



Chlamydia Connection: Is Coronary Artery Disease an Infectious Disease?

One third of patients with acute myocardial infarction lack known risk factors for atherosclerosis. Why do these individuals develop coronary artery disease? Although it is known that inflammation triggers coronary thrombosis, we do not know what causes this inflammatory event. Could an infectious agent like *Helicobacter pylori* (which causes peptic ulcer disease) or *Chlamydia pneumoniae* be responsible for coronary artery disease and myocardial infarction? The latest epidemiologic and treatment studies suggesting this exciting new connection will be discussed.

- Review the current literature that describes the association of *Chlamydia pneumoniae* with cardiovascular disease.
- Discuss the potential treatment modalities based on these studies.

TU-115
Tuesday, October 12, 1999
8:00 AM - 8:55 AM
Room # N204
Las Vegas Convention Center

**Research: Bayer, Viropharma, Lilly, Ortho-McNeil*

FACULTY

*David A Talan, MD, FACEP

Professor, Medicine, UCLA School of Medicine, Los Angeles; Chair, Department of Emergency Medicine; Faculty, Division of Infectious Diseases, Olive View-UCLA, Sylmar, California

The Chlamydia Connection

David A. **Talan**, MD, FACEP, FIDSA
Professor of Medicine
UCLA **School** of Medicine
Dept. of Emergency Medicine **and**
Division **of Infectious** Diseases
Olive View-UCLA Medical Center

Coronary Artery Disease: Risk Factors

- . Cholesterol
- . Smoking
- Hypertension
- . Diabetes

Coronary Artery Disease: No Risk Factors

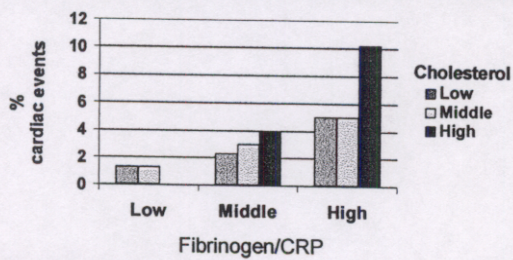
- **30%** Of MI patients - no **risk factors**
- . 1.5 million hospital admissions
- . **900,000** deaths

Site of Acute MI

- 78% of lesions - $\leq 50\%$ stenosis
- . Ulceration leads to accelerated stenosis
- . Length and roughness important

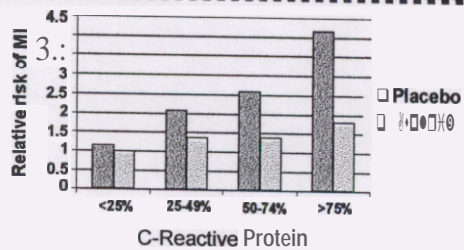
Giroud D. *Am J Cardiol* 1992;69:729.

Inflammation and CAD



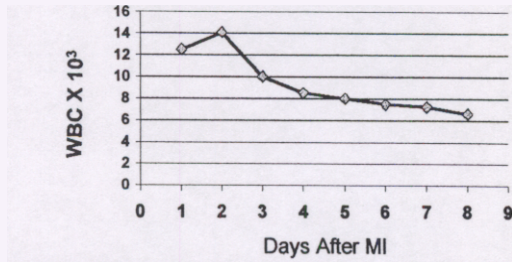
Thompson SG. *NEJM* 1998;339:635

Inflammation, CAD, and Aspirin



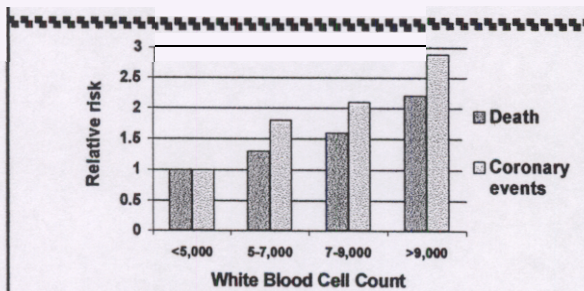
Ridker PM. *NEJM* 1997;336:973

White Blood Cell Count and AMI



Vallance BD. *Brit Heart J* 1978;40:64.

