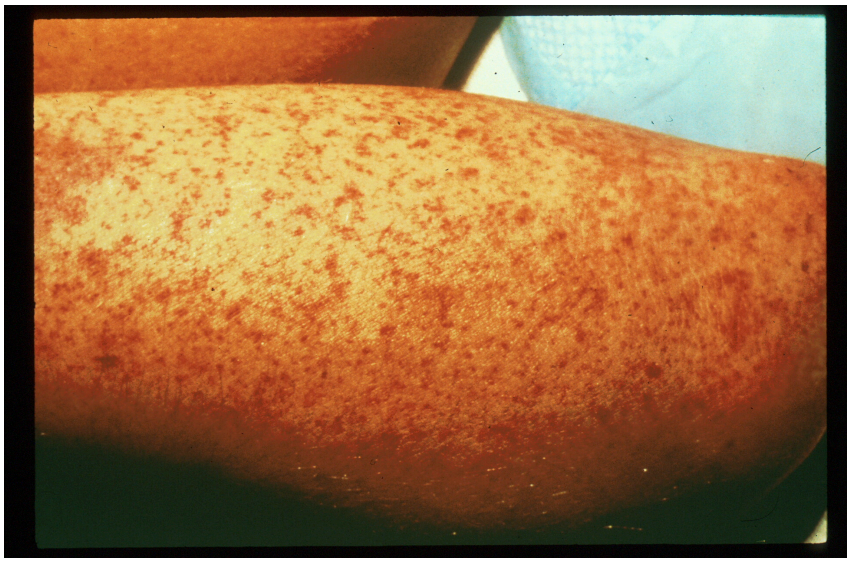
Clinical Presentation

SIGNS AND SYMPTOMS

Overwhelming Meningococcal Sepsis (10%)
• High mortality rate (20–60%)
In a recent European study, approximately 4% of survivors had sequelae
• Sudden onset of illness and rapid progression of clinical course
• Initial presentation may be mild
» Mild tachycardia
» Mild tachypnea/respiratory symptoms
» Mild hypotension
• Fever, chills, vomiting, headache, rash, muscle tenderness
• Toxic appearing
• Infants: lethargy, poor feeding, bulging fontanel
• Rash
» skin, mucous membranes/conjunctivae nonblanching rash (petechial or purpuric) subsequently develops in 80% of children. A maculopapular rash remains in 13%, and no rash occurs in 7%
– May later coalesce and necrose=purpura fulminans
» Macules/Papules (scrapings demonstrate the organism on Gram stain)



• Can deteriorate quickly over several hours
» Hypotension/shock,
» Acidosis
» Acute respiratory distress syndrome (ARDS)
» Disseminated intravascular coagulation (DIC)
• Meningitis may or may not be present
• Waterhouse-Friderichsen syndrome
» Bilateral hemorrhagic destruction of adrenal glands
» Vasomotor collapse
• Acute renal failure
» From prolonged hypotension (low renal perfusion causing acute tubular necrosis)

Meningococcal meningitis (25%)

- » Headache
- » Fever
- » Neck stiffness
- » Confusion
- » Lethargy
- » Obtundation

Septic Arthritis

• Occurs during active meningococcemia
• Multiple joints involved
• Joint pain, redness, swelling, effusion, fever, chills
• Extremely limited or no range of motion

Other Meningococcal Infections

• Occur with meningococcal infection elsewhere
• Conjunctivitis• Sinusitis
• Panophthalmitis
• Urethritis
• Salpingitis
• Prostatitis
• Pneumonia
• Myocarditis/pericarditis

MECHANISM/DESCRIPTION

• Acquired from close contact with an infected individual or an asymptomatic carrier by inhalation of airborne nasopharyngeal droplets carrying the bacteria
• Bacteria attach to and enter nasopharyngeal epithelial cells
• Bacteria spread from the nasopharynx through the bloodstream via entry of vascular endothelium
• Most circulating meningococci eliminated by the spleen—some penetrate endothelial cells at other sites to cause infection (meninges, synovium, conjunctivae)
• Meningococci produce an endotoxin (lipooligosaccharide)

- » Involved in pathogenesis of the skin, adrenal manifestations, and vascular collapse

Capillary leak; From presentation until 2-4 days after illness onset, vascular permeability massively increases. Albumin and other plasma proteins leak into the intravascular space and urine to cause severe hypovolemia and decreased venous return to the heart. Hypovolemia that is resistant to volume replacement is associated with increased mortality due to meningococcal sepsis. Children with severe disease often require fluid resuscitation involving volumes several times their blood volume in the first 24 hours of the illness, mostly in the first few hours. Pulmonary edema is common and occurs after approximately 40 mL/kg of fluid has been given. It is treated with artificial ventilation.

