a bacterial infection of the blood due to Neisseria meningitides also called meningococcal bacteremia or meningococcal sepsis. As the name suggests, this bacterium is best known for causing meningococcal meningitis, which occurs in up to 20% of those with meningococcemia. Up to 75% of those with meningococcal meningitis will also have bacteremia. Purpura fulminans, an often-fatal condition owing to the associated septic shock. These two clinical aspects of the meningococcal infection are consequences of a tight interaction of meningococcal with host endothelial cells. This interaction, mediated by the type IV pili, is responsible for the formation of microcolonies on the apical surface of the cells. This interaction is followed by the activation of signaling pathways in the host cells leading to the formation of a microbiological synapse. A low level of bacteremia is likely to favor the colonization of brain vessels, leading to bacterial meningitis, whereas the colonization of a large number of vessels by a high number of bacteria is responsible for one of the most severe forms of septic shock observed. Neisseria meningococcus is a Gram-negative coccus restricted to humans, which is responsible for two major diseases cerebrospinal meningitis and/or septicemia. Paradoxically, N. meningitides is a common inhabitant of the human nasopharynx, and as such is a normal, saprophytic organism that is transmitted from person to person by direct contact. Only in a small proportion of colonized subjects does the bacterium invade the bloodstream where they are responsible for septicemia and/or meningitis, after crossing of the blood-brain barrier. Fulminant meningococcemia accounts for 5% to 10% of patients with meningococcemia; it is rapidly progressive and is associated with high morbidity and mortality rates. The highest meningococcal incidence is found in the 6- to 20-month-old age group; whereas immunouncompetence is suggested in adults with the condition. Coincidentally, eating disorders are purported to be the most prevalent psychiatric or behavioral disturbance affecting adolescents, and studies indicate that vulnerability to infectious. Meningococcal disease caused by the gram-negative diplococcus Neisseria meningitides is a relatively common infectious disease in developing countries of Asia and Africa. Infection usually starts with a non-specific prodromal of fever, vomiting, malaise, and lethargy followed by signs of septicemia and shock tachycardia, tachypnea, cyanosis, oliguria, hypotension or meningitis stiff neck, headache, photophobia, and impaired sensorium. Neisseria meningitides is responsible for two major diseases: cerebrospinal meningitis or septicemia. The latter can lead to a purpura fulminans, an often-fatal condition owing to the associated septic shock. These two clinical aspects of the meningococcal infection are consequences of a tight interaction of meningococci with host endothelial cells. This interaction is followed by the activation of signaling pathways in the host cells leading to the formation of a microbiological synapse. A low level of bacteremia is likely to favor the colonization of brain vessels, leading to bacterial meningitis, whereas the colonization of a large number of vessels by a high number of bacteria is responsible for one of the most severe forms of septic shock observed. A characteristic meningococcal rash may not appear early in the disease course, potentially delaying the diagnosis and institution of appropriate antibiotic therapy in the patient and isolation and chemoprophylaxis in close contacts. We present here a patient who presented with fulminant meningococcal shock associated with characteristic skin lesions of meningococcemia and discuss the clinical presentation and management. The importance of early identification of the characteristic skin lesions of meningococcemia and timely institution of an appropriate antibiotic.

INTRODUCTION

Many bacteria can cause bloodstream infections septicemia, including staphylococci, Streptococcus B, or Streptococcus A. Also, other bacteria can cause meningitis, including Streptococcus pneumonia or leptospirosis. However, N. meningitides is the commonest cause of bacterial meningitis in the U.S. It is more readily contagious from person to person than these other bacteria and causes rapidly progressive and severe disease fulminant meningococcemia. Rates of infection are typically highest in older children and adolescents, although there are reports of meningococcemia in all age

groups. People with a deficiency of the complement immune system and those taking complement inhibitors eculizumab [Soliris] are at high risk for severe meningococcal disease, even if they are vaccinated. Other forms of meningococcal disease include pneumonia in up to 15% of cases and much less often bacterial (septic) arthritis, otitis media (middle ear infection) and other conditions. The case-fatality rate of meningococcal disease is high, up to 15%, even with antibiotic treatment; it is up to 40% with bacteremia. Up to 20% who survive have disabilities like deafness, neurologic problems, or amputations. Fulminant Meningococcemia is a bacterial infection of the blood due to Neisseria meningitidis, also called meningococcal bacteremia or meningococcal sepsis. As the name suggests, this bacterium is best known for causing meningococcal meningitis, which occurs in up to 20% of those with meningococcemia. Up to 75% of those with meningococcal meningitis will also have bacteremia. A relatively rare life-threatening disease caused by Neisseria meningitides. We report a case of a patient with fulminant meningococcemia and successfully recovered within 14 days of hospitalization N. meningitides, or meningococcus is a gram-negative bacillus. Under the microscope, the bacteria usually appear in pairs (diplococcus), like two small kidney beans side by side. Meningococcemia is another term for widespread bloodstream infection. Humans are the only known source (reservoir) for meningococcal infection. Some people can harbor the bacteria in their throats and not get sick (a "carrier" state), but others develop the infection.

Either can transmit the bacteria. People usually acquire meningococcus by breathing in respiratory droplets or by direct contact with oral secretions by sharing eating utensils, kissing, The presence of a capsule made of complex carbohydrates called polysaccharides increases the infectiousness, or virulence, of N. meningitides. This capsule protects the bacteria from initial immune defenses of the nose and throat. Risk factors for meningococcemia Children and adolescents 5 to 19 years of age are at the highest risk for meningococcemia. Newborns acquire antibodies from their mothers via the placenta, although these antibodies fade after a few weeks or months. Toddlers are not immune, and there have been several exposures in daycare settings. As children age, they gradually gain immunity to meningococcal strains by coming into contact with milder strains of the bacteria. However, because this immunity is imperfect, it is still possible for adults to get meningococcal disease. In the U.S., medical professionals routinely administer the meningococcal vaccine to children in the preteen and teen years. People who have been in close contact with an infected person for a long time are at increased risk to acquire the disease. People who live together in close quarters, such as military barracks or college dormitories, are at special risk for disease because one infected person can spread the disease to many others. One study showed that the attack rate in household contacts was 500 times greater than that of the general population. In some parts of the world, outbreaks of meningococcal disease occur regularly. This is true of a group of countries in sub-Saharan Africa (the "meningitis belt") where epidemics occur every five to 10 years, with an attack rate of up to 1,000 cases per 100,000 populations (compared to up to three per 100,000 population in the rest of the world). Outbreaks have occurred during the Islamic Hajj pilgrimage. Over 2 million Muslims from over 180 countries visit Saudi Arabia during the Hajj. The pilgrimage is long and arduous. Heat, throat irritation by dust, dense overcrowding, and inadequate hygiene contribute to infection. Saudi Arabia now requires proof of meningococcal (ACWY) vaccination on an International Certificate of Vaccination or Prophylaxis before admitting pilgrims. This has greatly reduced the occurrence of meningitis. Infected patients initially experience fatigue, fever, nausea, headache, and body aches, similar to those experienced by people with influenza, including swine flu or bird flu. Once symptoms appear, the disease usually gets rapidly worse over several hours. In a minority of cases, symptoms continue at a low-grade level for several days. If meningitis is present, headache, stiffness or resistance to bending the neck forward, and difficulty tolerating light (photophobia) are prominent features Common meningococcemia symptoms As the symptoms worsen, shaking chills and high fever occur. The rash is common and appears like small red dots (petechiae) or a bleed into the skin (purpura) associate with vasculitis, or inflammation of small blood vessels. Severe meningococcemia symptoms with severe meningococcal disease, vasculitis may be extensive and severe enough to cause death or necrosis of the skin (purpura fulminans).The petechial or purpuric rash may appear anywhere on the body, even on the palms or soles or inside the mouth. It may be limited to a small section of the body or cover extensive areas. Thus, a careful physical examination of the skin and mucosal surfaces is important. Petechiae do not disappear or Blanche when compressed; one way to diagnose them is to press a clear glass against the skin to see if they disappear. Petechial rash in a person with fever should raise concern for life-threatening meningococcal disease and the need for prompt antibiotics. In addition to the petechial rash, physical examination reveals a fast heart rate and often low blood pressure and other signs of septic shock. Laboratory examination usually shows increases in white blood cell counts and may show low platelet counts (thrombocytopenia). The bacteria may spread to the heart, causing myocarditis, or inflammation of the heart muscle. In severe cases, multiple organ systems may fail, including the kidneys, lungs and airways, liver, or heart. Fulminant meningococcemia is a rapidly progressive and life-threatening disease. Uncommonly, the bacteria may cause a low-grade bloodstream infection (chronic meningococcemia) with fever, joint pain, and rash that lasts one to three weeks. Severe low blood pressure and vacuities may cause necrosis of the hands and feet,

requiring amputation. Although meningococcemia refers to an infection of the bloodstream. It is important to note that up to 15% will develop meningococcal meningitis. Meningococcal sepsis poses a higher risk of shock and death than meningococcal meningitis alone. Although defined differently and having different prognoses, there is a significant overlap between meningococcemia and meningococcal meningitis.