White Blood Cell Count Predicts MI



Lowe GDO. *Thrombosis Haemostasis* 1985;54:700.

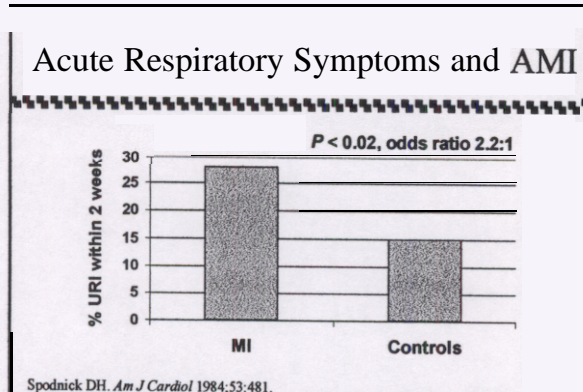
AMI/CAD and Infection

- . Etiology of **CAD/MI** in patients **without** risk factors?
- . Acute inflammatory **insult** = ? trigger

m j

Acute MI: Pathogenesis

- . Macrophage infiltration - "abscesses"
- . Platelet aggregation, thrombosis, occlusion



Chlamydia pneumoniae - History

- 1950s respiratory epidemics + *Chlamydia* CF.
no bird exposure - "para-ornithosis"
- 1980 + IgM to "new" strain of *C. psittaci*, TW-183
(1965), AR-39 -Taiwan acute resp. agent - "TWAR"
- 1986 cultured from seroconverting patients with
respiratory tract infection in Seattle

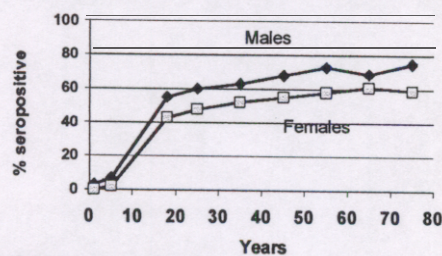
Kauppinen M *Clin Infect Dis* 1995;21 S244

C. pneumoniae - Epidemiology

- . 50% of adults seropositive
- . Prevalence rises from school age
 - Previous infection provides partial immunity
 - 2-3 infections in lifetime
 - Mostly mild, sub-acute uri
 - 5-15% of pneumonia cases

Kauppinen M. *Clin Infect Dis* 1995;21:S244.

Chlamydia pneumoniae: Seroprevalence



Grayston JT. *Clin Infect Dis* 1992;15:757.

C. pneumoniae - Pathogenesis

- . Peri-bronchial infiltration of lymphocytes
 - Inflammation lasts 2 months
 - Re-infections - more pronounced inflammation. CP more difficult to culture
 - Tendency of infections to recur after treatment

Kauppinen M. *Clin Infect Dis* 1995;21:S244.

C. pneumoniae - Clinical

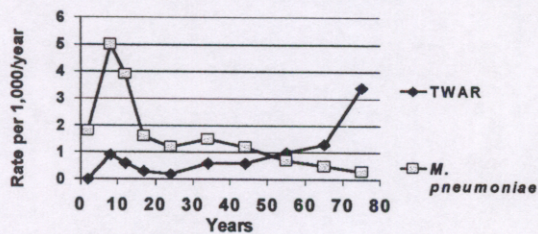
Mild atypical pneumonia

- . gradual onset prolonged course
- pharyngitis, hoarseness precede pneumonia
- . headache common
- . usually non-purulent sputum
- single sub-segmental infiltrate most common

Severe acute bronchopneumonia

- bacterial co-infection (66%)

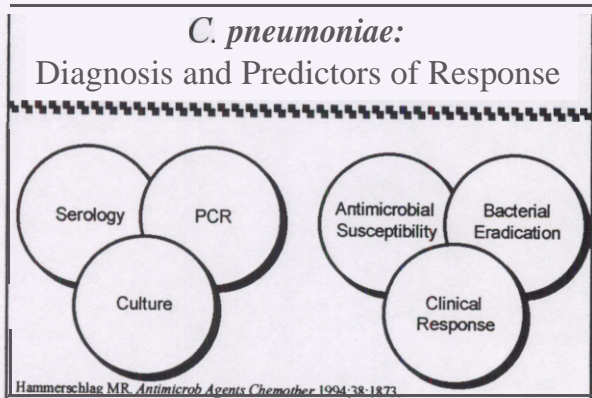
C. pneumoniae: Incidence of Pneumonia



Grayston JT. Clin Infect Dis 1992;15:757.

