Pathogenesis of Rickettsial Diseases

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### Rickettsial Spotted Fevers, Etiologic Agents, and Geographic Distribution

<table>
<thead>
<tr>
<th>Disease</th>
<th>Etiologic Agent</th>
<th>Geographic Distribution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rocky Mountain spotted fever</td>
<td><em>Rickettsia rickettsii</em></td>
<td>The Americas</td>
</tr>
<tr>
<td>African tick bite fever</td>
<td><em>R. africae</em></td>
<td>Africa, West Indies</td>
</tr>
<tr>
<td>American tick bite fever</td>
<td><em>R. parkeri</em></td>
<td>North and South America</td>
</tr>
<tr>
<td>Rickettsialpox</td>
<td><em>R. akari</em></td>
<td>USA, Russia, Croatia, Turkey</td>
</tr>
<tr>
<td>Boutonneuse fever</td>
<td><em>R. conorii</em></td>
<td>Europe, Africa, Asia</td>
</tr>
<tr>
<td>Disease</td>
<td>Etiologic Agent</td>
<td>Geographic Distribution</td>
</tr>
<tr>
<td>----------------------------------------------</td>
<td>-------------------</td>
<td>-------------------------</td>
</tr>
<tr>
<td>North Asian tick typhus</td>
<td><em>Rickettsia sibirica</em></td>
<td>Northern Asia</td>
</tr>
<tr>
<td>Queensland tick typhus</td>
<td><em>R. australis</em></td>
<td>Eastern Australia</td>
</tr>
<tr>
<td>Japanese spotted fever</td>
<td><em>R. japonica</em></td>
<td>Japan, Korea</td>
</tr>
<tr>
<td>Flinders Island spotted fever</td>
<td><em>R. honei</em></td>
<td>Australia, Southeast Asia</td>
</tr>
<tr>
<td>Flea borne spotted fever</td>
<td><em>R. felis</em></td>
<td>Presumably worldwide</td>
</tr>
<tr>
<td>Tick borne lymphadenopathy</td>
<td><em>R. slovaca</em></td>
<td>Europe</td>
</tr>
</tbody>
</table>
Rocky Mountain spotted fever
United States, 1920 - 2004
Comparison of *Rickettsia rickettsii* Infections in Brazil and US

**US**
- 4.4% of cases in household with another case
- Case fatality rate ~4% (23% pre-antibiotic era)
- Median fatal course: 11 days (pre-antibiotic era)
- Pathology seldom shows significant hemorrhage (scattered petechiae)

**Brazil**
- Frequently large clusters of cases
- ~50%
- ~6 days (currently)
- Fatal cases are frequently a severe hemorrhagic fever.
# Signs and Symptoms of African Tick Bite Fever and Boutonneuse Fever

<table>
<thead>
<tr>
<th>Agent</th>
<th>( R. ) africæ</th>
<th>( R. ) conorii</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever (%)</td>
<td>88</td>
<td>100</td>
</tr>
<tr>
<td>Eschar (%)</td>
<td>95</td>
<td>72</td>
</tr>
<tr>
<td>Multiple eschars (%)</td>
<td>54</td>
<td>0</td>
</tr>
<tr>
<td>Regional lymphadenopathy (%)</td>
<td>51</td>
<td>NA</td>
</tr>
</tbody>
</table>
# Signs and Symptoms of African Tick Bite Fever and Boutonneuse Fever

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<thead>
<tr>
<th>Agent</th>
<th>R. africæ</th>
<th>R. conorii</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rash (%)</td>
<td>46</td>
<td>97</td>
</tr>
<tr>
<td></td>
<td>maculopapular (%)</td>
<td>51</td>
</tr>
<tr>
<td></td>
<td>purpuric (%)</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>vesicular (%)</td>
<td>45</td>
</tr>
<tr>
<td>Deaths (%)</td>
<td>0</td>
<td>2</td>
</tr>
</tbody>
</table>
Study sites of African tick bite fever in Cameroon
Among 234 patients in whom malaria or typhoid fever was suspected and ruled out, 32% had IgM antibodies to *Rickettsia africae* (IFA titers 32 to 2,048).
African Tick Bite Fever among Africans

- Comparison of *R. conorii* titers and *R. africae* OmpA and OmpB immunoblotting showed that at least 26 of 75 patients had African tick bite fever. None were documented to have *R. conorii* infections.