PATHOPHYSIOLOGY

Neisseria meningitides are Gram-negative organisms that typically appear as diplococci morphologically. The diplococci may appear as ‚coffee bean' shapes with dimpling where they meet. Pathogenic strains are surrounded by a polysaccharide capsule that increases virulence by preventing phagocytosis. This is a particularly important virulence factor for those with functional or anatomic asplenia, complement deficiency, and young children under 2 who produce relatively poor polysaccharide antibody responses. Nasopharyngeal colonization with pathogenic strains typically precedes acute infection. Humans represent the only reservoir for Neisseria meningitides. Acute infection occurs when nasopharyngeal colonization precedes bacteremia and seeding in secondary sites such as the meninges. A systemic inflammatory response syndrome (SIRS) may occur when meningococci invade the bloodstream secondary to release of lipopolysaccharide (LPS) endotoxin, which is a potent promoter of the inflammatory cascade. Measures levels of LPS may directly correlate with the severity of infection and risk for mortality in meningococcal disease. This cascade may ultimately lead to the development of septic shock. Also, disseminated intravascular coagulopathy is common with severe meningococcal infection, leading to ischemia and infarction in the skin, soft tissue, and internal organs. The diffuse petechial or purpuric rash is seen in association with meningococcemia represents widespread embolization of organisms, and frequently viable bacteria may be seen on Gram stain or culture has taken directly from skin lesions. The morbidity and mortality from meningitis are typically secondary to the inflammatory response occurring in the subarachnoid space leading to increased intracranial pressure, CNS vasculitis, and ischemia.

EPIDEMIOLOGY

Meningococcal infections occur in two major patterns: epidemic outbreaks or endemic disease. For epidemic outbreaks, the period of onset to secondary cases is typically short, with a median of 2 days and a range of 1-31 days. For endemic sporadic cases among households, the median onset to secondary cases was 7 weeks in one study, with a range of 1-39 weeks. Given the short onset of secondary cases in outbreak settings, immediate prophylaxis of at-risk exposures is critical. The attack rate for household contacts is 500-800 times that of the general population. Five major serogroups of N. meningitides account for the vast majority of all invasive infections worldwide and include types A, B, C, Y, and W-135. Routine vaccination with a polysaccharide-protein conjugate vaccine directed against serogroups A, C, Y, and W-135 is recommended for all adolescents and those at high risk in the United States. The current vaccine will not eliminate the meningococcal disease, as serogroup B accounts for a significant percentage of reported cases.

PROGNOSIS

Meningococcal infections occur in two major patterns: epidemic outbreaks or endemic disease. For epidemic outbreaks, the period of onset to secondary cases is typically short, with a median of 2 days and a range of 1-31 days. For endemic sporadic cases among households, the median onset to secondary cases was 7 weeks in one study, with a range of 1-39 weeks. Given the short onset of secondary cases in outbreak settings, immediate prophylaxis of at-risk exposures is critical. The attack rate for household contacts is 500-800 times that of the general population. Five major serogroups of N. meningitides account for the vast majority of all invasive infections worldwide and include types A, B, C, Y, and W-135. Routine vaccination with a polysaccharide-protein conjugate vaccine directed against serogroups A, C, Y, and W-135 is recommended for all adolescents and those at high risk in the United States. The current vaccine will not eliminate the meningococcal disease, as serogroup B accounts for a significant percentage of reported cases.

PROGNOSIS

Despite antibiotic therapy and intensive care monitoring, meningococcemia still has overall case fatality rates of 40% in the United States. Up to 19% have long-term complications from a meningococcal infection. With early and aggressive management, most patients with meningococcal infection recover rapidly and do not suffer permanent sequelae. However, the overall mortality rate for meningococcal infections remains high at approximately 10%. The most significant complication leading to long term morbidity from meningococcemia is the potential for loss of extremities and digits associated with purpura fulminans. This complication may occur in up to 4% of survivors and often involves more than one extremity.

Meningitis from N. meningitides tends to produce somewhat lower rates of long-term neurologic sequelae in survivors than other common bacterial causes, such as pneumococcus and H. influenza. Several recent studies have looked at long term outcomes in patients with meningococcal infections. A 33-year review of complications from meningococcal infection in Denmark showed an overall case fatality rate of 7.6%, with the highest fatality rates in those over 50 (17.9%), and rates ranging from 3.5%-9.4% in those less than 50 years. Case fatality rates were highest for those presenting to the hospital on the day of or following the day of onset (9.7%) versus those presenting after 2-4 days of illness (range 0.8% to 2.7%) suggesting those with the more

fulminant disease are likely to present earlier in a profound shock-like state. Other long-term complications included a hearing loss in 1.9%, epilepsy in 1.4%, and cerebral palsy or limb plegia in 0.3%. Another long-term followup study of those surviving meningococcal septic shock reported outcomes of major physical sequelae in 24%, mild neurological impairments in 33%, problem behavior in 14% and total IQ under 85 in 16%. Adolescent patients with fulminant meningococcemia often have more severe infections than other age groups with higher rates of morbidity. One review of complications in college students in Pennsylvania reported an overall mortality rate of 11%, with 20% having permanent physical sequelae mainly due to tissue ischemia and necrosis. Another case-control study of outcomes in adolescents with meningococcal disease in the U.K. reported that 57% of survivors had major physical sequelae. Survivors also had greater depressive symptoms, greater fatigue, less social support, greater reduction in quality of life and lower educational attainment compared to controls.

DEFINITION

Meningococcemia is an infectious syndrome caused by gram-negative diplococci, Neisseria meningitides, a bacterium that is present in the nasopharynx of normal individuals. Meningococcal infection develops when the microorganism spreads from the nasopharyngeal mucosa and invades the bloodstream. Clinical manifestations of meningococcal disease vary, with some mild disease cases, but the most common manifestation is a septic syndrome or meningitis. Infectious meningitis is most often caused by bacteria or viruses. Fungal meningitis is rare, affecting individuals with immunodeficiencies, transplanted, and using immunosuppression patients, however, this disease is highly dangerous and requires rapid treatment to avoid sequelae.

Among the fungal meningitis types, cryptococcal meningitis caused by Cryptococcus neoformans is the most common, After entry into the body, the fungus spreads through the bloodstream, reaching the lungs, kidneys, lymph nodes, skin, and bones, prostate and ends up being introduced directly into the central nervous system, especially in the meninges. This type of infection is rare in people with a functional immune system and is considered an opportunistic fungus. The immune response and pathogen virulence play an important role in the disease progression and may lead to severe sepsis and, consequently, septic shock, when not immediately treated or inadequately treated. The manifestation of meningococcal disease associated with the presence of Cryptococcus neoformans is rare. Severe Meningococcal disease progresses rapidly to shock, multiple organ failure, and death within 24 hours if without urgent treatment. Non-specific symptoms such as fever, drowsiness, nausea and vomiting, irritability and poor appetite are present 4–6 hours after the disease onset. Non-specific sepsis signs, such as pain in the leg, cold hands and feet, and abnormal color, are also observed within 12 hours after disease onset. Classic ecchymotic patches resulting from rapidly developing meningococcal infection and neck pain or stiffness usually appear after 12 hours. Unfortunately, most cases of MD are diagnosed after these late signs onset and it is quite common to find hospitalized patients with an incorrect initial diagnosis. Coagulopathy associated with MD is frequent and usually multifactorial. There is an imbalance between coagulation and fibrinolysis and therefore, although formal coagulation tests may be significantly prolonged, there is a tendency for intravascular thrombosis.

