Rocky Mountain Spotted Fever

Background
1. General information
   - Febrile tick-borne illness characterized by non-specific symptoms
   - Under-recognized by healthcare providers
   - Deadly if antibiotic therapy initiated too late

Pathophysiology
1. Infection by *Rickettsia rickettsii*: obligate intracellular gram-negative coccobacillus
   - Zoonosis (tick-borne)
     - Salivary inoculation by tick feeding 2-20 hours, incubation 2-14 days.
     - Vectors
       - American dog tick (Dermacentor variabilis) eastern, central, and Pacific coastal U.S.
       - Rocky Mountain wood tick (Dermacentor andersoni) in western U.S.
       - Brown dog tick (Rhipicephalus sanguineus) in Mexico (isolated cases in Arizona)
       - Cayenne tick (Amblyomma cajennense) species in Central and South America (extends into Texas)
     - Case reports of transmission through blood vectors in healthcare setting, and in aerosolized form in a lab
     - Spread through lymphatic vessels from portal of entry to regional lymph nodes
       - Cell entry
         - Receptor-mediated adhesion to outer surface of endothelial cells, induction of phagocytosis
         - Escape from phagosome and replication within cytoplasm of endothelial cell or macrophage
         - Cell-to-cell intracellular spread via induction of filopodium using host-cell actin polymerization
       - Small-vessel vasculitis
         - Production of reactive oxygen species (ROS), lipid peroxidation of endothelial membrane
         - Release of cytokines from infected endothelium, CD8-mediated cell destruction
         - Prothrombotic state, diffuse endothelial injury, increase in endothelial permeability
       - Multi-organ damage
         - No small vessel lymphatic drainage in brain and lungs; leads to life-threatening edema
         - Hypovolemia and endothelial damage leads to poor perfusion of kidneys and other organs
2. Incidence, Prevalence
   - Annual incidence, 2.2 cases per million persons, most commonly fatal rickettsial disease in the U.S.
     - 56% from North Carolina, South Carolina, Tennessee, Oklahoma, and Arkansas
     - Few cases in Rocky Mountain area
     - 90%–93% of reported cases April – September
     - Males at higher risk due to increased exposure.
     - Highest incidence in children aged <10 years, with another peak in 40–64 year-old adults
     - Incidence higher in whites
   - Incidence likely underestimated due to inaccurate diagnosis or empiric treatment with no confirmatory test.
3. Risk Factors
   - Living in endemic areas
   - Frequent visits to woody or grassy area/poor protective practices
4. Morbidity / Mortality
   - Mortality - 5% treated and 20% untreated
     - Factors associated with increased morbidity/mortality
       - Increased serum Cr
       - Increased age
       - Presence of neurologic involvement
       - Increased AST
       - Increased bilirubin
       - Decreased serum sodium
       - Decreased platelet count
       - Male sex
   - Morbidity is case related, correlates with disease severity
     - Complications:
       - Skin necrosis/gangrene
       - Neurologic deficit
       - Acute respiratory distress syndrome (ARDS)
       - Myocarditis
       - Acute tubular necrosis
       - Disseminated intravascular coagulation (DIC) [rare]
       - 14% of children in one study suffered long-term neurologic defects (speech/swallowing dysfunction, global encephalopathy, gait disturbance, cortical blindness)
         - 2% suffered digital necrosis
Diagnostics

1. History
   o Classic historical findings
     ▪ History of tick bite or exposure, present in 60% of cases.²
       • Often patients report an erythematous or pruritic lesion of unknown origin
     ▪ Recent travel to endemic area²
     ▪ Similar illness in family members
   o Presenting signs and symptoms
     ▪ Classic symptoms, 5-7 days after tick bite, present in only 5% of cases in first 3 days, up to 60-70% by week 2¹
       • Sudden onset of headache, fever, and chills accompanied by rash beginning peripherally on palms, soles, ankles and forearms, then spreading centripitally.¹
         o A study in children ⁷ demonstrated presence of fever (98% of patients), rash (97%), nausea and/or vomiting (73%), and headache (61%).
     ▪ Other symptoms⁸
       • Generalized malaise
       • Myalgias (especially in the back and leg muscles)
       • Nonproductive cough
       • Sore throat
       • Pleuritic chest pain
       • Abdominal pain
     ▪ Symptoms associated with delayed diagnosis⁷
       • No history tick bite
       • No rash
       • No headache
       • Outside peak months of tick activity
       • Complaints other than fever, rash, headache
       • Presentation to healthcare provider early in disease (i.e. before onset of rash)

2. Physical Examination¹
   o Skin - initially blanching pink macules progressing to maculopapular then petechial rash. Classically centripetally spreading.
     ▪ May be confused with drug reaction if beta-lactams given for other presumed illness
     ▪ 10% have no rash, or may be difficult to detect in dark-skinned individuals
   o HEENT- Rarely retinal flame hemorrhage, papilledema, or conjunctivitis
   o Neuro - focal deficits, mental status change, coma, vision loss, hearing loss, seizures, meningeal signs
   o GI - abdominal pain and tenderness (occasionally confused with acute abdomen or cholecystitis)
   o Cardiopulmonary- nonspecific findings, when present, confused with pneumonia, pericarditis, or arterial occlusion
3. Diagnostic Testing
   - Serologic testing
     - Indirect fluorescent antibody (IFA) testing widely available and best method
       - Sensitivity low <10 days of symptoms, but increases to 94% from days 14-21, making this a confirmatory test.
         - Baseline seroprevalence of antibody titers >1:64 estimated around 12%.
       - Enzyme immunoassay, complement fixation, and latex agglutination tests are also used
       - Weil-Felix not recommended
       - Blood culture highly specific and sensitive, but need special laboratory