- In a subsequent study, 7 patients were diagnosed by real time PCR to have *R. africae* infection (fever, 7; headache, 5; myalgia and/or arthralgia 6; rash, 1; pulmonary signs, 2).
Documented Human Case of *Rickettsia parkeri* Infection in US

- Papules → pustules → ulcers → eschars
- Fever, headache, malaise, myalgias/arthalgias
- Maculopapular rash
- Lymphadenopathy
Documented Human Case of *Rickettsia parkeri* Infection in US

- Eschar biopsy: lymphohistocytic vaculitis, immunohistochemical detection of SFG rickettsiae
- Isolation and PCR identification of *R. parkeri*
- Serum antibody titer of 2048 to *R. parkeri* by IFA
Ecology of Tick-Bite Fever in the Western Hemisphere

Agent- *R. parkeri/R.africae*

**Arthropod Host-**
*Amblyomma maculatum, A. americanum, A. triste, A. cooperi, A. variegatum* ticks

**Established Geographic Distribution-**
U.S., Brazil, Uruguay, French West Indies
Uruguayan Tick-bite Fever

- Fever 100%
- Tender lymphadenopathy 100%
- Eschar 100%
- Maculopapular rash 20-50%

- Some cases confirmed by IFA for antibodies to SFG rickettsiae
- Associated with *R. parkeri*-infected *Amblyomma triste* tick bite

Rev Med Uruguay 17:2; 119-124, 2001
Percentage of Mexican Patients with Different Signs and Symptoms Compared According to the Serological Evidence of SFG Rickettsiosis and Dengue Fever

<table>
<thead>
<tr>
<th>Symptoms and Signs</th>
<th>SFG Rickettsiosis (n=20)</th>
<th>Dengue (n=16)</th>
<th>Neither (n=30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
<td>100</td>
<td>94</td>
<td>97</td>
</tr>
<tr>
<td>Myalgia</td>
<td>95</td>
<td>94</td>
<td>90</td>
</tr>
<tr>
<td>Headache</td>
<td>85</td>
<td>69</td>
<td>67</td>
</tr>
<tr>
<td>Nausea</td>
<td>33</td>
<td>63</td>
<td>33</td>
</tr>
<tr>
<td>Rash</td>
<td>85&lt;sup&gt;a&lt;/sup&gt;</td>
<td>69</td>
<td>27&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Chills</td>
<td>60</td>
<td>56</td>
<td>40</td>
</tr>
<tr>
<td>Eye pain</td>
<td>70</td>
<td>57</td>
<td>57</td>
</tr>
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<tbody>
<tr>
<td>Photophobia</td>
<td>35</td>
<td>31</td>
<td>33</td>
</tr>
<tr>
<td>Vomiting</td>
<td>5&lt;sup&gt;b&lt;/sup&gt;</td>
<td>38&lt;sup&gt;b&lt;/sup&gt;</td>
<td>10</td>
</tr>
<tr>
<td>Cough</td>
<td>15</td>
<td>6</td>
<td>27</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>15</td>
<td>25</td>
<td>7</td>
</tr>
<tr>
<td>Petechiae</td>
<td>10</td>
<td>6</td>
<td>10</td>
</tr>
<tr>
<td>Epistaxis</td>
<td>5</td>
<td>6</td>
<td>3</td>
</tr>
</tbody>
</table>
Clinical Manifestations of *Rickettsia felis* Infection in Four Patients in the State of Yucatán, Mexico

<table>
<thead>
<tr>
<th></th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exanthem</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Fever</td>
<td>+</td>
<td>NR</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Headache</td>
<td>NR</td>
<td>+</td>
<td>+</td>
<td>NR</td>
</tr>
<tr>
<td>Fatigue</td>
<td>NR</td>
<td>+</td>
<td>+</td>
<td>NR</td>
</tr>
<tr>
<td>Myalgia</td>
<td>+</td>
<td>0</td>
<td>+</td>
<td>NR</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>+</td>
<td>0</td>
<td>+</td>
<td>NR</td>
</tr>
</tbody>
</table>
Ecology of Flea-borne Spotted Fever

**Agent** - *R. felis*

**Arthropod Host** - Maintained transovarially in *Ctenocephalides felis* fleas

**Established Geographic Distribution** - U.S., Mexico, Brazil, Peru, Europe, Africa, Asia, presumably worldwide
World Distribution of Louse-borne Typhus Fever at the End of World War II
Recrudescent Typhus

- Latent human infection with *R. prowazekii* for years after primary typhus
- Waning immunity theoretically because of poor nutrition, age, alcohol, stress, or other factors
- Reactivation of *R. prowazekii* infection
- Rickettsiae grow in louse midgut epithelial cells
- After 5-7 days, infectious *R. prowazekii* are present in the louse feces
- Human body louse acquires *R. prowazekii* from human blood
- Rickettsemia
- Louse leaves febrile patient

Human body louse acquires *R. prowazekii* from human blood
Locations of Recent Louse-borne Typhus

Burundi
Rwanda
Congo
Algeria
Russia
Peru
France
Ethiopia
Enormous Epidemic of Louse-borne Typhus during Civil War in Burundi

- Outbreaks in louse-infected jail populations with high incidence and 15% case-fatality rate (1995)
- Diagnosis of typhus in fatal disease of a repatriated Swiss nurse suspected to be a viral hemorrhagic fever provided a delayed alert
Enormous Epidemic of Louse-borne Typhus during Civil War in Burundi

- 100,000 cases of typhus in refugee camps
- Doxycycline treatment (March 1997) and permethrin louse control (August 1997)
Distribution of *Glaucomys volans*
Contemporary Flying Squirrel-associated Typhus in the U.S.