The presence of meningococcal endotoxin in the blood generates a severe acute pro-inflammatory response. Cytokines stimulate the tissue factors release leading to the formation of thrombin and fibrin clots. Cytokines and thrombin inhibit tissue plasminogen activator by releasing the plasminogen activator inhibitor-1 (PAI-1), compromising the endogenous fibrinolytic route.

Thrombin formation stimulates inflammatory pathways and further weakens the endogenous fibrinolytic system by activation of the thrombin activatable fibrinolysis inhibitor (TAFI). Activation of the endotoxin complement (mainly via alternative and mannose-binding pathways) leads to the accumulation of anaphylatoxins, thereby compromising the activation of this protein, disabling fibrinolysis. The procoagulant and proinflammatory state associated with these changes produces endovascular injury, microvascular thrombosis, organ ischemia, and multisystem dysfunction. With inhalation entry port, Cryptococcosis is a systemic mycosis caused by the Cryptococcus complex, currently with two species: Cryptococcus neoformans and Cryptococcus gattii. Both species appear as globular or oval yeast, 3–8 μm in diameter, with single or multiple budding, narrow necks, and surrounded by characteristic mucopolysaccharides composed capsule. Cryptococcus neoformans is cosmopolitan, occurring on various organic substrates, often associated with bird habitat, dry excreta rich in nitrogen sources such as urea and creatinine. Favorable conditions to the abundant growth of this yeast form microfocus noted mainly in urban centers and pigeon-related. The home environment, particularly in domestic dust, can be positive, between 13% and 50%.

Meningoencephalitis is the most commonly diagnosed clinical form, occurring in more than 80% of cases, either in isolation or associated with pulmonary involvement. It most commonly presents an acute or subacute meningitis or meningoencephalitis, however, single or multiple focal lesions in the central nervous system (CNS), simulating neoplasias, associated or not with the meningeal condition, are observed in the immunocompetent host. In immunocompetent patients the clinical picture, resulting from nervous system inflammation, is exuberant: meningeal signs (nausea, vomiting and stiff neck); signs of meningoencephalitis in

one-third of patients on admission (changes in consciousness; memory, language, and cognition deficit); and involvement of cranial pairs (strabismus, diplopia, or facial paralysis (III, IV, VI and, VII).

Temporary or definitive visual impairment or amaurosis throughout the course and treatment reflects injury to the I cranial pair (ophthalmic). There is great clinical pleomorphism in cryptococcal meningoencephalitis, and dementia may be the only disease manifestation. Physical examination may show meningeal irritation signs (Kerning, Brudzinski, Lasègue, neck stiffness and Lewinson), intracranial hypertension signs, such as papilledema, which usually corresponds to intracranial pressure>350 mmHg. Other neurological signs, such as ataxia, sensory impairment, and aphasia may be observed. Complications such as fungal ventriculitis, obstructive block hydrocephalus without meningitis, and cerebrospinal fluid (CSF) malabsorption hydrocephalus by meningitis are frequent.

DIAGNOSIS

The diagnosis of Meningococcemia may be confirmed by a thorough clinical evaluation and specialized blood tests. A patient's history and physical exam may suggest a diagnosis of meningococcemia, although a definitive diagnosis requires laboratory testing. Because the disease can progress rapidly, patients should start treatment promptly without waiting for laboratory test results. Health care professionals diagnose meningococcal infection by culturing N. meningitides from blood cultures. The bacteria grow in one to two days in most cases, and medical professionals use biochemical methods to identify them as N. meningitides. Samples of the growth can also be stained and examined under the microscope to detect the characteristic double kidney bean (diplococcus) appearance of the bacteria, although additional biochemical tests are performed to confirm the identification of the organism. Once the organism is growing on a culture medium, medical professionals perform tests to determine which antibiotics are likely to kill the bacteria (susceptibility testing) because increased resistance to several antibiotics has been documented. In some instances, skin biopsies from the rash can reveal the organisms under the microscope, but this is difficult and a negative result is not a reliable means of ruling out meningococcemia. Investigators have used a PCR (polymerase chain reaction) laboratory test to detect N. meningitides in the blood, although they developed the test for spinal fluid. The drawbacks of PCR are that it cannot determine how susceptible the bacteria are too specific antibiotics and that the test is not available in all hospital laboratories. Primary care health professionals such as internists, family practice specialists, pediatricians, and emergency room specialists may be the first clinicians to evaluate and suspect meningococcemia. Critical care specialists, infectious disease specialists, and nephrologists (kidney or renal specialists) may treat people who are seriously ill or have meningitis or have immune suppression in the hospital or intensive care unit.

CASE PRESENTATION

N. S. B five years old female, child was admitted to PICU13.12.2019 with bad general condition at 7-hour a.m. by pediatrician because of high fever and body rash, headache, general weakness, projectile vomiting the patient connected to mechanical ventilation, introps was given due to septic shock PRBC and FFP given, skin ecchymosis was over all the body skin smear +ve. The Child was examined previously that day by primary health care pediatrician and sent to a county hospital. Heteroanamnestic data obtained from mother by pediatrician showed the presence of high fever and shivering (abo-ve 41°C) resistant to drugs given by mother, which lasted for one day, presence of maculous body rash for few hours before the examination. Other anamnestics findings were normal. After obtaining anamnestic data pediatrician performed clinical examination: rectal body temperature was 40°C, on skin, there were three different sorts of rash: unspecified partially conflating white-pink macular rash 1–2 mm in diameter on body hull, traces of mosquitoes bites, Vital functions were abnormal, neurological exam was within normal parameters: with positive meningeal sign, and with signs of conscience disturbance. Lymph nodes were normal, nasal secretion was absent, a pharynx mucosa didn't show signs of inflammation. Pulmonary, cardiac, and abdominal statuses were within normal parameters. Laboratory findings were: CBC, HB9.9, WBC3.8, L31%,G64%,PLT157,PT19,PTT56,ABG.PH7.09,PCO2 40,HCO12,RBS126.UREA31,NA138,K3.3.CA8.1,protei n 5.3ALB3.2, bilirubin t 0.7, D0.3.treatment meropenam650mg IV/8hr, ciprofloxacin 160mg IV/12hr, phenytoin40mg p.o/12hr, phenbarbital30mgp.o/12hr, Enaxparin8mg/12hr,gentamycin skin cream/12hr, fuciedine, amikacin120mgIV/12hr, G/S IV FLUIDE. Upon completed examination and laboratory findings Microbiological samples taken from pharynx were positive for Neisseria meningitides. The pathologist conclusion was that the child caused by fulminant meningococcal sepsis and Epilepsy.

DISCUSSION

The meningococcal disease manifestation associated with the presence of Cryptococcus neoformans is rare. There are no reports in the literature about these simultaneous infections in immunocompetent patients.

The inflammatory response related to Neisseria meningitides infection may progress to multiple organ dysfunction, particularly circulatory and renal failure, acute respiratory distress syndrome, and common findings in meningococcal sepsis.

Fulminant septic shock associated with meningococcemia causes coagulation disorders, with thrombus formation, and rapid evolution to disseminated intravascular coagulation.

Meningococcemia is a life-threatening medical emergency requiring immediate recognition and treatment with antimicrobials and, in some cases, even after appropriate treatment, progresses to death.