4. Laboratory evaluation
   - CBC: thrombocytopenia, normal WBC
   - CMP: hyponatremia, mildly elevated liver transaminases
   - CSF: lymphocytic pleocytosis, normal glucose, and mildly elevated protein
   - Peripheral blood smear: normal (rule out Human Granulocytic Ehrlichiosis)
   - Coag Panel: rule out DIC

5. Diagnostic imaging
   - CXR: rule out pneumonia, ARDS

6. Other studies
   - Direct immunofluorescence or immunoperoxidase tests on biopsy of tissue 70% sensitive, 100% specific: vasculitis with distinctive, unique perivascular lymphocytic infiltrate

7. Diagnostic “Criteria”
   - Diagnosis based on high clinical suspicion: fever + headache in endemic area suggestive; rash, thrombocytopenia, and hyponatremia presumptive.
   - Serology - confirmatory test of choice, but high prevalence in asymptomatic population; not specific.
   - Biopsy only 100% specific test

Differential Diagnosis

1. Key Differential Diagnoses
   - Meningococcemia (can occur simultaneously)
   - Staphylococcus aureus bacteremia
   - Other tickborne illness
     - Ehrlichiosis (very similar)
     - Lyme disease
     - Babesiosis
     - Tularemia
     - Colorado tick fever
   - Typhus
   - Viral illness (EBV, HSV-6, parvo B-19, Coxsackie, dengue fever)
   - Drug reaction
2. Extensive Differential Diagnoses
   - Disseminated gonnococcal infection
   - Mycoplasma pneumoniae infection
   - leptospirosis
   - Secondary syphilis
   - Vasculitis
   - TTP
   - Rheumatic fever
   - Toxic shock syndrome
   - Erythema multiforme; Stevens-Johnsons syndrome

Therapeutics
1. Acute Treatment
   - At least 50% of patients will need hospitalization for supportive care\(^2\)
     - Patients with signs of organ dysfunction, severe thrombocytopenia, mental status changes, or need for supportive therapy
     - May need admission to ICU, bolus fluids, transfusion, oxygen therapy, mechanical ventilation, hemodialysis, etc.
   - Appropriate antibiotic therapy should be initiated immediately when suspicion of Rocky Mountain spotted fever, ehrlichiosis, or relapsing fever rather than waiting for laboratory confirmation. (SOR: C)\(^8\)
     - Adverse outcomes increase with delays in diagnosis
   - Treatment with doxycycline or tetracycline is recommended for Rocky Mountain spotted fever, Lyme disease, ehrlichiosis, and relapsing fever. (SOR: C)\(^8\)
     - Minimum 5-7 days of treatment, or 3 days after resolution of fever.\(^2\)
       - Doxycycline 100mg PO/IV BID
       - Alternative: chloramphenicol 500mg IV QID
   - If Meningococcal disease cannot be ruled out, add intramuscular ceftriaxone.\(^2\)
2. Further Management (1-5 days)\(^2\)
   - Fulminant cases lead to death within 5 days of symptoms; common in G6PD deficiency
   - Monitor for prolonged fever, renal failure, myocarditis, meningoencephalitis, hypotension, ARDS, multiple organ failure.
   - Report disease to public health department

Follow-Up\(^3\)
1. Return to Office
   - If being managed as outpatient, follow-up closely to establish treatment success
   - Follow up as appropriate with PCP for long term deficits and complications after hospital admission
2. Consult intensivist or infectious disease subspecialist if:
   - diagnosis unclear
   - severe disease: hypotension requiring aggressive fluid management and pressors, renal failure, pulmonary infiltrates, seizures, or cardiac arrhythmia

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3. Admit to Hospital
   - Signs of organ dysfunction, severe thrombocytopenia, mental status changes, need for supportive therapy, or patient unlikely to be compliant with oral antibiotics

Prognosis
1. Untreated: 80% survival; Treated: 95% survival
   - Worse prognosis:
     - Children under 4 years,
     - Patients older than 40,
     - Lack of tick bite in history,
     - Delayed onset of rash,
     - Prolonged interval between symptom onset and effective antibiotic therapy,
     - G6PD deficiency,
     - Presence of hepatomegaly, jaundice, neurologic deficits,
     - Laboratory evidence of renal impairment.

Prevention
1. Avoidance of tick-infested areas
2. Wearing long pants and tucking the pant legs into socks
3. Applying N,N-diethyl-m-toluamide (DEET) insect repellents
4. Use of bed nets when camping
5. Carefully inspecting oneself frequently while in an at-risk area. (SOR: C)
   - Remove attached ticks promptly (longer attachment increases chances for infection)
     - Grasp body of tick (preferably with blunt, medium-tipped, angled forceps), and apply vertical traction until detachment.
     - Improper removal can lead to detachment of parts of tick proboscis in skin, leading to infection.

Patient Education

References
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