C. pneumoniae - Diagnosis

- | | |
|-----------|---|
| ■ Culture | only 50% seroconverted cases, colonizer |
| ■ EIA LPS | small amnts., common chlamydial LPS |
| ■ CF Ab | (-) in re-infections, IgG4, IgA interfere |
| ■ EIA Ab | to chlamydial LPS (seroconvert 5 days) |
| ■ MIF Ab | ?best but subject to interpretation |
| ■ CIC | (+) chronic infection, CAD |
| ■ PCR | proper sample? |



C. pneumoniae - Susceptibility

	<u>MIC</u>	<u>MCC</u>
Erythromycin	0.01-0.25	0.06-0.25
Azithromycin	0.06-0.5	0.125-0.5
Clarithromycin	0.004-0.25	0.008-0.25
Doxycycline	0.03-0.25	0.125-0.5
Ciprofloxacin	0.25-16	0.25->16
Ofloxacin	0.5-2	0.5-2
Levofloxacin	0.125-0.5	0.125-0.5
Ampicillin	>100	0.8-1.6
Sulfasoxazole	>400	>400

Hammerschlag MR. *Antimicrob Agents Chemother* 1994;38:1873.

- C. pneumoniae* - Treatment
- Tetracycline 2-3 weeks duration
 - Macrolide/azalide
 - Rifampin
 - Fluoroquinolones
- Kauppinen M. *Clin Infect Dis* 1995;21:S244.

Reiter's Syndrome and Treatment of *C. trachomatis*

- 40 patients (90% HLA B27 +) with Reiter's arthritis
- Randomized, double-blind lymecycline vs. placebo 11 wks

Time 50% Recovered (weeks)

CT (n=17) Other (n=23)

Lymecycline	15 (p=0.02)	30
Placebo	40	27

Leubke A. *Arth Rheum* 1991;34:6.

C. pneumoniae and CAD - History

1908	Osler
1913	Anitschkow high-cholest. diet → atherosclerosis
1940's	LGV occludes arteries, hypersensitivity CAD pts
1984	Mattila tested for various infections AMI patients
1988	Saikku found men with AMI/CAD t CP IgG/IgA
1993	Kuo et al. cultured CP from plaque

Chlamydia pneumoniae and AMI/CAD: Theories

• "Innocent bystander"

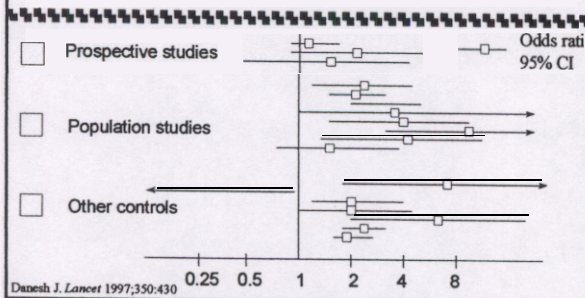
- Causes the development of atherosclerosis
- Causes the promotion of atherosclerosis

• Triggers AMI

Chlamydia pneumoniae and AMI/CAD: Epidemiology

- Since 1994: 18 epi studies 12,700 patients
- Case-control: ↑ IgG, IgA, IC's AMI/CAD patients
- Cohort: Seropositivity → acute coronary events

C. pneumoniae and AMI/CAD: 18 Sero-epi. Studies - 2,700 Cases



Chlamydia pneumoniae: Specificity for Coronary Tissue

Presence by CIC/PCR among 38 autopsy cases

Coronary arteries	34%
Lung	13%
Liver	10%
Granuloma	10%
Spleen	5%

Jackson LA. *Am J Path* 1997;150:1785.