Meningococcemia usually presents with petechial or purpuric eruption, including mucous membranes, especially in the extremities, and may progress to disseminated eruptions and bruising related to meningococcal septic shock. Cryptococcus neoformans is an opportunistic fungus usually associated with immunodeficiency, especially in patients with HIV who are using antiretroviral therapy irregularly. Also, it may affect patients on prolonged use of corticosteroids, diabetics, Hodgkin's disease, systemic lupus erythematosus, lymphoproliferative diseases, transplantation, sarcoidosis, liver cirrhosis, alcoholism and during chemotherapy.

In our case, the patient exhibited superficial disseminated purpuric lesions with marked ecchymosis, rapidly evolved into a consuming syndrome, disseminated intravascular coagulation, respiratory failure, and circulatory and renal failure, besides the loss of consciousness, due to a fulminant picture of septic shock, due to meningococcemia, with multiple organ failure in less. We describe the first case of fulminant septic shock due to meningococcemia associated with the presence of Cryptococcus neoformans in CSF in an immunocompetent patient. It is noteworthy that the patient had no comorbidity reported in the literature that could lead to infection with Cryptococcus, which leads us to the hypothesis of susceptibility to opportunistic fungal infection associated with meningococcemia. Meningococcemia is a rare infectious disease characterized by upper respiratory tract infection, fever, skin rash and lesions, eye and ear problems, and possibly a sudden state of extreme physical depression (shock) which may be life-threatening without appropriate medical care. There are two forms of meningococcemia.

Fulminant meningococcemia develops very rapidly and is more severe than chronic meningococcemia, which has a waxing and waning course. Signs & Symptoms Meningococcemia is characterized by sudden intense headache, nausea, fever, vomiting, and skin rash. The affected individual may first complain of an upper respiratory infection. Chills may develop, then skin rash on the arms or legs and the trunk. Diarrhea may also be present. Later the rash may become widespread or develop into bleeding spots under the skin (petechiae, ecchymoses, or purpura). There may be associated with swelling, muscle pain, skin deterioration or gangrene in the arms and legs. Pneumonia may also develop along with the other symptoms if the affected individual has a suppressed immune system. In cases where meningitis occurs along with meningococcemia, the affected individual may have the symptoms listed above along with the combination of headache, confusion, stiff neck, and muscle pain from irritation of membranes surrounding the brain and spinal cord (meningismus). Fulminant Meningococcemia is also known as Waterhouse-Friderichsen Syndrome and is the most severe form of the disorder. The disease comes on very suddenly and the progression of the symptoms is very rapid. In less than a few hours the affected individual may experience very high fever, chills, weakness, vomiting and severe headache. A red rash appears on the arms and legs and spreads very quickly over the body including the eyes and nose. Also, the affected individual's blood pressure may drop dangerously, the fever may drop dramatically, and they may go into shock. Without immediate medical treatment, this disorder can be life-threatening. Chronic Meningococcemia is a rarer form of the disease. It is characterized by a fever that comes and goes over of weeks or months. Muscle and joint pain with headaches as well as a skin rash may also come and go. This form of the disorder may also include an enlarged spleen.

Meningococcemia is caused by infection with the meningococci bacteria (Neisseria meningitides) which are gram-negative diplococci bacteria. Various groups of this bacteria that cause different forms of the disease. These groups can be identified by testing the blood, scrapings of the skin rash and samples of the cerebrospinal fluid of the patient. Testing may take up to five days as the cultures are very slow-growing. Infection with the bacteria is usually caused by a carrier. The natural place for the bacteria to be located is in either the nose or throat of the carrier and they can be spread the infection through airborne or close contact methods. The carrier may spread the infection for weeks or months if they are not diagnosed and treated.

Affected Populations Meningococcemia affects males and females in equal numbers. However, most cases develop in persons twenty years of age or younger and half of these cases are in children under five years of age. In the United States, 1.2 cases per 100,000 occur annually. Winter and spring are the most common seasons of the year when cases are reported. Epidemics can occur under crowded conditions and tend to occur at 20 to 30-year intervals. In other parts of the world, epidemics are usually caused by the Group A strain of the bacteria. During epidemics, rates of 5 to 24 cases per 100,000 persons have occurred. In Sao Paulo, Brazil, during 1974 the epidemic rate was 370 per 100,000 persons infected with Meningococcemia.

Related Disorders

Symptoms of the following disorders can be similar to those of Meningococcemia. Comparisons may be useful for a differential diagnosis: Rocky Mountain spotted fever is a tick-borne disease that begins with an incubation period of from two to twelve days. A gradually or abruptly beginning fever may be followed after three to five days by a pink or purplish colored rash on the wrists and ankles. The fever and rash usually become more severe for seven to fourteen days. The rash

may not develop in all cases, possibly making diagnosis difficult. A blood test is necessary to confirm the diagnosis. Henoch-Shonlein Purpura is one of a group of disorders characterized by purplish or brownish-red discolorations on the skin. These spots may be large or small. Internal bleeding may occur in various areas of the body. This blood vessel disorder may affect the skin, joints, gastrointestinal system, kidneys, and in a very few cases the central nervous system.

Rheumatic Fever is an inflammatory syndrome that can occur following a streptococcal infection. Patients initially experience moderate fever, a general feeling of ill health, a sore throat, fatigue, and a red rash. Major complications can include heart disease, joint pain, and arthritis, involuntary abrupt limb movements with characteristic grimaces and skin symptoms.

Toxic Shock Syndrome symptoms appear very suddenly. Initially, there is a fever of 102 to 105 degrees F, headache, sore throat, and conjunctivitis. Other early symptoms include profound lethargy, periods of disorientation, vomiting, severe diarrhea, and a diffuse sunburn-like rash leading to sloughing of skin after several days. In severe cases, the syndrome may progress to shock (dangerously low blood pressure and circulatory collapse) within forty-eight hours.

Infective Endocarditis usually has a very sudden onset. Complaints of low back pain, pain in the joints (arthralgia) or in one or more muscles (myalgia) are common. These symptoms usually appear early in the disease, occasionally as the only initial symptoms. Fever, night sweats, chills, headache and loss of appetite may also occur. Blood or blood cells may be present in the urine (hematuria), small red or purple spots composed of blood (petechiae) may cover the skin of the upper trunk and there may also be pale, oval spots on the retina of the eye. The classic clinical presentation associated with meningococcal sepsis (fever and petechiae, or fever and purpuric rash) is late findings that portend a worse outcome if present. Clinical features and laboratory tests may both be unreliable in ruling out an early meningococcal infection.

Based on a recent large retrospective review, symptoms may be classified as early, classic or late. Most children in this study had only non-specific symptoms in the first 4-6 hours but we're close to death by 24 hours. Limb pain or refusal to walk are occasional complaints in young children with meningococcemia. Nonspecific very early symptoms (first 4-6 hours):

Fever Headache
Myalgia Influenza-like symptoms of early symptoms (median time to onset = 7-12 hours)

Leg pains
Thirst Diarrhea Abnormal skin color breathing difficulty Cold hands and feet Classic symptoms (median time to onset = 13-22 hours):
Hemorrhagic rash Neck pain or stiffness Photophobia

Bulging fontanelle Late symptoms (median time to onset = 16-22 hours):
Confusion or delirium Seizure Unconsciousness.

N. meningitides may have several forms of presentation aside from fulminant meningococcal sepsis presenting with fever and a petechial rash. Other forms include occult bacteremia typically in the setting of an upper respiratory infection, meningitis, pneumonia, septic arthritis, pericarditis, endopthalmitis, and chronic meningococcemia.

