Update on Australian Rickettsial Infections

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What are rickettsiae?
• Bacteria
• Rod-shaped (0.4 x 1.5µm)
• Gram negative
• Obligate intracellular growth
• Energy parasite of host cell
• Invertebrate → vertebrate

Vertical transmission through life stages
• Egg
• Larva
• Nymph
• Adult (♀♂)

Horizontal transmission via invertebrate bite/faeces (larva “chigger”, nymph, adult♀)

Classification of Rickettsiae
(phylum) α-proteobacteria
(genus)
1. Rickettsia – Spotted Fever Group
   Typhus Group
2. Orientia – Scrub Typhus
3. Ehrlichia (not in Australia?)
4. Anaplasma (veterinary only in Australia?)
5. Rickettsiella (? Koalas)

NB: Coxiella burnetii (Q fever) is a γ-proteobacterium NOT a true rickettsia despite being tick-transmitted (not covered in this presentation)
### Rickettsiae from Australian Patients

#### Rickettsiae (human disease)

<table>
<thead>
<tr>
<th>Rickettsiae</th>
<th>Vertebrate Host</th>
<th>Invertebrate Host</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A. Spotted Fever Group Rickettsia</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>i. <em>Rickettsia australis</em> (Queensland Tick Typhus)</td>
<td>Native rats</td>
<td>Ticks (Ixodes holocyclus, <em>I. tasmani</em>)</td>
</tr>
<tr>
<td>ii. <em>R. honei</em> (Flinders Island Spotted Fever)</td>
<td>Native reptiles (blue-tongue lizard &amp; snakes)</td>
<td>Tick (Haemophysalis novaeguineae)</td>
</tr>
<tr>
<td>iii. <em>R. honei</em> sub sp. <em>marmionii</em> (Australian Spotted Fever)</td>
<td>Unknown</td>
<td>Tick (Amblyomma triguttatum)</td>
</tr>
<tr>
<td>iv. <em>R. gravesii</em> (Human pathogen)</td>
<td>Macropods (kangaroo, wallabies)</td>
<td>Feral pigs (WA)</td>
</tr>
<tr>
<td>v. <em>R. felis</em> (cat flea typhus)</td>
<td>cats/dogs</td>
<td>Flea (Ctenocephalides felis)</td>
</tr>
</tbody>
</table>

All these rickettsiae grown in pure culture.

#### Rickettsiae in Australian patients (cont.)

<table>
<thead>
<tr>
<th>Rickettsiae</th>
<th>Vertebrate Host</th>
<th>Invertebrate Host</th>
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<tbody>
<tr>
<td><strong>B. Typhus Group Rickettsia</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>R. typhi</em> (murine typhus)</td>
<td>Rodents (rats, mice)</td>
<td>Fleas (Ctenocephalides felis)</td>
</tr>
<tr>
<td>(R. prowazekii) (epidemic typhus) (Brill’s disease)</td>
<td>(Humans)*</td>
<td>(Human body louse)*</td>
</tr>
<tr>
<td><strong>C. Scrub Typhus Rickettsia</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Orientia tsutsugamushi (various antigenic forms)</td>
<td>Bandicoots, various native rodents</td>
<td>Mites (larval stage only &quot;chiggers&quot;) (Leptotrombidium deliense)</td>
</tr>
</tbody>
</table>

* Migrants from endemic countries; returned soldiers after WWII
† not in Australia?

### Rickettsiae from Australian animals

1. **Anaplasma platys**
   - Dog cyclic thrombocytopenia.
   - Tx by brown dog tick, *Rhipicephalus sanguineus* (outback Australia)

2. **Anaplasma marginale**
   - Cattle tick fever (~10% cases)*
   - *Rhipicephalus* (*Boophilus*) *micropus* (endemic in northern Australia)

3. **Rickettsia felis**
   - Dogs may be bacteraemic but asymptomatic (~9% prevalence in Brisbane)
   - Reservoirs for flea infection.

4. **No *Ehrlichia canis* in Australian dogs**
   - 90% cases caused by *Babesia spp.*
Rickettsia present in Australian animals but unlikely to be human pathogens

<table>
<thead>
<tr>
<th>Rickettsia (Spotted Fever Group)</th>
<th>Vertebrate Host</th>
<th>Invertebrate Host</th>
</tr>
</thead>
<tbody>
<tr>
<td>R. antechini</td>
<td>Antechinus (marsupial mouse) (WA)</td>
<td>(? Tick (Ixodes antechini))</td>
</tr>
<tr>
<td>R. argasii</td>
<td>Microbat (VIC)</td>
<td>Bat tick (Argus dewae)</td>
</tr>
</tbody>
</table>

Both rickettsiae in pure culture

† these ticks do not bite humans

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Rickettsiae present in Australia as identified genomes only (not yet isolated nor grown in pure culture)

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<th>Rickettsia</th>
<th>Vertebrate Host</th>
<th>Invertebrate Host (ticks)</th>
</tr>
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<tbody>
<tr>
<td>1. R. tasmanensis</td>
<td>Tasmanian Devil (TAS)</td>
<td>Ixodes tasmani</td>
</tr>
<tr>
<td>2. R. massiliae – like (Koala genotype) /Rickettsiella sp.</td>
<td>Koala (VIC &amp; NSW)</td>
<td>I. tasmani</td>
</tr>
<tr>
<td>3. R. bellii – like</td>
<td>Echidna (VIC)</td>
<td>Bothriocroton concolor</td>
</tr>
<tr>
<td>4. R. massiliae – like</td>
<td>Wombat (VIC)</td>
<td>B. auruginans</td>
</tr>
<tr>
<td>5. R. tamurae – like</td>
<td>Reptiles (NT)</td>
<td>Amblyomma fimbriatum</td>
</tr>
</tbody>
</table>

