

Community-Acquired Pneumonia: Perspectives for Clinicians

- **Etiology**
- **Pattern recognition**
- **Prevention**
- **Therapy**

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Community-Acquired Pneumonia



5.1 million cases/year



**1.3 million
hospitalized**

**>100,000 deaths
6th leading cause
~50,000 pneumococcal
deaths**

Up to 10% hospitalized to ICU

NCHS, Nat. Vital Stats Reports 49 (9) 1998
Am J Resp Crit Care Med 2001; 163: 1730-54
HCPA 1999 data VS PAS
Vital Health Stat 13 2005; 158:1-99
NEJM 1997; 335:243-50

The Patient with Cough: Just Bronchitis?

1. Absence of SIRS criteria, rales or egophany minimize probability of pneumonia to point where further diagnostic testing unnecessary

Metlay *JAMA* 1997; 278:1440-5

2. Exception: elderly

- 17/18 symptoms underreported with increasing age

- > 75 years – T>38°-30%

HR>100 – 37%

Have low threshold for CXR

Metlay *Arch Int Med* 1997; 157:1453-9

A 4-year Prospective Study
Community-Acquired Pneumonia
(n=170)

Std questionnaire - patients > 15 yr

median age 43

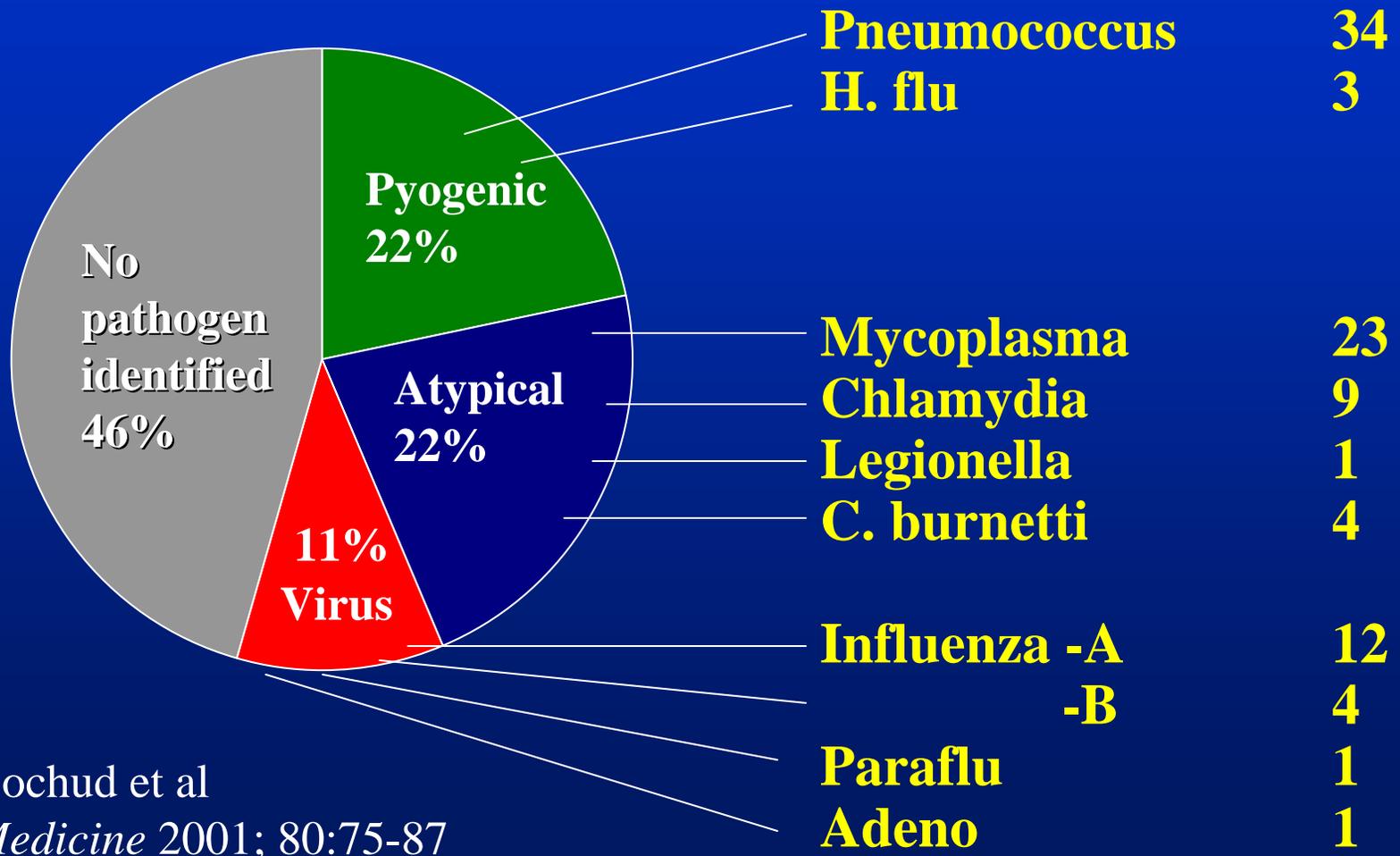
Sputum - Gram ST, C+S, Pneumo Ag

Blood - Cults

Throat - Viral Cults

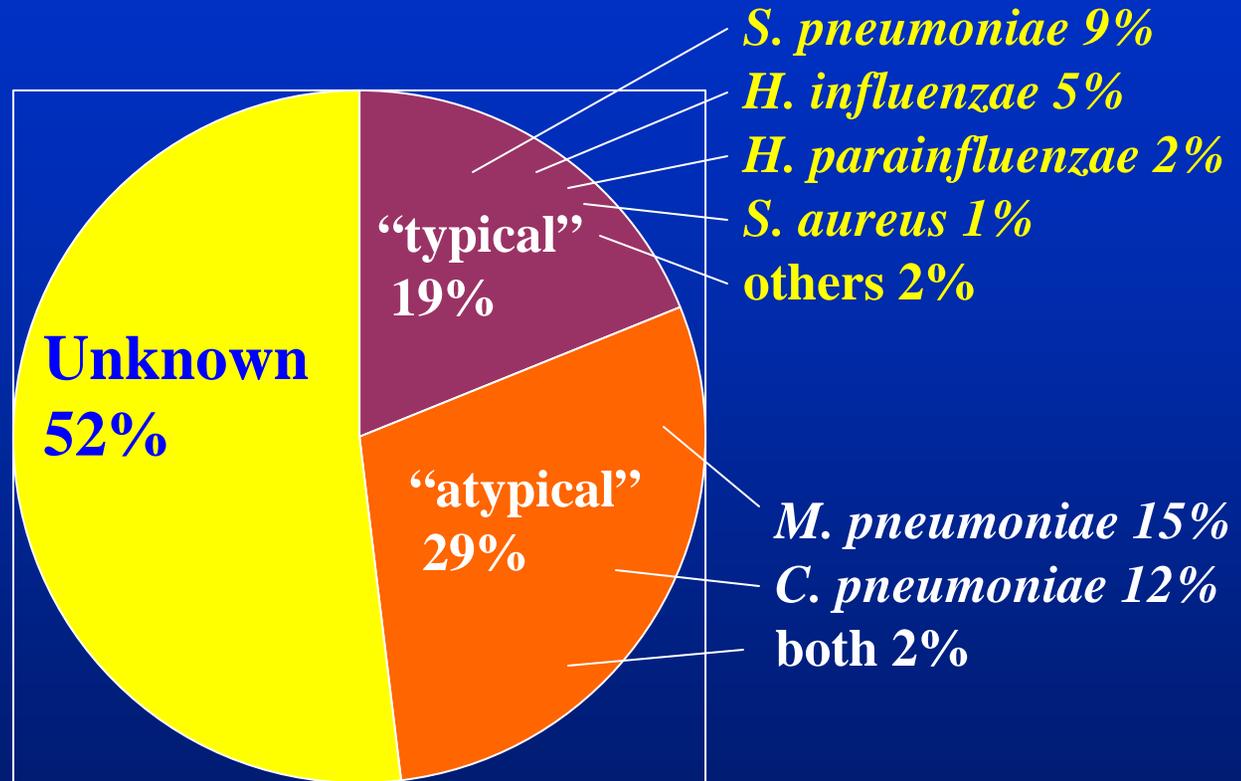
**Serology - Mycoplasma, *Legionella*,
Coxiella, Viruses, Pneumococcus (ELISA)**

Etiology of CAP(n=170)



Bochud et al
Medicine 2001; 80:75-87

Etiology of CAP (n=507)



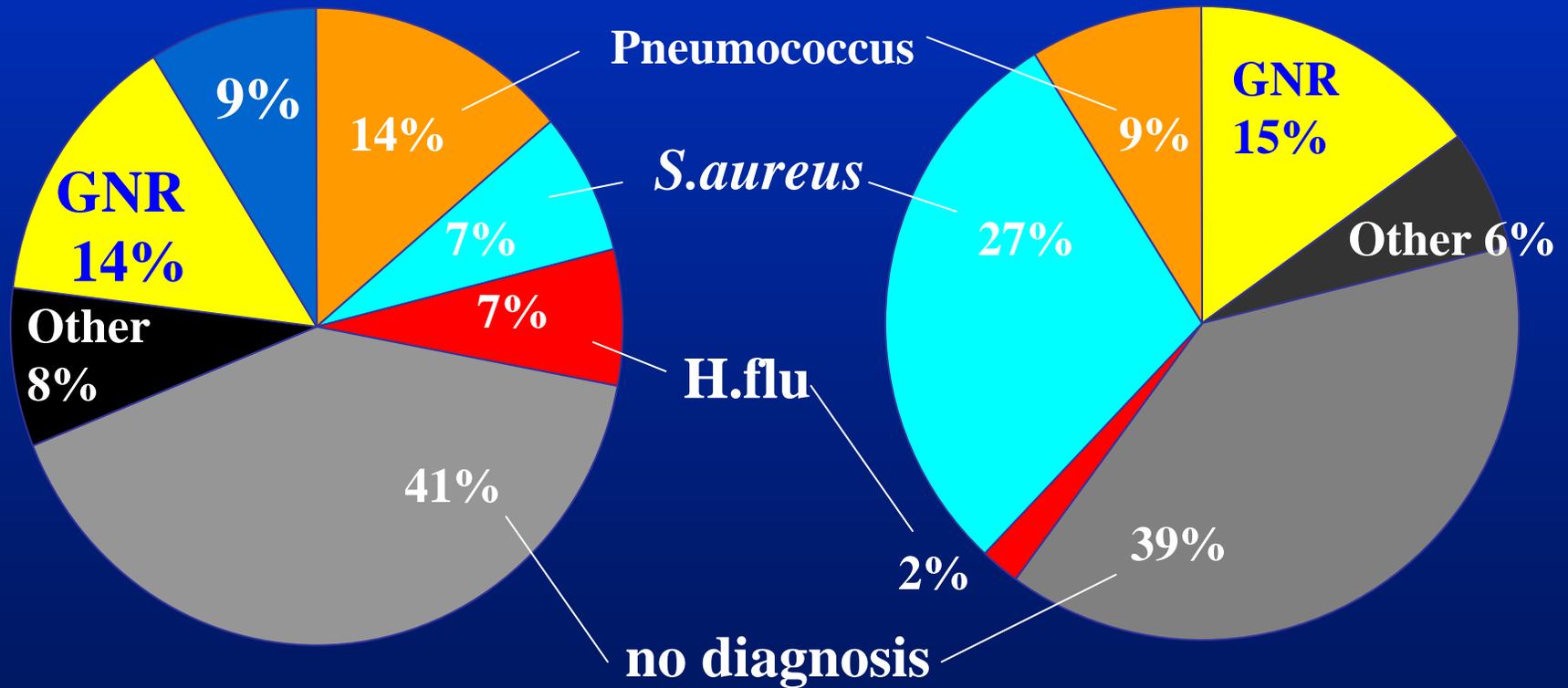
Marrie et al *Resp Med* 2005; 99:60-65

Distribution of Respiratory Pathogens Home vs Nursing Home Elderly (n=104)

Home (n=57)

Nursing Home (n=47)

L.pneum.