The rash of meningococcemia may initially start as a blanching, nonpalpable macular rash. A rash is not invariably present, and its absence should not rule out a possible diagnosis of meningococcemia. It is important to completely disrobe the patient when looking for rash and to evaluate mucous membranes so that hidden lesions are not missed. Over a short period of hours, the rash typically becomes petechial and then may progress to widespread purpura, potentially leading to loss of digits or extremities. The petechial rash is most commonly found on the trunk and lower extremities but can be hidden in places such as the conjunctiva. The lesions may be found underneath areas of skin pressure, such as the elastic band from underwear. Although a history of fever and a petechial rash should prompt early consideration of meningococcus as a cause, less than 15% of all children presenting with this combination are found to have N. meningitides infection. In young children, fever and vomiting may be the only symptoms, and children may not present until seizures or altered mental status occur. The symptoms of meningitis are nonspecific, and up to 20% of children may have seizures with meningococcal meningitis. The term purpura fulminans refers to a severe, often fatal illness characterized by symmetric, progressive purpura, usually of the extremities, and typically occurring in children. The main association is with acute infection from Neisseria meningitides, although the constellation of findings may also occur from other causes. He terms Waterhouse-Friderichsen syndrome refers to the clinical findings of diffuse purpuric lesions and disseminated intravascular coagulation, coupled with adrenal hemorrhage, adrenal insufficiency, and shock. The most classic presentation of this illness is secondary to a meningococcal infection, although other agents also may be causative.

Treatment
Meningococcemia is usually treated with Penicillin or Ampicillin. In adults the method of treatment is often through intravenous Penicillin G. In children penicillin is still the treatment of choice, however, other organisms

must be ruled out before treatment is begun. For persons who are unable to take penicillin, other antibiotics are used such as cefuroxime, cefotaxime or ceftriaxone. In persons who survive severe meningococcal septicemia, there may be ongoing problems with veins and arteries. There are usually serious orthopedic problems. If gangrene occurs amputation may be necessary. These patients should have continuing medical evaluations as a precaution against other conditions that can arise in later years. During times of epidemics, prophylaxis with other antibiotics (i.e., Rifampin, minocycline, and sulfadiazine) is used to protect persons exposed to or in close contact with infected patients.

Investigational Therapies

A new orphan product used for the prevention and treatment of purpura fulminans in Meningococcemia is being developed by Immuno Clinical Research Corp. of New York. The name of the new product is Protein C Concentrate (Protein C Concentrate (Human) Vapor Heated, Immuno). Researchers are studying the safety and effectiveness of an experimental vaccine for Meningococcemia. The drug recombinant bactericidal/permeability-increasing protein (Neuprex) has received an orphan drug designation for use in the treatment of Meningococcemia. More studies are needed to determine the long-term safety and effectiveness of this treatment of Meningococcemia, Early suspicion of meningococcus as a cause of an illness is critical to appropriate management and therapy. The signs and symptoms of infection may be non-specific in the early course. The classic presentation of fever with petechiae or purpura is a late finding. Examination of mucous membranes and the entire body surface area for rash is important to see potentially hidden lesions that may help confirm the diagnosis (completely disrobe patient). For those with meningococcal sepsis/bacteremia/shock, aggressive fluid resuscitation is critical to improving outcomes. For those with suspected meningococcal meningitis, the management of raised intracranial pressure is critical to improving outcomes. Antibiotics should be administered as soon as possible once a potential diagnosis of meningococcal infection has been considered. Close contacts should receive prophylaxis as soon as possible as secondary cases may have a rapid onset.

Emergency Management

The initial priorities in the management of meningococcal infections are the management of acute shock and if present, raised intracranial pressure. Aggressive fluid resuscitation is important for those presenting with shock. For those with raised intracranial pressure, neurointensive management should be considered. Consensus guideline recommendations (NICE Clinical Guideline 102) for fluid management of children and young adults <16 years of age with meningococcal septic shock include: If shock is present give an immediate fluid bolus of 20 ml/kg sodium chloride 0.9% over 5-10 minutes. If shock persists, immediately give a second bolus of 20 ml/kg of intravenous or intraosseous sodium chloride 0.9% or human albumin 4.5% solution over 5-10 minutes. If shock persists after the first 40 ml/kg, immediately give a third bolus of 20 ml/kg of intravenous or intraosseous sodium chloride 0.9% or human albumin 4.5% solution over 5-10 minutes, and: Urgently intubate and mechanically ventilate. Start treatment with vasoactive drugs Consider further fluid boluses at 20 ml/kg of intravenous or intraosseous sodium chloride 0.9% or human albumin 4.5% solution over 5-10 minutes based on clinical signs and appropriate laboratory investigations including urea and electrolytes. Antibiotics should be administered as soon as possible when the diagnosis is considered. Some studies indicate that early antibiotic administration (even orally in the outpatient pre-hospital setting) may reduce morbidity and mortality. If possible, blood cultures or cultures of skin lesion scrapings should be obtained before the administration of antibiotics, as therapy dramatically reduces the likelihood of organism recovery. Consider adjunctive dexamethasone therapy with the first dose of antibiotics if meningococcal meningitis is suspected (adult patients only). Lumbar puncture should be considered as part of the diagnostic workup, but maybe contraindicated in certain situations, including Raised intracranial pressure. Relative bradycardia and hypertension. Focal neurological signs. Abnormal posture or posturing. Unequal, dilated or poorly responsive pupils.

Papilledema. Abnormal ‘doll’s eye’ movements. Shock. Extensive or spreading purpura.

Uncontrolled seizures. Coagulation abnormalities, thrombocytopenia.

Local superficial infection at the lumbar puncture site. Respiratory insufficiency. Metabolic derangements are common and need to be considered in patients presenting with severe meningococcal infections. These include Hypoglycemia, hypokalemia, hypocalcemia, hypomagnesemia, hypophosphatemia Anemia. Thrombocytopenia. Coagulopathy.

Metabolic acidosis. Myocardial dysfunction can occur directly from meningococcal myocarditis or indirectly from acidosis and electrolyte abnormalities. Droplet precautions are indicated for health professionals caring for patients with suspected meningococcal infections until adequate antimicrobial therapy has been administered. Suspected or proven disease should be reported to the local health department. Prophylaxis should be administered to at-risk close contacts given the rapidity with which secondary cases can occur.

Diagnosis Establishing a specific diagnosis characteristic clinical findings plus the isolation of the causative agent, Neisseria meningitides, in normally sterile samples are

the gold standards for diagnosis of meningococcal infections.

In patients presenting with suspected meningococcal infections, cultures should be obtained from clinical sites of likely infection. These include blood culture in almost all cases, CSF cultures in those with suspected meningitis and cultures of other sites such as joint fluid, pericardial fluid, etc. if clinically indicated. For those with petechial or purpuric rash, viable organisms may be found in aspirates or scrapings of lesions, and Gram stain and culture from lesions may yield the diagnosis. Receipt of prior antibiotics significantly reduces the recovery of meningococcal organisms from culture specimens and may render Gram stains negative for visible organisms.

Prior antibiotics may reduce the recovery of bacteria from blood cultures by more than 90%. Blood culture bottles containing sodium polyanethol sulfonate (commonly found in adults, but not pediatric blood culture bottles) may inhibit the growth of the organism and lead to a falsely negative result. N. meningitides is relatively fastidious, and culture recovery may be impaired by refrigeration or delay in transport to the microbiology lab.

Cultures from sites that are not normally sterile, such as the throat or nasopharynx, are not acceptable specimens for diagnosis, as up to 10-15% of individuals may have asymptomatic carriage of N. meningitides bacteria. Latex agglutination for antigen detection on CSF from patients who have received prior antibiotics is occasionally used as an adjunctive measure for diagnosis. However, this test has poor sensitivity and specificity, and CSF latex agglutination tests, in general, have been shown to have little impact on overall patient management and outcome.

Polymerase chain reaction (PCR) testing has been extensively used for the diagnosis of meningococcal infections in the United Kingdom but is not routinely available in most centers in the United States. More than 50% of cases in the U.K. are confirmed by PCR testing, and this modality may increase sensitivity over blood cultures by 30-40%. PCR based testing can also be performed successfully in some patients who have previously received antibiotics.