- Fever 100%
- Headache 81%
- Maculopapular rash 66%
- Confusion 44%
- Myalgia 42%
- Case fatality ratio 0%
Among 394 suspected cases of dengue fever, 25.1% had antibodies to typhus group rickettsiae.
Isolation and genetic and antigenic identification of *Rickettsia prowazekii* in cayenne ticks in Nuevo Leon

*Amblyomma cajennense*
Geographic Distribution of Murine Typhus
Ecology of Murine Typhus

Epidemiological cycle of murine typhus.
Rickettsial Genomes in Decay

- The coding sequences of most bacterial genomes range from 87 to 94%.
- The coding sequences of rickettsial genomes range from 76 to 81%.
- 229 intact genes of *R. conorii* that have remnant sequences in *R. prowazekii*.
- *R. typhi* has the most pseudogenes (41).
- Genomes of TG rickettsiae have decayed faster than SFG rickettsiae.
Conclusions

- Loss of genes for sugar metabolism, lipid biosynthesis, nucleotide synthesis, and amino acid synthesis may explain failure of cultivation.
- Strong genetic similarities of the genomes suggest that our seemingly endless creation of new species should terminate.
Rickettsial Genes Effecting Pathogenesis

- **Adhesins**: \textit{ompA}, \textit{ompB}
- **Phagosomes escape**: \textit{pld}, \textit{tlyC}
- **Actin-based mobility**: \textit{rickA}
- **Other potential membranolytic activity**: \textit{tlyA}, \textit{pat-1}
- **Autotransporters**: OmpA, OmpB and Sca proteins
- **Type IV secretion system**: \textit{virB/virD} genes
- **\textit{invA} and others such as \textit{sodB} and \textit{Ip xl}**
Recruitment of Ku70 to bacterial entry site
Binding of bacteria results in recruitment of Ku70 and ubiquitin ligase to cell surface.
Ubiquitin ligase catalyzes ubiquitination of Ku70.
Actin rearrangement results in ruffles that engulf the bacterium

R. conorii

Actin

Ub Ub Ub Ub

Intracellular signaling
Rickettsia phagocytosed by host cell
Rickettsial Propulsion by Host F-actin
Rickettsia conorii Infection of Microcirculation
Pathogenic Mechanisms of Cell and Tissue Injury in Rocky Mountain Spotted Fever

- Production of reactive oxygen species by rickettsia-infected endothelial cells → oxidative stress
- Host factors: older age, glucose-6-phosphate dehydrogenase deficiency (? oxidative stress-induced hemolysis), sulfonamide treatment (? oxidative stress), diabetes, male gender
Cerebral Perivascular Edema in Rickettsial Encephalitis
Rickettsial Vasculitis: the Host Defense Components
Cytokine-activated NO-dependent Rickettsial Killing by Autophagy
Phagolysosomal Rickettsial Death
Relative Susceptibility of Normal C57BL/6, IFN-γ Gene Knockout, and MHC Class I Gene Knockout Mice to *Rickettsia australis*

<table>
<thead>
<tr>
<th>Mouse strain</th>
<th>LD$_{50}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wild-type C57BL/6</td>
<td>3.6 x 10$^4$</td>
</tr>
<tr>
<td>IFN-γ KO</td>
<td>1.95 x 10$^2$</td>
</tr>
<tr>
<td>Perforin KO</td>
<td>31</td>
</tr>
<tr>
<td>MHC – I KO</td>
<td>0.5</td>
</tr>
</tbody>
</table>
Differential Diagnosis of Rickettsial Infections

**Early stage:** dengue, typhoid fever, malaria, drug reaction, hepatitis, secondary syphilis, measles, rubella, enteroviral and other arboviral infections

**Severe stage:** meningococcemia, staphylococcal bacteremia, toxic shock syndrome, leptospirosis, viral hemorrhagic fever, thrombotic thrombocytopenic purpura
Differential Diagnosis of Rickettsial Infections

Prominent gastrointestinal symptoms: viral or bacterial enterocolitis, acute surgical abdomen

Prominent neurologic signs: viral or bacterial meningoencephalitis

Prominent pulmonary signs: pneumonia, ARDS
Why Rickettsial Diseases Are Neglected and Seldom Diagnosed

- Diagnostic assays are rarely available in the tropics
- Single sample acute serologic diagnosis is insensitive
- Lack of epidemiologic data (incidence, geographic distribution, seasonality) in most tropical locations bury rickettsioses among malaria, typhoid, acute viral syndrome, FUO considerations
- Paucity of clinical studies that address rickettsioses in tropics
Opportunities

- Absence of established centers of excellence for the study of rickettsioses in the tropics.
- Growing cadre of well trained rickettsiologists in South America and Africa.
- Regions with sufficiently high incidence to investigate prospectively mechanisms of human immunity, host risk factors for severity of illness, basic science of diverse interesting rickettsial strains, and vector biology.