El-Solh et al *Am J Respir Crit Care Med* 2001; 163:645-51

Severe CAP

Consecutive 204 patients, median age 60

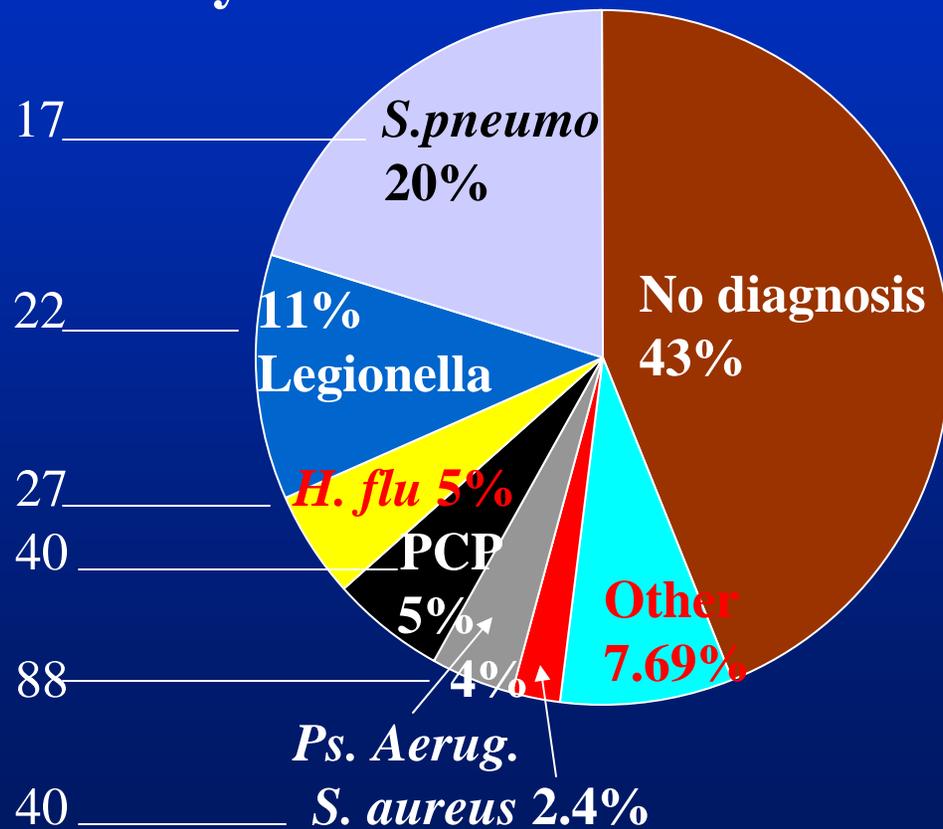
Intubated - 106

No intubation - 98

Mortality - 24%

If intubated - 43%

Mortality



In 42% :

**bacteriology led to
change of antibiotics**

Rello et al

Chest 2003; 123:174-180

**7% of intubated had *Ps. Aeruginosa*
15% of intubated had Legionella**

Improved Diagnosis of Pathogens with CAP by use of real-time PCR

	Pathogens detected (105 cases)	
	Conventional	PCR
S.pneumoniae	22	*
H. influenzae	6	*
Legionella	2	6
M. pneumoniae	5	10
Influenza A	8	9
Rhinovirus	2	18
Coronavirus	0	14
Mixed	3	28*
Single pathogen	49	52
Total patients with a pathogen	52 (50%)	80(76%)

***included in calculation of mixed infections with PCR**

Templeton et al CID 2005; 41:345-51

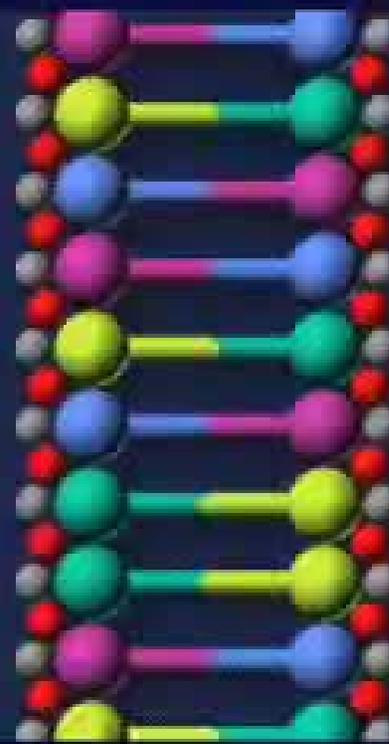
Understanding Classic PCR

Generates billions of copies of target DNA or RNA.

Allows detection of concentrations too low for other methods.

