Brucellosis

By
Steven Phillips, MD
Brucellosis—Basics

• The Most Common Zoonosis in the World

• Cousin to Bartonella, Similar Antibiotic
• Resistance, Generally More Severe Illness

• The Many Names of Brucellosis:
  – Mediterranean Fever
  – Bang's Disease
  – Malta Fever
  – Undulant Fever (fevers worse in afternoon-eve)
  – Gibralta Fever
  – Rock Fever (as in rock of Gibralta)
Brucellosis—Cause

Multiple Species of Brucella Genus

Six Initially Recognized Species

B. melitensis
B. suis
B. abortus
B. neotomae
B. ovis
B. canis
Brucella—
Newly Discovered Species

New Species Continue to be Discovered

B. ceti
B. pinnipedialis
B. microti (not to be confused with babesia)
B. inopinata

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Percentage</th>
</tr>
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<tbody>
<tr>
<td>Fever</td>
<td>78%</td>
</tr>
<tr>
<td>Malaise</td>
<td>71%</td>
</tr>
<tr>
<td>Sweats</td>
<td>54%</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>65%</td>
</tr>
<tr>
<td>Myalgia</td>
<td>47%</td>
</tr>
<tr>
<td>Back Pain</td>
<td>45%</td>
</tr>
<tr>
<td>Chills</td>
<td>45%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>39%</td>
</tr>
<tr>
<td>Headache</td>
<td>35%</td>
</tr>
<tr>
<td>Weight Loss</td>
<td>26%</td>
</tr>
<tr>
<td>Splenomegaly</td>
<td>26%</td>
</tr>
<tr>
<td>Hepatomegaly</td>
<td>23%</td>
</tr>
<tr>
<td>Spondylitis</td>
<td>16%</td>
</tr>
<tr>
<td>Sacroiliitis</td>
<td>16%</td>
</tr>
<tr>
<td>Orchitis</td>
<td>10%</td>
</tr>
<tr>
<td>Neurologic</td>
<td>4%</td>
</tr>
<tr>
<td>Endocarditis</td>
<td>2%</td>
</tr>
</tbody>
</table>

Dean, Crump, Greter et al., 2012
Brucellosis—Ocular Disease

132 Patients Evaluated

Ocular Disease in 21%

Of Those:
- Anterior Uveitis 41%
- Choroiditis 32%
- Panuveitis 9%
- Papilledema 9%
- Retinal Hemorrhage 9%

Sungur, Hazirolan, Gurbuz, et al., 2012
<table>
<thead>
<tr>
<th>Laboratory Feature</th>
<th>Percentage</th>
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<tbody>
<tr>
<td>Elevated CRP</td>
<td>58%</td>
</tr>
<tr>
<td>Elevated ESR</td>
<td>51%</td>
</tr>
<tr>
<td>Anemia</td>
<td>40%</td>
</tr>
<tr>
<td>Lymphomonocytosis</td>
<td>28%</td>
</tr>
<tr>
<td>Elevated ALT/AST</td>
<td>25%</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>11%</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>10%</td>
</tr>
<tr>
<td>Leukocytosis</td>
<td>9%</td>
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Buzgan, Karahocagil, Irmak, et al., 2010
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<tr>
<th>Most Often Disabling</th>
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<tbody>
<tr>
<td>“debilitating and chronic”</td>
</tr>
<tr>
<td>Dean, Crump, Greter et al., 2012</td>
</tr>
<tr>
<td>“significant morbidity and mortality” (2%)</td>
</tr>
<tr>
<td>Buzgan, Karahocagil, Irmak, et al, 2010</td>
</tr>
<tr>
<td>asymptomatic infection occurs mainly from low virulence species, ie B. canis</td>
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<tr>
<td>Zhen Q1, Lu Y, Yuan X, et al, 2013</td>
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## Brucellosis—Microbiology

<table>
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<th>Aerobic coccobacillus</th>
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<td>Intracellular</td>
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<tr>
<td>Gram negative</td>
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### Intracellular Survival: Co-opts Autophagy Via Type IV Secretion System

- Forms Brucella Containing Vacuole (BCV)
- Replicative Niche within BCV
### Brucellosis—Transmission

- **Unpasteurized Dairy**

- **Animal Exposures—Multiple Body Fluids**

- **Laboratory Exposures—Aerosolization**

- **Humans Considered 'Dead End' Hosts**
  - But Uncommonly: Transplacental, Breast Milk, & Sexual Transmission Have Occurred
Brucellosis—Seasonality

12.8% of Cases Present in the Winter
Hasanjani Roushan, Mohrez, Smailnejad Gangi, et al, 2004

78% Present in the Spring/Summer
Lulu, Araj, Khateeb, 1988
Brucellosis—Vector-born?

Isolated from ticks

Gudoshnik, 1958
Sidorov, 1960
Sidorov, Gubina, 1962
Taran, Pogorelov, Kulikova, et al, 1966
Sidorov, Gubina, 1976

Isolated from fleas

Ozsan, 1962
Brucellosis—Vector-born?