Coagulopathy; In meningococcemia, a severe bleeding tendency often simultaneously exists with severe thrombosis in the microvasculature of the skin, often in a glove-and-stocking distribution that can necessitate amputation of digits or limbs. Clinicians face a dilemma because supplying platelets, coagulation factors, and fibrinogen may worsen the process. Meningococcal infection affects the following three main pathways of coagulation:

- Endothelial injury results in platelet-release reactions.
- The protein C pathway is thought to be crucial in the development of purpura fulminans. A similar rash is seen in neonates with congenital protein C deficiency and in older children who develop antibodies to protein S after varicella infection.
- The fibrinolytic system is also down-regulated in meningococcal disease, reducing plasmin generation and removing an aspect of endogenous negative feedback to clot formation. In addition, plasminogen activator inhibitor levels are dramatically increased, further reducing the efficacy of endogenous tissue plasminogen activator and casting doubt on the use of recombinant tissue plasminogen activator as an effective treatment.

Metabolic derangement; Profound acidosis occurs with severe metabolic abnormalities (which occur paradoxically in the presence of acidosis), including hypokalemia, hypocalcemia, hypomagnesemia, and hypophosphatemia.

Myocardial failure; Myocardial function remains impaired even after circulating blood volume is restored and metabolic abnormalities are corrected. Reduced ejection fractions and elevated plasma troponin levels indicate myocardial damage. A gallop rhythm is often audible, with elevated central venous pressure and hepatomegaly.

• Human oropharynx/nasopharynx—only reservoir
• Carrier usually has developed immunity to serotype-specific antibody (not immune to all serotypes)
» Age <5 years: 1% carrier rate
» Age 20–40 years: 30–40% carrier rate
» Lower rate of immunity in children, which is reflected by the higher rates of infection
• Most common in fall and spring
• Increased incidence in military recruits/close living conditions
• Epidemics—ages 5–9 years most/earliest affected

AETIOLOGY
• *Neisseria meningitidis* (gram negative diplococcus)
» Serotypes A, B, C, D, H, I, K, L, X, Y, Z, 29E, and W135
» Serotype B most common in United States
In Europe, the prevalence varies from 1 to 6.4 per 100,000 persons.
Approximately 2,000-3,000 cases occur each year in the United Kingdom,

where strains in serogroup B cause as many as 70% of cases and those in group C cause 30-40% of cases (1995 data)
» >95% of infections caused by A, B, C, Y, and W135
• Available vaccines offer protection against serotypes A, C, Y, W135 (consider in epidemics)

ESSENTIAL WORKUP

• Do not allow workup (including delay in lumbar puncture) to postpone administration of antibiotics in suspected cases of meningococcemia
• Suspect diagnosis in setting of dramatic clinical presentation
• Gram stain and culture of
» Peripheral blood, CSF, sputum, urine, joint aspirate, or petechial/papular scrapings
» Gram stain: intracellular or extracellular gram-negative diplococci

LABORATORY

• FBC
» Elevated WBC initially, later may be suppressed in severe disease
» Decreased platelet count when large areas of purpura/petechiae or DIC
• U&E's, creatinine, glucose
• CSF: Gram stain, culture, protein and glucose, cell count with differential
» Consistent with bacterial infection in meningococcal meningitis
• Arterial blood gases for acidosis, hypoxia
• Fibrinogen levels, fibrin degradation products, prothrombin time (PT), partial thromboplastin time (PTT) if DIC suspected
• Throat/nasopharyngeal swab
» Positive swab does not establish the diagnosis of meningococcemia
• Analysis of buffy-coat layer of peripheral blood for bacteria if sepsis is suspected
• Blood culture
» Often negative with chronic meningococcemia
» Positive in mild and overwhelming meningococcemia
• Immunoassays (beware false negatives)
• Polymerase chain reaction (PCR), especially useful when antibiotics given before specimen collection

IMAGING/SPECIAL TESTS

• Chest x-ray
» If pneumonia suspected
» For the source of meningococcal sepsis
» To rule out ARDS

Procedures:

- In the presence of a purpuric or petechial rash, lumbar puncture may be hazardous and may add few data to aid in the diagnosis. In a patient with a depressed level of consciousness, shock, or any of the features listed below, lumbar puncture can be delayed, and treatment can begin immediately.