The PCR process consists of three steps:

1. Denaturation
2. Annealing
3. Extension



Failure to Treat Adequately: Severe Pneumonia in the Elderly

- Nursing home pathogens differ from those in the community
- Mortality is approximately 55% among elderly patients with pneumonia
- Mortality predicted by

	<u>Odds Ratio</u>
– Inadequate treatment	2.6
– Multilobe	3.7
– Septic shock	4.3
– 24-h urine output	5.6

Effective Antibiotic in First 24 Hours
and 28 Day Mortality with Bacteremic
Pneumococcal Pneumonia (n=100)
(Prospective Observational Study)

<u>Risk Factors</u>	<u>OR</u>	<u>CI₉₅</u>
INEFFECTIVE (discordant) Rx*	27.35	1.82-410.16
Multilobe disease	14.27	2.4-85.0
COPD	9.18	1.69-49.82
Prior hospitalization	7.99	1.49-42.7

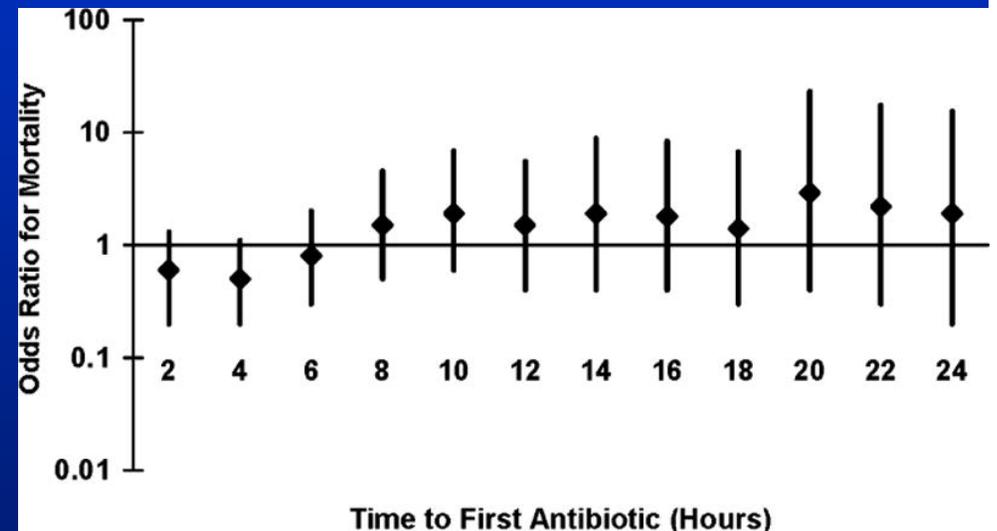
*(nursing home residence OR=14.87 and immunocompromize
OR=11.56 independent risk factors)

Lujan et al
Crit Care Med 2004; 32:625-31

Early Therapy for Pneumococcal Bacteremia Reduced Mortality

(n=363 adults from 43 PA hospitals)

- Retrospective cohort
- In hosp mortality – 10%
- If effective antibiotic within 4 hours: OR – 0.47 (.2-1.0)



Medicine 2008; 87:160-6

Confirms earlier retrospective study of 18,000 medicine patients

Arch Intern Med 2004; 164:637-44

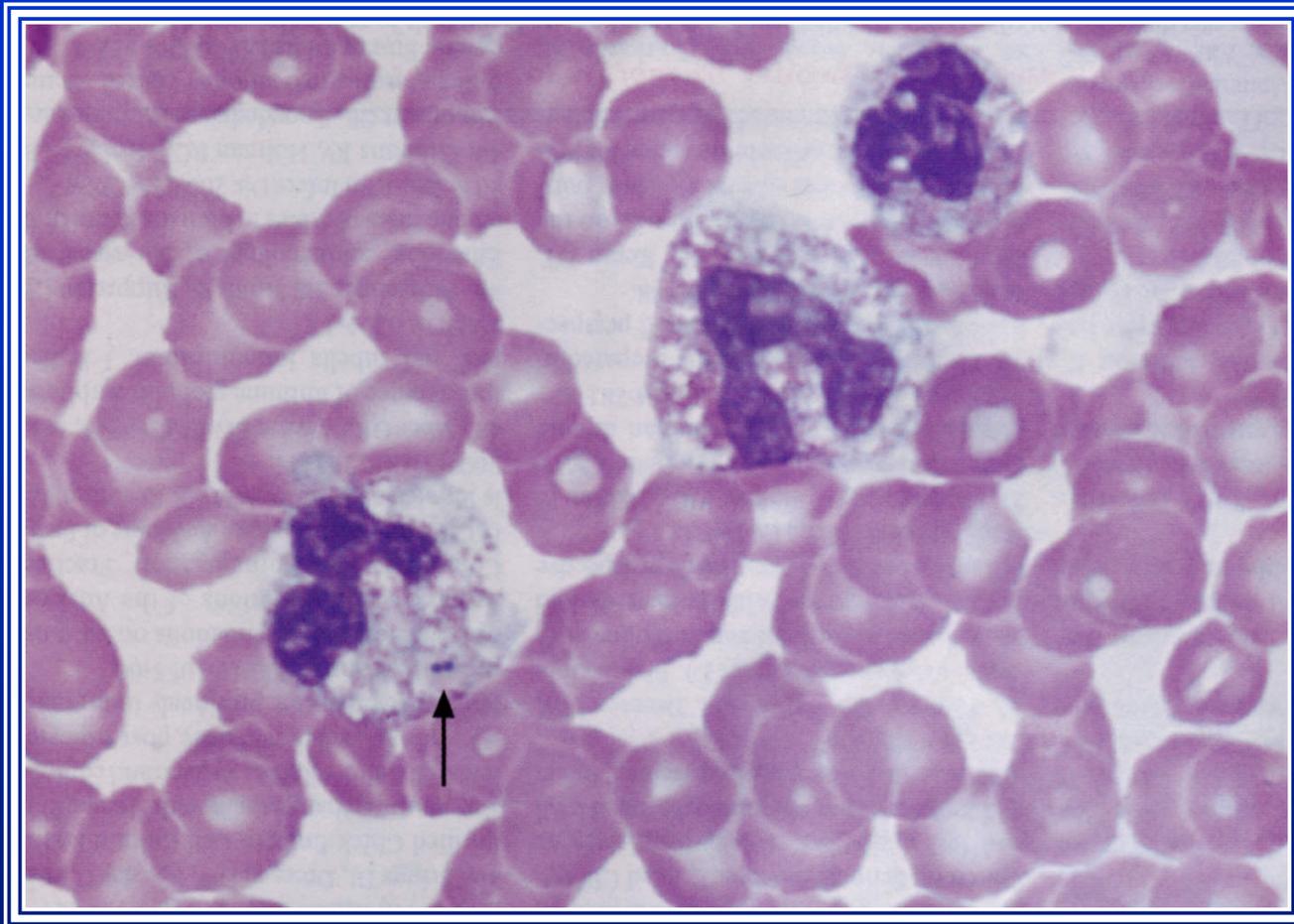
So far...