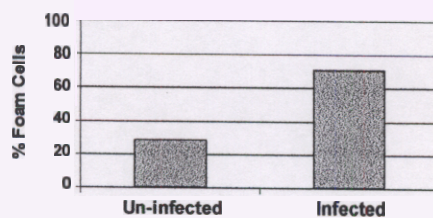
Endovascular *C. pneumoniae* in CAD

Plaques from 70 myocardial revascularized patients
17 re-stenotic bypass grafts

- 11 (16%) viable CP
- 21 (30%) PCR DNA + vs. OH7 non-atheromatous samples
 - all culture + were PCR +
- MIF Ab no correlation with culture

Maass M. *JACC* 1998;31:827

C. pneumoniae Induces in Vitro LDL- Foam Cell Formation



Kalayoglu MV. *J Infect Dis* 1998;177:725.

Can Antimicrobials Prevent Atherosclerosis in Animals?

- NZW rabbits, cholesterol-free diet. sac. at 10 wks
- Infected intranasally with *C. pneumoniae* Q 2 wks X 3
- Azithromycin 5 days and 2 weeks after last inoculation

	Ath	Aortitis	p
No tx	8 (35%)	8 (35%)	-
Early tx 5 days	1 (4%)	0	0.02
Delayed tx - 6 wks	8 (33%)	0	NS

Fong IW 38th ICAAC, San Diego 1998

C. pneumoniae Accelerates, Azithro Prevents Atherosclerosis in Animals

- 30 NZW rabbits, cholesterol-sup. diet, sac. at 3 months
- Infected intranasally with *C. pneumoniae* Q 3 wks X 3
- Azithromycin 3 days after last inoculation X 7 weeks

	Infected			
	No Tx	AZ	Control	p
MIT (mm)	0.55	0.20	0.16	0.009
PLCI (%)	50	32	22	0.01

Mahlestein JB. *Circulation* 1998;97:633.

Roxithromycin for Prevention of Cardiac Events

- . Design: Random&d. double-blind, pros.
- . Patients: Unstable angina or non-Q wave MI
- . Comparison: Roxithromycin 150 mg BID vs. placebo for 30 days
- . Outcome: Severe angina/revascularization, AMI, cardiac death over 31 days

Roxithromycin for Prevention of Cardiac Events

	Roxithromycin (n=102)	Placebo (n=100)	p
Cardiac events	2.0%	9%	0.032

Gurfinkel E. *Lancet* 1997;350:404.

Azithromycin for Prevention of Cardiac Events

- Design: Randomized, doubleblind, pros.
- Patients: Post-MI > 6 mo. and CP tier > 1:64
- Comparison: Azithromycin 500 mg QD vs. placebo for 3 days
- Outcome: AMI, sev. angina/revascularization, cardiac death over 16 months

Azithromycin for Prevention of Cardiac Events

	CP(+)Azithro (n=40)	CP(+)PI-NR (n=40)	CP(I) (n=74)	CP (-) (n=59)
Cardiac events	8 %	26 %	15%	7%
CP < 1:16	43 %	10 %		
* p < 0.05				

Gupta S. *Circulation* 1997;96:404.

2nd Azithromycin Study

- 88 PCTA patients
- Randomized: AZ 500 mg/d X 2 d. 250 mg/d X 28 d vs. placebo
- Followed 6 months

	AZ	Placebo
Re-stenosis	9%	16%
Recurrent angina	40%	60%

Jackson LA. 4th International Conference on the Macrolides, Azalides, Streptogramins and Ketolides, 1998, Barcelona, Spain, Abstract 4.16.

Antibiotics and Risk of First MI

	No. cases (n=3,315)	No. controls (n=13,139)	OR (95% CI)
No abx	1403	5318	1.00
Tetracyclines	82	452	0.70 (0.55-0.90)
Quinolones	8	62	0.45 (0.21-0.95)

* p < 0.05

Meier CR. *JAMA* 1999;281:427

Chlamydia pneumoniae and MI

- Genetically predisposed population
- . Acts alone and with other etiologies

Chlamydia pneumoniae and MI: An ED-Based Treatment Trial

- Rapid ID high-risk cardiac patients
Bedside Troponin I testing
- Rapid CP diagnosis
ELISA/PCR
- . Bactericidal antimicrobials
Macrolides, azalides, fluoroquinolones
- . ED-base, research network
EMERGENCY ID NET