Clinical presentation of rickettsial disease in Australian patients

Not a lot of difference between the different rickettsiae in presenting symptoms

- Fever
- Rash (macular, papular, vesicular)
- Eschar (following tick or mite bite)
- Myalgia
- Headache
- Acute fatigue chronic fatigue (“post-infectious fatigue”)

Severity and duration of illness varies significantly
Laboratory findings in rickettsial disease in Australian patients.

- Blood film often normal (△△ "viral")
  - ↑ Polymorphs
  - ↓ Lymphocytes
  - ↓ Platelets
- ↑ Liver function tests (transaminitis)
- ↓ Na
- ↑ CRP (>100)

Specific investigations for diagnosis of rickettsial infection

1. Doctor must think of rickettsia as part of differential diagnosis.
2. Early in infection (day 1 – 5)
   i. PCR
      Assays can differentiate
      - Spotted Fever Group/Typhus Group rickettsiae
      - Scrub typhus Group rickettsiae
      If sufficient DNA available it may be possible to sequence rickettsia specific genes (e.g. omp A, omp B, citrate synthase) and compare them with sequences of known rickettsiae and thus definitively identify the rickettsia.
      Samples:
      - Eschar swab (+++)
      - Eschar biopsy (+++)
      - Blood (EDTA) (+) (bacteraemia transient)

ii. Culture
    Research technique, only done in reference laboratories.
    Slow, difficult
    Requires tissue culture facilities (e.g. VERO, DH82)
    Sample:
    - blood (EDTA)
    - Eschar biopsy
Later in infection (> day 6)

iii. Serology – main laboratory diagnostic modality

"Microimmunofluorescence" is gold-standard assay type.

**Spotting Fever Group antigens used in ARRL.**
- *R. australis* (Queensland Tick Typhus)
- *R. honei* (Flinders Island Spotted Fever)
- *R. conorii* (Mediterranean Spotted Fever)
- *R. africae* (African Tick Bite Fever)
- *R. rickettsii* (Rocky Mountain Spotted Fever)
- *R. felis* (cat flea typhus/ Flea-borne Spotted Fever)

**Typhus Group**
- *R. typhi* (murine typhus)
- *R. prowazekii* (Epidemic typhus)

**Scrub Typhus Group**
- *Orientia tsutsugamushi*
- *O. chuto* (new species).

For refugees from endemic countries (reactivation, Brill’s disease).

**Microimmunofluorescence serology for diagnosis of rickettsial infection**

Patient sera is screened at 1:128 dilution.

If negative, reported (titre < 1:128)

If positive, titration done:
- 1/128
- 1/256
- 1/512
- 1/1024 (if + reported as “titre ≥ 1:1024”)*

* If comparing two strongly positive sera from the same patient it is necessary to titrate both sera to end-point to look for changing titres.

* If laboratory has earlier serum please advise them of this on pathology request form and ask the laboratory to titrate both sera together (“in parallel”). This reduces run to run variability in the IF assay and will demonstrate genuine changes in antibody titre if present (e.g. 1:1024 → 1:4096) or not (e.g. 1:1024 → 1:1024).
Treatment

**Doxycycline**
100mg q12hr 7 days

or

**Azithromycin**
250mg q24hr 7 days

Response is usually rapid in rickettsial infections

Where does rickettsial disease occur in Australia

[Map of Australia showing rickettsial disease distribution]
Australian Spotted Fever

Where does rickettsial disease occur in Australia

Where does rickettsial disease occur in Australia

Where does rickettsial disease occur in Australia
SPOTTED FEVER GROUP

SPOTTED FEVER GROUP RICKETTSIA
R. akari
Detected (titre = 512)
R. australis
Detected (titre = 1024)
R. alexander
Detected (titre = 1024)
R. australis
Detected (titre = 512)
R. ferris
Not detected (titre = 128)
R. typhi
Not detected (titre = 128)

TYPHUS GROUP RICKETTSIA
R. prowazekii
Not detected (titre = 128)
R. mooseri
Not detected (titre = 128)
R. prowazekii
Not detected (titre = 128)
Request for Australian ectoparasites!

Medical doctors and veterinarians.
Please send us ectoparasites for analysis:
Ticks, fleas, lice, mites

Contact: Dr Stephen Graves
Ph: 0407 506 380
(expenses will be reimbursed)

Conclusion
Australia has an almost complete set of rickettsial infections transmitted to human by:
- Tick bite (Spotted Fever Group rickettsia)
- Mite bite (scrub typhus)
- Flea bite (murine typhus or cat flea typhus)
- Inhaled infected flea faeces (murine typhus or cat flea typhus)

Conclusion (cont.)
- Other rickettsial infections occur in returned travellers, especially R. africae (African Tick Bite Fever).
- Doctors must think of rickettsial diagnosis in the differential.
- Clinical diagnosis alone is difficult.
- Laboratory tests (especially serology) are usually very helpful.
- Treatment relatively easy usually.
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