- Elderly with respiratory symptoms: order CXR early
- Retrospective data suggest that early therapy with effective antibiotics save lives
- Etiology of CAP can be established only 50% time without PCR
- 10-30% of causes are "atypical organisms"
- GNR/S.aureus – more prominent in elderly
- Pneumococcus – 10-20% cases; 50% deaths



“The patient has a severe chill, lasting from ten to thirty minutes... pain in the side, often of agonizing character. A short, dry, painful cough... on the second or third day... he lies flat in bed, often on the affected side; the face is flushed... The breathing hurried; the alae nasi dilate with each inspiration... a frequent short cough makes the patient wince and hold his side. The expectoration is blood tinged... Temperature rises rapidly to 104° or 105°.”

William Osler



NEJM 2004; 351:2636

~ 20% patients with pneumococcal CAP have positive blood cultures

Staph aureus Pneumonia - 1918

8100 \bar{c} flu

1409 pneumonia (17%)

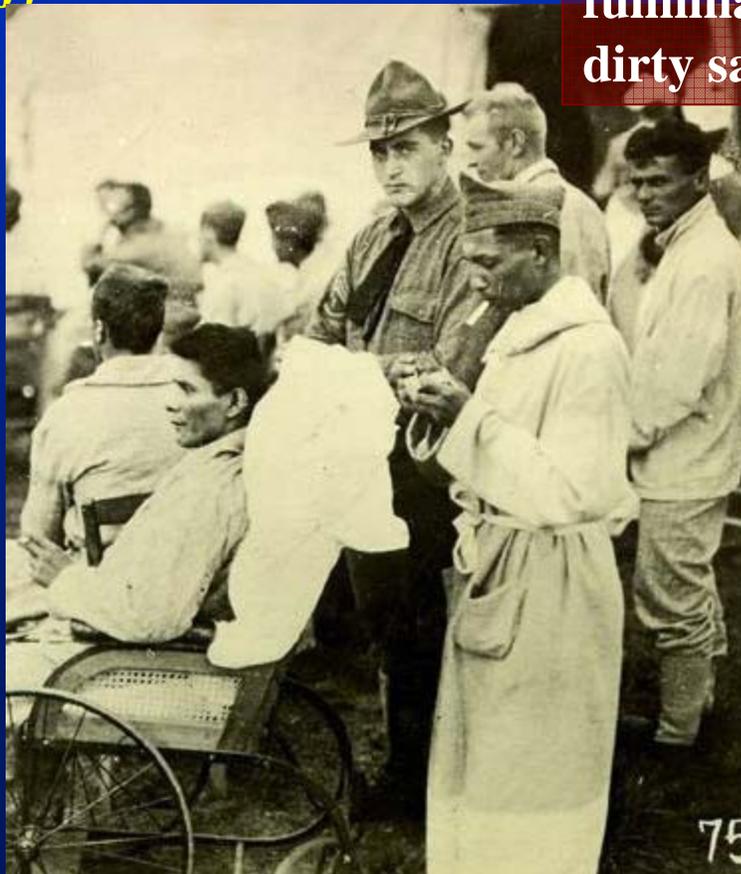
385 died (27%)

~half of deaths (153)