In lice, replication & transovarial transmission demonstrated


“suggests possible Brucella transmission by blood sucking insects in nature”

Vitry, Hanot, Deghelt et al, 2014
Brucellosis—Diagnosis

Clinical Diagnosis

Laboratory Diagnosis

- Culture—Fastidious, Slow Growing, False Negatives

- PCR—Strain Limitations, Multiple Sampling

- Serologies—Subject to False Seronegativity
  - ELISA & Agglutination Antibody (Most Common)
  - Complement Fixation, Brucellacapt (Neither in US)
Brucellosis—Treatment

Antibiotics Most Commonly Used

- Streptomycin or Gentamicin
- Doxycycline
- Rifampin
- Bactrim
- Quinolones

Resistant to Ceftriaxone
Brucellosis—Treatment

Agreed Upon Facts:

- Earlier Treatment = Better Outcomes
- Single Agent Antibiotics Don't Work
- Treatment < 6 Wks = Very High Failure Rates
Brucellosis—Minimum Treatment

Aminoglycoside x 3 wks + Doxy x 6 wks
or
Doxy + Rifampin x 6 wks

-Aminoglycoside + Doxy is More Effective
-Streptomycin = Gentamicin in Efficacy

10% Failure in Early Uncomplicated Disease
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<th>Brucellosis—Treatment</th>
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<tbody>
<tr>
<td>• Even with Longer Treatments—</td>
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<tr>
<td>• High Failure Rate in Complicated Disease</td>
</tr>
<tr>
<td>• Brucella Spondylitis</td>
</tr>
<tr>
<td>• 40% Failure/Relapse Despite 120 Days of Combination Antibiotics</td>
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</table>

Solera, Lozano, Martinez-Alfaro, 1999
Brucellosis—Long Term Combination Antibiotics

18 Brucellar Spondylitis Patients—
- Triple Antibiotics for 18 Months
- Result: All Patients No Longer Disabled

Aminoglycoside, doxy, rifampin—3 wks

Then, doxy/rifampin/tmp-smx or doxy/rifampin/cipro for 18 months

Ioannu, Karadima, Pneumaticos, et al. 2011
Chronic Brucellosis

Been Formally Studied for Over 100 Years
First Pubmed Article for Undulant Fever Dated 1912

Still No Agreed Upon Curative Treatment

Chronically Symptomatic & Repeatedly Relapsing Brucellosis Occurs Despite Every Antibiotic Treatment Known
Chronic Brucellosis

2-33 years after diagnosis & treatment

- 3 Groups
  - Chronic Focal Symptoms
  - Chronic Subjective Symptoms
  - Asymptomatic

“B. melitensis DNA after therapy in 80% of patients”
Required up to 28 PCR samples from each patient

Castaño, Solera, 2009
## Brucellosis—Mechanisms of Virulence & Persistence

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Author(s)</th>
<th>Year</th>
</tr>
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<tbody>
<tr>
<td><strong>L-forms</strong></td>
<td>Schmitt-Slomska, Caravano, Anoal, et al</td>
<td>1981</td>
</tr>
<tr>
<td><strong>Biofilms</strong></td>
<td>Almirón, Roset, Sanjuan</td>
<td>2013</td>
</tr>
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</table>
Brucella Induced Anergy

'Cured' seronegative patients have continued T-cell anergy as if they were still infected

Skendros, Sarantopoulous, Tselios, et al., 2008
Reversing Brucella Induced Anergy

Levamisole: Dual Activity:
- Antiparasitic
- Immunopotentiator

Taki, Schwartz, 1994

Antibiotics + Levamisole Superior to Only Antibiotics

Irmak, Buzgan, Karahocagil et al, 2003
Levamisole Toxicity

Can Cause Severe Auto-Immune Disease

- Neutropenia
- Vasculitis

Arora, 2013

Withdrawn from the US Market in 1999
Other Possible Immunopotentiation Options

Ivermectin—Antiparasitic

Immunopotentiation Demonstrated

Njoo, Hack, Oosting, 1994
Blakley, Rousseaux, 1991

-Does Not Cause Auto-Immune Side Effects

-Has Not Been Studied for Brucellosis
Other Possible Immunopotentiation Options

14 patients with relapsing chronic brucellosis, anergic to brucella antigens

- Vitamin C—1 gm per day orally for 15 Days
- Significant Reversal of Brucella-Induced Anergy

Boura, Tsapas, Papadopoulou, et al., 1989
Other Possible Immunopotentiation Options

**Polyporus Umbellatus—Edible Mushroom**

Reversal of Brucella-Induced Anergy

Zhang, Gao, Cun, et al., 1993

Activates Macrophages Via TLR-4

(Bruccella Not Evaluated in this Study)

Li, Xu, 2011
Immunology: Gamma Interferon

Animal Inoculation

- Attenuated Brucella = Strong Gamma Interferon Response
- Virulent Brucella = Aborted Gamma Interferon Response

Pérez-Sancho, Durán-Ferrer, García-Seco, et al., 2014
“interferon-gamma is the principal cytokine active against Brucella infection”

Skendros, Boura, 2013

Immunotherapy Studies with Gamma Interferon Have Not Been Done
Immuno-Therapy

32 Anergic Chronic Brucellosis Patients

Group 1: Interferon Alpha
Group 2: Levamisole
Group 3: Conventional Antibiotics

Groups 1 & 2: Clinical Improvement and Augmented Immune Response to Brucella

Group 1 > Group 2; Group 3 Was No Change

Printzis, Raptopoulou-Gigi, Orphanou-Koumerkeridou, et al., 1994
Ever Get the Feeling that Nobody’s Listening?

Will Work For a Cure