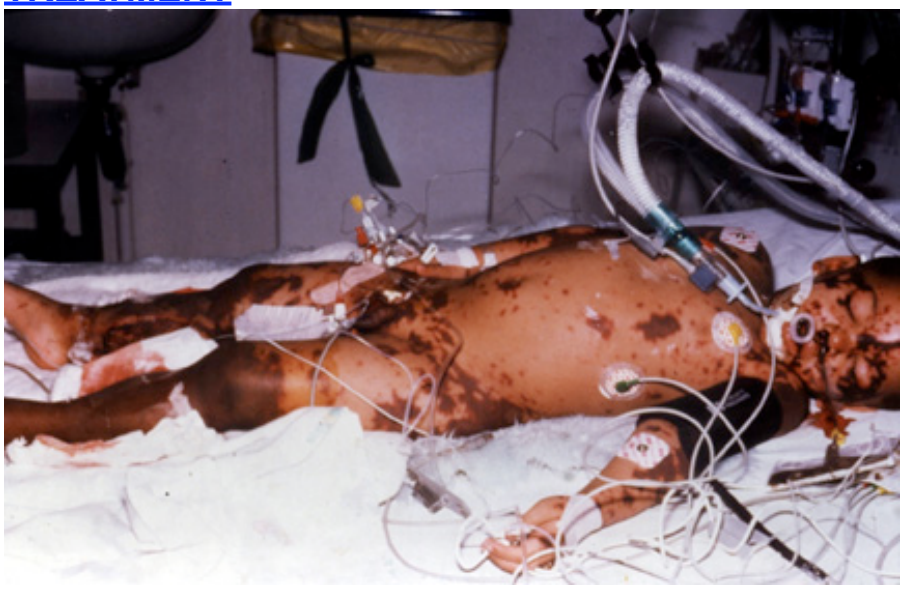
- The following are contraindications to lumber puncture unless increased ICP is ruled out:
  - Prolonged or focal seizures
  - Focal neurological signs
  - Widespread purpuric or petechial rash
  - Glasgow Coma Scale score of less than 13
  - Pupillary dilatation or asymmetry
  - Impaired oculocephalic reflexes (ie, doll's eye reflexes)
  - Abnormal posture or movement, decerebrate or decorticate movement or cycling
  - Coagulation disorder
  - Papilledema
  - Hypertension
  - Signs of impending brain herniation (inappropriately low pulse, increased BP, irregular respiration)
- Although lumbar puncture is generally required to confirm the diagnosis of meningitis, some brainstem herniation (coning) seems to be temporally related to lumbar puncture. If safe to perform, lumbar puncture is useful to establish the presence of meningitis and to identify the causative organism and its antibiotic sensitivity to antibiotics.
  - CSF findings are characteristic in 90% of cases.
  - Findings may include the following: Neutrophil level, 100-60,000 cells/mL; protein level, 100-1,000 mg/dL; and CSF glucose less than 60% of plasma glucose.
  - Results of CSF Gram staining are positive in 40-60% of acute bacterial meningitis cases, even after initial antibiotic treatment. However, results may be negative if antibiotics have been given on an outpatient basis.
  - While lumbar puncture findings remain the criterion standard for diagnosis, current practice is to avoid the procedure in any child with the contraindications listed above.