with *S. aureus* cults

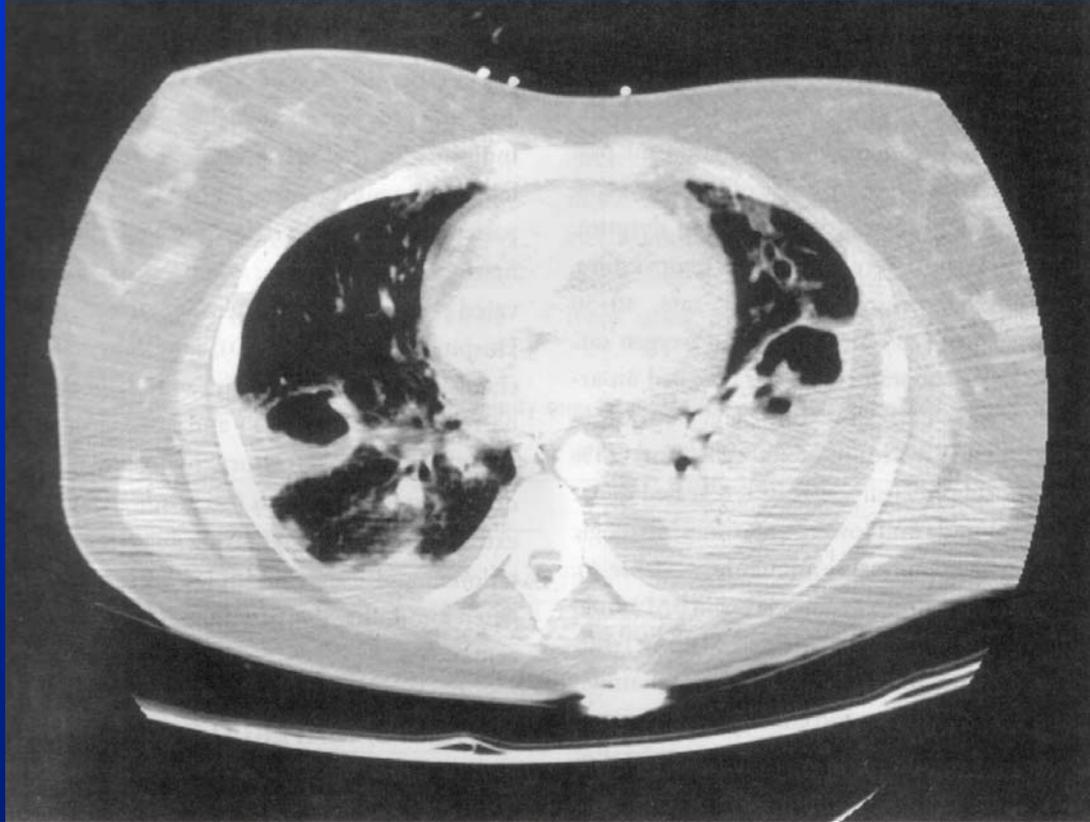
92 of 153 (60%) *S. aureus* only

Cherry red indigo blue
cyanosis
no chills, localized CP
no signs consolidation
fulminating septic course
dirty salmon-pink sputum



Chickering & Park
JAMA 1919;
72:617-26

CA-MRSA Pneumonia



Necrotizing pneumonia on a chest CT with intravenous contrast, obtained on hospital day 3 from patient 1. The CT shows multiple bilateral nodular and cavitary lesions (some of which have surrounding ground halos that are likely to represent hemorrhages) and left lower lobe consolidation, with small left-side pleural effusion.

CID 2005;40:100-7

A 17-Year-Old Patient With Pulmonary Infiltrate and Rash

A 17 y.o. male; fever, headache, and mouth sores. Treatment with amoxicillin ineffective.

T= 39.1°C, AND HE HAD CRUSTED LIPS WITH SUPERFICIAL ULCERS ON THE GUMS AND BUCCAL MUCOSA (figure 1); HEMORRHAGIC CONJUNCTIVITIS (figure 2). Bronchial breath sounds were heard over the right lower lung field, and an infiltrate was seen on a chest radiograph.

The results of laboratory tests were all normal. Blood and urine cultures were negative.

Intravenously ceftriaxone and oral roxythromycin were given, and valacyclovir for suspected herpes simplex.

During the next 48 hours a new symptom, dysuria, evolved. NEW, SPARCELY SCATTERED PLEOMORPHIC LESIONS IN THE FORM OF A TARGET, OR IRIS, LESION ON THE PATIENT'S LIMBS (figure 3) AND IN HIS GENITAL AREA.



Figure 1



Figure 2



Figure 3

Legionella Pneumonia

Gram Negative bacilli with fastidious growth requirements

Consolidating pneumonia:

Myalgia, diarrhea, confusion, HA!

↓Na, ↓P, ↑liver enzymes

↓WBC, ↓platelets, ↑CK

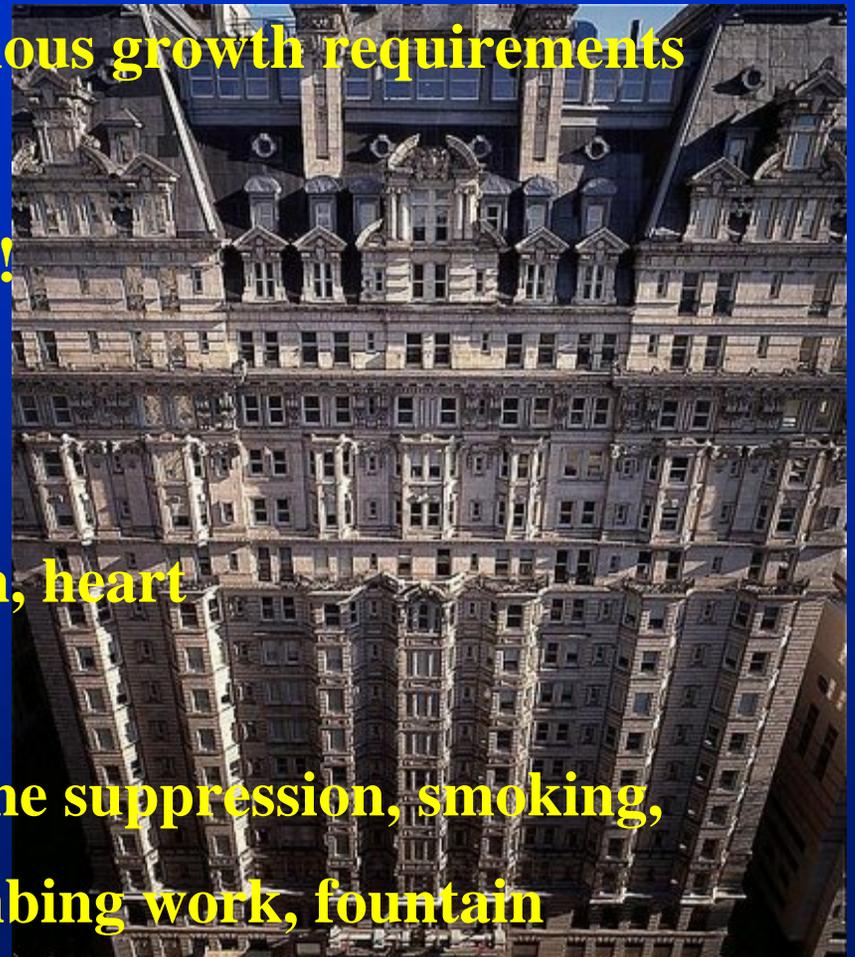
Metastatic infection: brain, spleen, heart