Routine laboratory values are generally neither sensitive nor specific for the diagnosis of meningococcal infections, but rather should be obtained to evaluate for hematopoietic and metabolic derangements. Evaluation of white blood counts may show leukocytosis or leukopenia (which may have poor prognostic significance). Anemia may occasionally be seen. Thrombocytopenia is common. Electrolyte abnormalities are common and may occur in association with metabolic acidosis. Hyponatremia may occur as a result of SIADH secondary to meningitis. Generalized coagulopathy may be present, often in the setting of disseminated intravascular coagulopathy (DIC). For this reason tests of coagulatory function and factors may be indicated. A compatible clinical history coupled with culture confirmation of Neisseria meningitides organisms provides a definitive diagnosis of meningococcal infection, however, definitive diagnosis is often not possible and culture confirmation may take hours or days. Therefore, the initial diagnosis should be made on clinical grounds, as therapy should be instituted immediately and not delayed pending definitive confirmation. Gram stain results from clinical specimens such as CSF or skin scraping may provide valuable immediate information. It is important to consider that some blood culture bottles may have inhibitors that prevent the growth of N. meningitidis in a culture system. This has particular relevance when standard ‚adult' blood culture bottles are used, which are more likely to be inhibitory. Knowing which blood culture bottles were used for culture samples and whether they contain the inhibitor sodium polyanethol sulfonate may be helpful if the culture results are negative in a clinically compatible case. Prior studies have indicated that more than 50% of blood cultures are positive when the meningococcal disease is present. The positivity of CSF Gram stains and cultures has ranged from 46% to 94% in various reports for those with meningitis. Skin lesion Gram stains and cultures have been reported to have sensitivities ranging from 50-70% when both tests are used in combination. Confirmed case of meningococcal infection A clinically compatible case and isolation of N. meningitides from a usually sterile site, for example:

Blood CSF.
Synovial fluid. Pleural fluid. Pericardial fluid. Isolation from skin scrapings of petechial or purpuric lesions. A probable case of meningococcal infection: A clinically compatible case with either a positive result of antigen test or immunohistochemistry of formalin-fixed tissue or a positive polymerase chain reaction test of blood or CSF without a positive sterile site culture Suspect case of meningococcal infection:
A clinically compatible case and Gram-negative diplococci in any sterile fluid

- Clinical purpura fulminans without a positive blood culture

The differential diagnosis of meningococcal infections includes:

- **Infectious causes**

Sepsis and/or meningitis from Streptococcus pneumonia. May also present with purpura fulminans type picture. Rocky Mountain spotted fever.
Group A Streptococcal sepsis and/or toxic shock syndrome.
Staphylococcus aureus sepsis and/or toxic shock syndrome. Fulminant staphylococcal bacteremia has been reported to present with a purpura fulminans picture similar to

- **Meningococcemia.**

Haemophilus influenzae type B meningitis.
Disseminated gonococcal infection.
Enteroviral infections. A common cause of a well-appearing child with fever and a petechial rash. A most common cause of meningitis in children
Epstein-Barr virus infection. May be associated with a petechial rash from autoimmune thrombocytopenia. Parvovirus infection. especially papular-purpuric gloves and socks syndrome in adolescents/young adults. Gram-negative rod sepsis.

Consider sources from the urinary tract and/or intraabdominal. Disseminated strongyloidiasis (immune-compromised host).

Non-infectious causes

Henoch-Schoenlein purpura. Inherited coagulation disorders such as protein S or C deficiency. Thrombotic thrombocytopenic purpura (TTP). Idiopathic thrombocytopenic purpura (ITP).Connective tissue disorders. Trauma (especially children). Side effects from drug anticoagulation. Culture confirmation from normally sterile sites provides definitive evidence of meningococcal infection. Other tests that may be used to provide evidence of meningococcal infection include Gram stain from sterile sites showing Gram-negative diplococci. Latex agglutination test from CSF positive for N. meningitides antigens. PCR from normally sterile samples positive for N. meningitides.

4. SPECIFIC TREATMENT

Antimicrobial agents

The treatment of meningococcal infections is most often initially empiric. Antimicrobial therapy should be given directed against meningococci as well as other common treatable causes with similar presentations. Although most meningococci are susceptible to penicillin, and this remains the drug of choice in many parts of the world, resistance has been documented, and penicillin may not provide adequate therapy empirically against other potential agents. In the United States, penicillin resistance among N. meningitides remains below 5%. For patients presenting with fever, shock, and/or petechial/purpuric rash considerations for empiric therapy should include Ceftriaxone or cefotaxime. Vancomycin. To provide coverage for drug-resistant S. pneumonia and S. aureus, including MRSA. Consider in areas with a high incidence of community-acquired MRSA. Doxycycline. Provides coverage for Rocky Mountain spotted fever (endemic areas only).

For patients presenting with meningitis as a distinct syndrome, the age of the patient must be taken into account when providing empiric therapy: Birth to 2 months: Ampicillin. Cefotaxime. +/- Gentamicin if Gram-negative rod meningitis suspected. +/- Acyclovir if Herpes Simplex Virus encephalitis is suspected. 2 months to 55 years: Ceftriaxone or cefotaxime. Vancomycin.> 55 years: Ceftriaxone or cefotaxime. Vancomycin. Ampicillin. Once a definitive diagnosis of meningococcal infection has been obtained, antimicrobial therapy can be tailored specifically to cover N. meningitides: Penicillin G remains the drug of choice for treatment of meningococcal infections in most parts of the world. Alternative drugs should be used in areas with high endemic rates of resistance (e.g. Spain) Ceftriaxone or cefotaxime are acceptable alternatives Ceftriaxone offers the advantages of once-daily dosing, eradication of nasopharyngeal carriage with a single dose, and some data indicate it may have greater efficacy for treating meningococcal infections than comparator drugs. Ceftriaxone should not be administered concurrently with calcium- containing solutions. In that event, cefotaxime should be used instead. Chloramphenicol may be used for patients with a history of severe anaphylactic reactions to penicillins or cephalosporins.

The treatment duration for meningococcal infections is typically 5-7 total days of therapy.

Adjunctive agents

- Steroids in conjunction with antibiotics for therapy of acute meningitis

Dexamethasone therapy in conjunction with antibiotics just before, or with the first dose of initial antibiotics, has been shown in adults to provide benefit in meningitis from all causes, and may also provide benefit in meningococcal meningitis.

Recommended regimen: dexamethasone 0.15 mg/kg q6h for 4 days started with or just before the first dose of antibiotics.

There is no benefit to dexamethasone therapy if it started after the initial dose of antibiotics.

In children, the use of steroids as adjunctive therapy for meningitis is recommended routinely only for Haemophilus influenzae type B meningitis. The use of adjunctive steroids in this manner is considered controversial for pneumococcal and meningococcal infections in children due to conflicting and limited data.

- **Steroids for adrenal replacement**
- Physiologic low dose replacement steroid therapy may be beneficial in the subset of patients presenting with shock and adrenal insufficiency.

This may particularly apply to patients presenting with meningococcemia and the Waterhouse-Friderichsen syndrome characterized by adrenal hemorrhage causing adrenal insufficiency and shock.

Patients most likely to benefit include those with absolute or relative adrenal insufficiency who are already requiring vasopressor support of blood pressure.

This practice varies by center and is considered controversial based on conflicting reports in the

literature. If used, the possible side effects of superinfections, hyperglycemia, and bleeding need to be carefully monitored for and managed if present.

Agents specifically indicated for N. meningitides infections:
Penicillin G: 250,000 Units/kg/day in divided doses IV every 4-6 hours. Maximum dosage 12 million Units/day. Ceftriaxone: 75-100 mg/kg/day in divided doses IV every 12-24 hours. Maximum dosage 4 grams/day. Cefotaxime: 200 mg/kg/day in divided doses IV every 6 hours. Maximum dosage 8 grams/day. Chloramphenicol: 75-100 mg/kg/day in divided doses IV/PO every 6 hours. Maximum dosage 2 grams/day Agents which may be indicated empirically for patients with suspected septic shock or meningitis: Ampicillin: Children older than 7 days: 200-400 mg/kg/day in divided doses IV every 6 hours. Maximum dosage of 12 grams/day. Adults: 150-200 mg/kg/day in divided doses IV every 6 hours. Maximum dosage of 12 grams/day.