DIFFERENTIAL DIAGNOSIS

Antiphospholipid Antibody Syndrome
Bernard-Soulier Syndrome
Bone Marrow Transplantation
Cholestasis
Cytomegalovirus Infection
Dengue
Enterococcal Infection
Enteroviral Infections
Hemophilia A and B
Hemophilia C
Herpes Simplex Virus Infection
Kawasaki Disease
Leptospirosis

Marfan Syndrome
Measles
Mycoplasma Infections
Nephrotic Syndrome
Osteogenesis Imperfecta
Polyarteritis Nodosa
Rocky Mountain Spotted Fever
Rubella
Streptococcal Infection, Group A
Syphilis
Vasculitis and Thrombophlebitis
Von Willebrand Disease

TREATMENT



Overwhelming Meningococcal Sepsis
• ABCs—immediate endotracheal intubation for severe acidosis, hypoxia, or decreased mental status

• Treat hypotension
  » 0.9% NS boluses of 20 mL/kg; cautious rehydration with ARDS, congestive heart failure. Some units use 4.5% albumin.
  » Begin dopamine or norepinephrine (epinephrine if no response) if hypotensive after 2 boluses of IV fluids
• Initiate IV antibiotics
  » see below
• Insert Foley catheter to monitor urine output
• Dexamethasone 0.15mg/kg iv: ***controversial*** used in St Mary's, London and Alder Hey, Liverpool. Not standard practice in RMCH, Pendlebury
  » In *Haemophilus influenza* meningitis (APLS Manual)
  » Administer with adrenal gland injury

• DIC treatment
» Administer fresh-frozen plasma and platelet transfusions
» Heparin not indicated unless significant thrombotic complications evident clinically (e.g., cyanosis or cold digits, low urine output despite adequate volume status, and blood pressure)

MEDICATIONS

Meningitis: Initial 'blind' therapy (BNF for Children)

- Transfer patient urgently to hospital.
- If bacterial meningitis and especially if ***meningococcal*** *disease* suspected, general practitioners should give benzylpenicillin (see Benzylpenicillin for dose) before urgent transfer to hospital; cefotaxime may be an alternative in penicillin allergy; chloramphenicol may be used if history of anaphylaxis to penicillin or to cephalosporins
- Consider adjunctive treatment with dexamethasone starting before or with first dose of antibacterial; avoid dexamethasone in septic shock, suspected **meningococcal** disease, or if immunocompromised, or in meningitis following surgery
- In hospital, if aetiology unknown:
Neonate and Child 1–3 months, cefotaxime + amoxicillin
Child 3 months–18 years, cefotaxime

CEFOTAXIME

By intramuscular or by intravenous injection or intravenous infusion
neonate under 7 days 25 mg/kg every 12 hours; dose doubled in severe infection and meningitis
neonate 7–21 days 25 mg/kg every 8 hours; dose doubled in severe infection and meningitis
neonate 21–28 days 25 mg/kg every 6–8 hours; dose doubled in severe infection and meningitis
child 1 month–18 years 50 mg/kg every 8–12 hours; increase to every 6 hours in very severe infections and meningitis (max. 12 g daily)

Prevention of secondary case of meningococcal meningitis (BNF for Children)
if close contact only
Rifampicin by mouth

Neonate 5 mg/kg every 12 hours for 2 days

Child 1 month–1 year 5 mg/kg every 12 hours for 2 days

Child 1–12 years 10 mg/kg (max. 600 mg) every 12 hours for 2 days

Child 12 -18 years 600 mg every 12 hours for 2 days

or

Ciprofloxacin by mouth [not licensed for this indication]

Child 5–12 years 250 mg as a single dose

Child 12–18 years 500 mg as a single dose

or

Ceftriaxone by intramuscular injection [not licensed for this indication] (preferred if pregnant)

Child 1 month–12 years 125 mg as a single dose

Child 12–18 years 250 mg as a single dose

References:

1. Hayden SR, Wolfe R, Barkin RM, Rosen P 'Rosen & Barkin's 5-Minute Emergency Medicine Consult', Second Edition 2005, Lippincott Williams & Wilkins

2. Mackway-Jones K, Molyneux E, Phillips B, Wieteska S, 'Advanced Paediatric Life Support-The Practical Approach' Third Edition 2001, BMJ Books

3. BNF for children 2005, British National Formulary Publications

4. www.emedicine.com 'Meningococcal Infections' (Last Updated: January 26,

2005) Saul Faust, Clinical Lecturer in Pediatric Infectious Diseases, Department of Pediatrics, Imperial College School of Medicine at St Mary's Hospital AND Michael Levin, Head, Professor, Department of Pediatrics, Imperial College School of Medicine at St Mary's Hospital, London, England,

5. A very helpful paediatric medical registrar at RMCH, Pendlebury!