(rare hyperthermia – A. Lipke)

**Risk factors: recent travel, immune suppression, smoking,
older age, well water, recent plumbing work, fountain**

Eur Respir J 1989; 2:130-4

Frazer et al *NEJM* 1977; 297:1189-97



Bellevue Stratford Hotel

221 patients (5%) ill in 1976/34 died

Chlamydomphila Pneumoniae: Outbreaks in Military Conscripts and Nursing Home Residents

Finnish Recruits

	primary (n=23)	re-infect (n=20)
pneumonia	10	0
hospitalizat. rales	12 14	1 4
T ≥ 38°	9	1
IgM mif ≥ 16	23	1
30 day case-case interval		

NH (n=3) residents(n=549)

AR: 44-68%
 cough - 100%
 fever (>37° ax) - 64%
 16 cases pneumonia (7%)
 6 deaths (2.5%)
 more women (p=0.04)
 interval after index
 16 d - smokers
 22 d - nonsmokers
 (p=0.007) JAMA 1997;277:1214

CID 1993; 17:420-5
JID 1990; 161:618-25

Chlamydophila Psittaci

75% bird (5-8% prevalence) contact

- **Kissing a parrot**
- **Mouth to mouth resuscitation**
- **Visit to bird park**
- **Turkey farm worker**

Complications: hepatitis

Reactive arthritis, meningoencephalitis

Pericarditis, BE

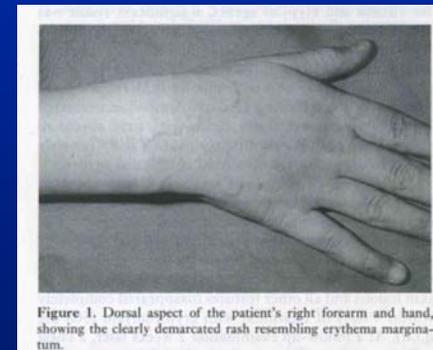
Original Paper: 1890 J Ritter

"Pneumotypus." Switzerland

**Low lobe consolidation
(90%)**

**HA, myalgia, chills,
cough (late)**

**Hepatomegaly (50%);
Splenomegaly.**



E.M.

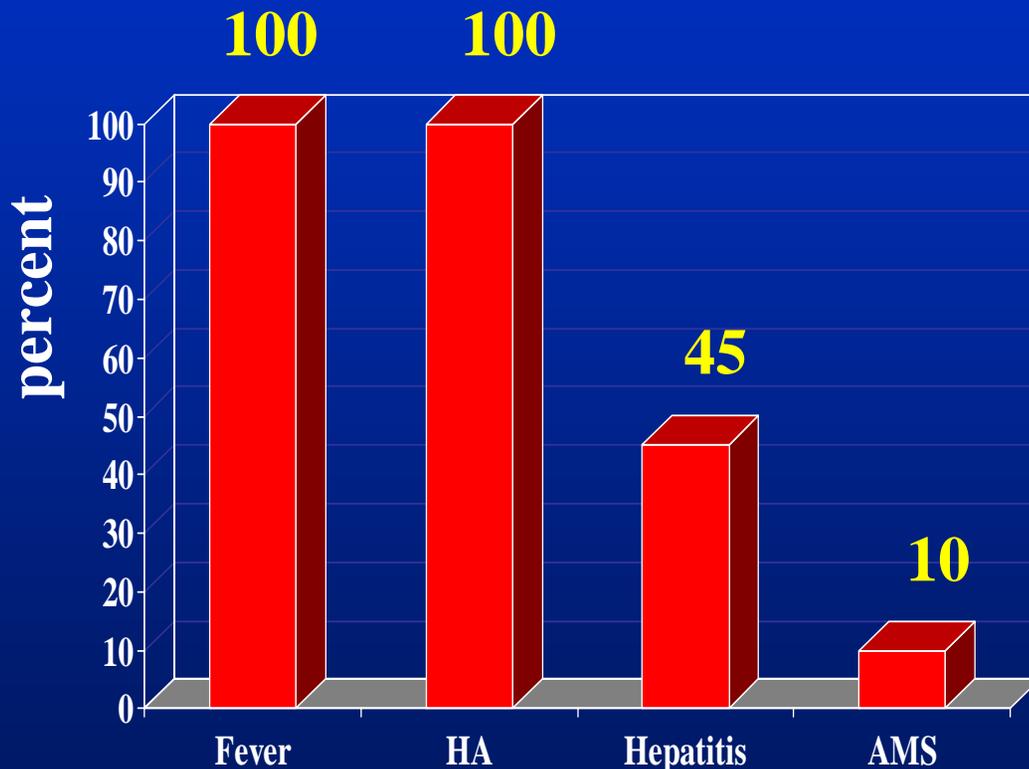
Figure 1. Dorsal aspect of the patient's right forearm and hand, showing the clearly demarcated rash resembling erythema marginatum.

**Horder's spots: pink, blanching,
resembling rose spots**

Clin Exper Derm 1990; 15:225

Curr Inf Dis Reports 1999 1:73-79

Q Fever Pneumonia (n=49)



Europ J Epidemiol 2004; 19:1051-4

RESERVOIRS: cattle, sheep, goats => urine, feces, milk, birth products

Many other animals: horses, cats, geese, mice, camels...