Vancomycin
- Adults: 45-60 mg/kg/day in divided doses IV every 8-12 hours.
- Children: 60 mg/kg/day in divided doses IV every 6-8 hours.

Doxycycline
- Adults: 100 mg/dose IV/PO every 12 hours.
- Children: 4.4 mg/kg/day in divided doses IV/PO every 12 hours. Maximum dosage 200 mg/day.

Refractory cases
For refractory cases of meningococcal sepsis, several additional therapy options may be considered: Steroids for adrenal replacement Physiologic low dose replacement steroid therapy may be beneficial in the subset of patients presenting with shock and adrenal insufficiency. May particularly apply to patients presenting with meningococcemia and the Waterhouse-Friderichsen syndrome characterized by adrenal hemorrhage causing adrenal insufficiency and shock. Patients most likely to benefit include those with absolute or relative adrenal insufficiency who already require vasopressor support of blood pressure. This practice varies by center and is considered controversial based on conflicting reports in the literature. If used, the possible side effects of superinfections, hyperglycemia, and bleeding need to be carefully monitored for and managed if present. Activated protein C (drotrecogin alfa, Xigris) may be considered for adult patients only. Administration of activated protein C has been demonstrated in a large, randomized, double blind, placebo-controlled trial of adult patients to significantly reduce mortality in adult patients with severe sepsis. The incidence of severe bleeding was increased in those patients receiving activated protein C. Activated protein C should not be administered to any patients with baseline bleeding risk factors, including meningococcal shock patients with evidence of bleeding. Activated protein C administration is contraindicated in pediatric patients due to a lack of efficacy in published trials and increased risk of bleeding events noted in children receiving therapy. In particular, CNS hemorrhage was noted more commonly in those children receiving drotrecogin alfa. Plasmapheresis, hemofiltration, extracorporeal membrane oxygenation (ECMO): For patients with severe or refractory septic shock, alternative therapies including plasmapheresis, hemofiltration and ECMO may be considered. Published data is mainly limited to single-center experiences and no randomized, controlled trials have been performed.

Monitoring and follow-up
Meningococcal infections have a high fatality rate, with an overall mortality rate of 10%.

For uncomplicated, non-severe disease, rapid improvement is generally expected. The organism is typically exquisitely sensitive to antibiotic therapy, often with a single dose of effective antibiotic therapy rendering body tissues sterile. Patients with uncomplicated meningitis tend to improve quickly, with a return to normal function in a matter of days. Those with fulminant meningococcemia tend to fare worse, often with long term morbidity. Unlike patients with only meningitis, a rapidly progressive course with death occurring within a matter of hours sometimes occurs. Severe ischemic skin or soft tissue damage may lead to loss of extremities or digits.

Specific complications that must be considered include SIADH in the setting of meningitis. Acute interstitial myocarditis leading to depressed myocardial function, as a direct result of disseminated meningococcemia. Adrenal hemorrhage leading to adrenal insufficiency and compounding shock (Waterhouse-Friderichsen syndrome). Hearing loss from meningitis. Skin, soft tissue, and musculoskeletal morbidity as a result of ischemic necrosis. Post-infectious inflammatory syndromes: Secondary to immune complex deposition. May lead to arthritis, vasculitis, iritis, pericarditis typically occurs several days after the onset of infection. Generally self resolves, therapy with NSAIDs may provide benefit.

Incorrect diagnosis
When adequate therapy is being provided for meningococcemia and the patient continues to worsen, alternative etiologies that are not currently being treated should be considered. Also, although rare in the United States, drug resistance to penicillin and alteration in therapy to include ceftriaxone or cefotaxime should be considered, if therapy was initiated with penicillin.

However, it is difficult to use clinical deterioration while on therapy as a single marker of lack of response due to a possible incorrect diagnosis, as many patients with meningococcal sepsis have hypotension and multiorgan system dysfunction at the time of presentation, and

mortality rates remain high even with appropriate therapy. New clinical findings that support a different syndrome or disease, or identification of an organism other than Neisseria meningitides from a diagnostic specimen, should prompt consideration of a different diagnosis. In areas with endemic Rocky Mountain spotted fever, consideration should also be given to that diagnosis at the time of presentation, and empiric therapy with doxycycline may be indicated.

Patients with meningitis will need followup hearing screens and close neurodevelopmental screens. The rates of sequelae are lower for meningococcal meningitis than for other pyogenic causes of meningitis (3-7%). Patients with significant skin, soft tissue or extremity ischemia may need followup with orthopedic or plastic surgeons. It is generally recommended to allow ischemic limbs sufficient time to self demarcate viable from non-viable tissue before to performing amputations to provide for maximum potential extremity recovery. Patients with significant end-organ dysfunction (myocarditis, acute renal insufficiency) typically have a complete recovery, but some may need followup with subspecialists if persistent deficits remain.

There are several ways to prevent meningococcemia.

- Infected people are contagious, and health care providers will place them in private isolation rooms in the hospital. Health care workers will wear masks and gloves when entering the room to administer care. Isolation duration varies but usually lasts at least 24 hours after the start of intravenous antibiotics People who have come in contact with an infected patient should strongly consider taking antibiotics to reduce the risk of disease, a process called prophylactic treatment or chemoprophylaxis. Physicians may have patients take prophylactic antibiotics such as rifampin Rifadin)or ciprofloxacin (Cipro) in pill form. Sometimes they will administer a shot of ceftriaxone. The choice of antibiotic is based on the age of the patient, resistance patterns in the community, and whether the person is pregnant or not. Close contact usually means household contacts, daycare or child care contacts, or those exposed to potentially infected saliva in the week before the patient got sick. Routine patient care does not warrant prophylaxis in health care workers, unless the worker has had very close contact with respiratory secretions, such as when giving mouth-to-mouth resuscitation or inserting a breathing tube. People should begin prophylaxis as soon as possible after the exposure but certainly within two weeks of the event. The antibiotics help eliminate carriage of the bacteria and physicians may also use them in the final step of treatment for infected patients. Doctors should monitor people exposed to N. meningitides for 10 to 14 days to make sure they do not develop symptoms. Caretakers and health care workers should wash their hands frequently to minimize the transfer of infected secretions to the mouth or nose.

CONCLUSION

Meningococcal disease associated with Cryptococcus neoformans coinfection is rare. In this case, an immunocompetent patient had acute fulminant meningococcemia associated with neurocriptococcosis, which progressed with the general condition worsening and died due to septic shock and multiple organ dysfunctions, in less than 48 hours. This case report highlighted the possibility of coinfections related to Neisseria meningitides and Cryptococcus neoformans, even in immunocompetent patients, which represents a diagnostic challenge for clinicians, thus encouraging further studies for a better understanding.

REFERENCES

1. Pickering, LK, Baker, CJ, Kimberlin, DW, Long, SS. “Meningococcal Infections”. Red Book: 2009 Report of the Committee on Infectious Diseases, 2009; 455-63. (Standard reference for pediatric infectious disease management with up to date consensus treatment recommendations including prophylaxis guidelines.)
2. Visintin, C, Mugglestone, MA, Fields, EJ, Jacklin, P, Murphy, MS. “Management of bacterial meningitis and meningococcal septicaemia in children and young people: summary of NICE guidance”. BMJ., Jun 28, 2010; 340: c3209. (Summary of important consensus guidelines on the management of meningococcal infections in children in the U.K.)
3. Long, SS, Pickering, LK, Prober, CG. “Neisseria meningitidis”. Principals and Practice of Pediatric Infectious Diseases, 2008; 734-43. (Excellent general reference on all aspects of meningococcal infections.)
4. Stephens, DS, Greenwood, B, Brandtzaeg, P. “Epidemic meningitis, meningococcaemia, and Neisseria meningitidis”. Lancet, Jun 30, 2007; 369: 2196-210. (Excellent general review on meningococcal infections.)
5. Thompson, MJ, Ninis, N, Perera, R, Mayon-White, R, Phillips, C. “Clinical recognition of meningococcal disease in children and adolescents”. Lancet, Feb 4, 2006; 367: 397-403. (Significant article describing clinical features and timeline of symptoms in meningococcal infections.)
6. Brierley, J, Carcillo, JA, Chong, K. “Clinical practice parameters for hemodynamic support of pediatric and neonatal septic shock: update from the American College of Critical Care Medicine”. Crit Care Med., 2007; 37.
7. Feb, 2009; 666-88. (Consensus guidelines on management of septic shock in children.)
8. MacLaren, G, Butt, W, Best, D, Donath, S. “Central extracorporeal membrane oxygenation for refractory pediatric septic shock”. Pediatr Crit Care Med., Mar, 2011; 12: 133-6. (Study describing the utility of central ECMO for children with septic shock syndromes.)

