

# Rocky Mountain Spotted Fever

## Background

### 1. General information<sup>1</sup>

- 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<sup>1</sup>

- Zoonosis (tick-borne)
  - Salivary inoculation by tick feeding 2-20 hours, incubation 2-14 days.<sup>2</sup>
    - 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<sup>1</sup>
- Spread through lymphatic vessels from portal of entry to regional lymph nodes.<sup>3</sup>
  - 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<sup>4</sup>
    - 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<sup>2</sup>

- 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<sup>1</sup>
- Incidence likely underestimated due to inaccurate diagnosis or empiric treatment with no confirmatory test.<sup>1</sup>

## 3. Risk Factors<sup>2</sup>

- Living in endemic areas
- Frequent visits to woody or grassy area/poor protective practices

## 4. Morbidity / Mortality

- Mortality - 5% treated and 20% untreated<sup>2</sup>
  - Factors associated with increased morbidity/mortality<sup>5</sup>
    - 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<sup>6</sup>:
    - 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<sup>7</sup> suffered long-term neurologic defects (speech/swallowing dysfunction, global encephalopathy, gait disturbance, cortical blindness)
    - 2% suffered digital necrosis

## Diagnostics

### 1. History

- Classic historical findings
  - History of tick bite or exposure, present in 60% of cases.<sup>2</sup>
    - Often patients report an erythematous or pruritic lesion of unknown origin
  - Recent travel to endemic area<sup>2</sup>
  - Similar illness in family members
- 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 2<sup>1</sup>
    - Sudden onset of headache, fever, and chills accompanied by rash beginning peripherally on palms, soles, ankles and forearms, then spreading centripitally.<sup>1</sup>
      - A study in children<sup>7</sup> demonstrated presence of fever (98% of patients), rash (97%), nausea and/or vomiting (73%), and headache (61%).
  - Other symptoms<sup>8</sup>
    - Generalized malaise
    - Myalgias (especially in the back and leg muscles)
    - Nonproductive cough
    - Sore throat
    - Pleuritic chest pain
    - Abdominal pain
  - Symptoms associated with delayed diagnosis<sup>7</sup>
    - 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 Examination<sup>1</sup>

- 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
- HEENT- Rarely retinal flame hemorrhage, papilledema, or conjunctivitis
- Neuro - focal deficits, mental status change, coma, vision loss, hearing loss, seizures, meningeal signs
- GI - abdominal pain and tenderness (occasionally confused with acute abdomen or cholecystitis)
- Cardiopulmonary- nonspecific findings, when present, confused with pneumonia, pericarditis, or arterial occlusion

3. Diagnostic Testing<sup>1</sup>
  - 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%.<sup>7</sup>
    - 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<sup>2</sup>
  - 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<sup>1</sup>
  - CXR: rule out pneumonia, ARDS
6. Other studies<sup>1</sup>
  - 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.<sup>8</sup>
  - Serology - confirmatory test of choice, but high prevalence in asymptomatic population; not specific.<sup>1</sup>
  - Biopsy only 100% specific test

## Differential Diagnosis<sup>2</sup>

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 gonococcal 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<sup>2</sup>
    - 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)<sup>8</sup>
    - 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)<sup>8</sup>
    - Minimum 5-7 days of treatment, or 3 days after resolution of fever.<sup>2</sup>
      - Doxycycline 100mg PO/IV BID
      - Alternative: chloramphenicol 500mg IV QID
  - If Meningococcal disease cannot be ruled out, add intramuscular ceftriaxone.<sup>2</sup>
2. Further Management (1-5 days)<sup>2</sup>
  - 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<sup>2</sup>

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

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<sup>1</sup>

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)<sup>8</sup>
  - 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.<sup>8</sup>

### Patient Education

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2. <http://www.cdc.gov/rmsf/>

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