



Brucellosis

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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-even)
 - Gibraltar Fever
 - Rock Fever (as in rock of Gibraltar)

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

Zygmunt, Jacques, Bernardet, et al, 2012

Brucellosis—Clinical Features

Metanalysis from 57 Studies

Fever	78%	Weight Loss	26%
Malaise	71%	Splenomegaly	26%
Sweats	54%	Hepatomegaly	23%
Arthralgia	65%	Spondylitis	16%
Myalgia	47%	Sacroiliitis	16%
Back Pain	45%	Orchitis	10%
Chills	45%	Neurologic	4%
Fatigue	39%	Endocarditis	2%
Headache	35%		

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

Brucellosis— Laboratory Features

Review of 1028 Cases

Elevated CRP	58%
Elevated ESR	51%
Anemia	40%
Lymphomonocytosis	28%
Elevated ALT/AST	25%
Leukopenia	11%
Thrombocytopenia	10%
Leukocytosis	9%

Buzgan, Karahocagil, Irmak, et al., 2010

Most Often Disabling

“debilitating and chronic”

Dean, Crump, Greter et al., 2012

“significant morbidity and mortality” (2%)

Buzgan, Karahocagil, Irmak, et al, 2010

asymptomatic infection occurs mainly
from low virulence species, ie B. canis

Zhen Q1, Lu Y, Yuan X, et al, 2013

Brucellosis—Microbiology

Aerobic coccobacillus

Intracellular

Gram negative

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

Neglia, Veneziano, De Carlo E, et al, 2013

“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

Brucellosis—Treatment

- Even with Longer Treatments—
- High Failure Rate in Complicated Disease
- **Brucella Spondylitis**
- **40% Failure/Relapse Despite 120 Days of**
- **Combination Antibiotics**

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

Blebs

Gamazo C, Winter AJ, Moriyón, et al, 1989

L-forms

Schmitt-Slomska, Caravano, Anoal, et al, 1981

Biofilms

Almirón, Roset, Sanjuan, 2013

Brucella Induced Anergy

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

Skendros, Sarantopoulos, 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 Immunopotential Options

Ivermectin—Antiparasitic

Immunopotential Demonstrated

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

- Does Not Cause Auto-Immune Side Effects
- Has Not Been Studied for Brucellosis

Other Possible Immunopotential 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 Immunopotential Options

Polyporus Umbellatus—
Edible Mushroom

Reversal of Brucella-Induced Anergy

Zhang, Gao, Cun, et al., 1993

Activates Macrophages Via TLR-4
(Brucella 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

Immunology: Gamma Interferon

“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?