9. Fortenberry, JD. "Pediatric critical care management of septic shock prior to acute kidney injury and renal replacement therapy". Semin Nephrol, Sep, 2008; 28: 447-56. (Review on management measures for pediatric septic shock, including adjunctive measures such as ECMO.)
10. De Kleijn, ED, Joosten, KF, Van Rijn, B, Westerterp, M, De Groot, R. "Low serum cortisol in combination with high adrenocorticotrophic hormone concentrations are associated with poor outcome in children with severe meningococcal disease". Pediatr Infect Dis J., Apr, 2002; 21: 330-6. (Report describing the high incidence and impact on mortality of adrenal insufficiency in children presenting with meningococcal disease.)
11. Hebbar, KB, Stockwell, JA, Leong, T, Fortenberry, JD. "Incidence of adrenal insufficiency and impact of corticosteroid supplementation in critically ill children with systemic inflammatory syndrome and vasopressor-dependent shock". Crit Care Med., May, 2011; 39: 1145-50. (Study showing the importance of evaluating for and managing adrenal insufficiency in children presenting with shock, and impact of steroid replacement on reducing vasopressor use.)
12. Sprung, CL, Annane, D, Keh, D, Moreno, R, Singer, M. "CORTICUS Study Group. Hydrocortisone therapy for patients with septic shock". N Engl J Med., Jan 10, 2008; 358: 111-24. (Randomized, placebo control trial showing lack of survival benefit or shock reversal in patients treated with low dose steroid replacement.)
13. M.B. Salzman, L.G. RubinMENINGOCOCCEMIA
14. Infect. Dis. Clin. North Am., 1996; 10: 709-725, 10.1016/S0891-5520(05)70323-8
15. ArticleDownload PDFView Record in Scopus Google Scholar
16. S. Takada, S. Fujiwara, T. Inoue, Y. Kataoka, Y. Hadano, K. Matsumoto, K. Morino, T. ShimizuMeningococcemia in adults: a review of the literature
17. Intern. Med., 2016; 55: 567-572. 10.2169/internalmedicine.55.3272
18. CrossRefView Record in ScopusGoogle Scholar
19. J.R. Perfect, A. CasadevallCryptococcosis
20. Infect. Dis. Clin. North Am., 2002; 16: 837-874, 10.1016/S0891-5520(02)00036-3
21. ArticleDownload PDFView Record in ScopusGoogle Scholar
22. M.J. Thompson, N. Ninis, R. Perera, R. Mayon-White, C. Phillips, L. Bailey, A. Harnden, D. Mant, M. LevinClinical recognition of meningococcal disease in children and adolescents
23. Lancet, 2006; 367: 397-403. 10.1016/S0140-6736(06)67932-4
24. ArticleDownload PDFView Record in ScopusGoogle Scholar
25. S.N. Faust, M. Levin, O.B. Harrison, R.D. Goldin, M.S. Lockhart, S. Kondaveeti, Z. Laszik, C.T. Esmon, R.S. HeydermanDysfunction of endothelial protein C activation in severe meningococcal sepsis
26. N. Engl. J. Med., 2001;' 345: 408-416. 10.1056/NEJM200108093450603
27. View Record in ScopusGoogle Scholar
28. K.J. Kwon-Chung, J.E. BennettEpidemiologic differences between the two varieties OF cryptococcus NEOFORMANS1
29. Am. J. Epidemiol., 1984; 120: 123-130, 10.1093/oxfordjournals.aje.a113861
30. CrossRefView Record in ScopusGoogle Scholar
31. D. Swinne, J.B. Nkurikiyinfura, T.L. MuyembeClinical isolates ofCryptococcus neoformans from Zaire.
32. Eur. J. Clin. Microbiol., 1986; 5: 50-51, 10.1007/BF02013464
33. View Record in ScopusGoogle Scholar
34. R. Rozenbaum, A.J.R. GoncalvesClinical epidemiological study of 171 cases of cryptococcosis
35. Clin. Infect. Dis., 1994; 18: 369-380. 10.1093/clinids/18.3.369
36. CrossRefView Record in ScopusGoogle Scholar
37. W.E. Dismukes, G. Cloud, H.A. Gallis, T.M. Kerkering, G. Medoff, P.C. Craven, L.G. Kaplowitz, J.F. Fisher, C.R. Gregg, C.A. Bowles, S. Shadomy, A.M. Stamm, R.B. Diasio, L. Kaufman, S. Soong, W.C. BlackwelderTreatment of cryptococcal meningitis with combination amphotericin B and flucytosine for four as compared with six weeks
38. N. Engl. J. Med., 1987; 317: 334-341. 10.1056/NEJM198708063170602
39. View Record in ScopusGoogle Scholar
40. B.C. Hellerud, O.K. Olstad, E.W. Nielsen, A.-M.S. Trøseid, Ø. Skadberg, E.B. Thorgersen, Å. Vege, T.E. Mollnes, P. BrandtzægMassive organ inflammation in experimental and in clinical meningococcal septic shock
41. Shock, 2015; 44: 458-469. 10.1097/SHK.0000000000000441
42. CrossRefView Record in ScopusGoogle Scholar
43. O.H. Owuor, P. ChegeCRYPTOCOCCAL meningitis in a HIV negative newly diagnosed diabetic patient: a CASE report
44. BMC Infect. Dis., 2019; 19: 5. 10.1186/s12879-018-3625-4
45. Google Scholar
46. M. Núñez, J.E. Peacock, R. ChinPulmonary cryptococcosis in the immunocompetent host
47. Chest, 2000; 118: 527-534, 10.1378/chest.118.2.527
48. ArticleDownload PDFView Record in ScopusGoogle Scholar
49. B. Wu, H. Liu, J. Huang, W. Zhang, T. ZhangPulmonary cryptococcosis in non-AIDS patients
50. Clin. Investig. Med., 2009; 32: E70-E77.
51. DAVID S. STEPHENS, Vaccine, 275 (2009)71. — 2. VIEUSSEUX
52. M, J Med Chir Pharmacol, 11 (1805) 163. — 3. S KALENI], E MLINA-

53. RI]-MISSONI I SUR, Medicinska bakteriologija i mikologija (Prehram-beno tehnolo{ki in`enjering, Zagreb, 1995). — 4. MARDE[I] D I SUR.,
54. Pedijatrija, 6. izmjenjeno i dopunjeno izdanje ([kolska Knjiga, Zagreb,
55. 2000). — 5. JC MERCIER, Med Mal Infect, 2009; 39: 452. — 6. SANEZ.
56. -LORENS X, MCCRACKEN JR GH, Lancet, 2003; 361: 2139. — 7. KLEIN
57. JO, FEIGIN RD, MCCRACKEN JR GH, Pediatrics, 1986; 78: 959. THOMPSON MJ, NINIS N, PERERA R, MAYON-WHITE R, PHILIPS C,
58. BAILEY L, HARNDEN A, MANT D, LEVIN M, Lancet, 2006; 367: 397. 9. DELLINGER RP, LEVY MM, CARLET JM, BION J, PARKER MM,
59. JAESCHKE R, REINHART K, ANGUS DC, BRUN-BUISSON C, BEALE
60. E. Horvati} et al.: Meningococcal Sepsis, Coll. Antropol, 2010; 34(4): 1461–1465
61. 1464.