COMPLICATIONS: endocarditis, osteo, encephalitis

Original description in Brisbane Meat Workers
Derrick EH *Med J Aust* 1937;2:281-9

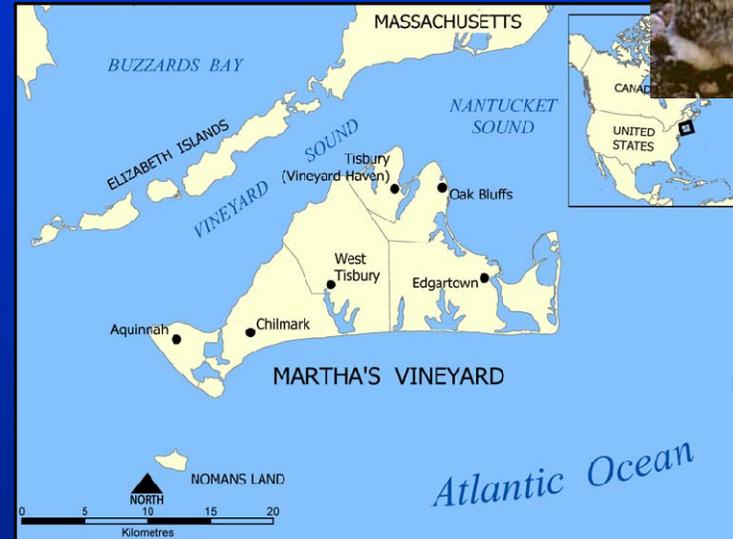
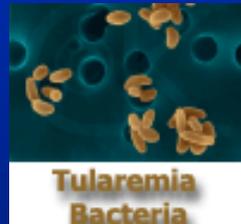
Epidemic Pneumonic Tularemia Martha's Vineyard

15 patients:

11 pneumonic

2 ulceroglandular

2 fever



Parsimonius model

<u>Variable</u>	<u>OR</u>
Lawn mowing	9.1 (1.7-47.6)
Work with bark chips	7.8 (1.3-48.2)
2/40 trapped animals +:	
- striped skunk	
- Norway rat	

Feldman et al *NEJM* 2001; 345:1601-6

Hantavirus Pulmonary Syndrome

Rodent-borne viral infections

335 cases in 31 states - mortality 38% (ARDS)

SS RNA - *Sin nombre virus*

Deer mouse - *Peromyscus maniculatus*

Incubation: 1-6 weeks

Low platelets suggestive (1st week) ↑ HCT (2nd week)

Dx: ELISA Ab IgM

PCR of tissue



Original description (17 pts – "4 corners")

Duchin et al *NEJM* 1994; 330:949-55

100% - 4 SIRS

Wenzel *NEJM* 1994; 230:1004-5

ARDS and Blastomycosis

8.4% (9 of 107 patients) @ U of Mississippi
Mississippi highest rates in US for blastomycosis

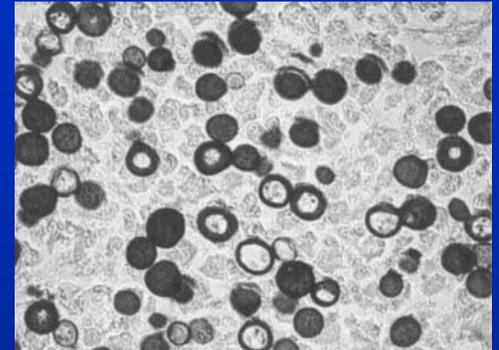
Mean age 44

7/9 (78%) died of resp failure

Only 1/9 immunocompromized

PaO₂/FIO₂ < 200 mm Hg

Mean Duration Resp failure 7 d

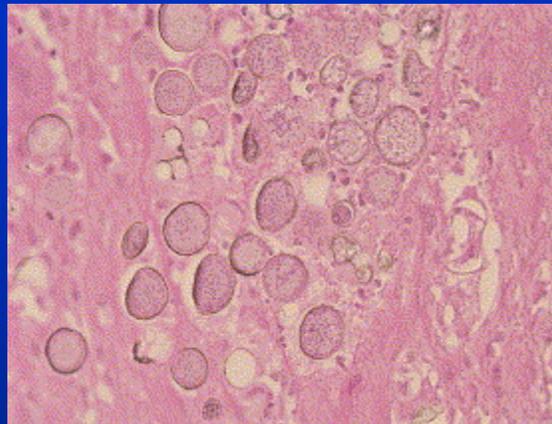


Ann Diag Pathol 2001; 5:1-9

Acute Coccidioidal Pneumonia

C.immitis

C.Posadasii (outside
California)



Coccidioides posadasii

1-3 weeks after
inhaling arthroconidia
Severe HA and severe
pleuritic C.P. suggestive
Hilar/paratracheal nodes
25%

Pl effusion 5-10% -
eosinophilic
E.N. – favorable
prognosis



Mayo Clin Proc 2008; 83:343-9
Infect Dic Clin N Am 2006;
20:621-43

CAP: Demographics, Social History Important!

- **Young adult –**
 - *Erythema multiforme* – *M. pneumoniae*
 - Hemoptysis/shock – CA – MRSA; prior influenza
 - Bacteremia pneumococcal
- **-Older adult**
 - *S. aureus*/GNR (NH)
 - *C. pneumoniae* (NH)
 - Legionella (travel, water exposure)
- **Birds – *C. psittaci*/Histo/H5N1**
- **Cats/cattle/goats: *Coxiella burnetii***
- **Mice – Hantavirus**
- **Rabbits/Lawn mowing/ Martha's Vineyard – *F. tularensis***
- **Camping/Mississippi – Blasto; San Joaquin Valley - cocci**
- **HIV: pneumococcus/*S. aureus*/PCP/crypto**

Age and Lifestyle: CAP Risk Factors

Prospective Cohort 26,000 Men 78,000

Women (Health Professionals)



58% former or current smokers

RR

age < 49=1

≥ 70 = 4.1

No age effect

Exercise protective in women



59% former or current smokers

	<u>Current smokers</u>	
≤ 25 cig/d	1.42	1.67
≥25 cig/d	2.52	1.42
40 lb weight gain since age 21	1.71	2.13
No BMI risk		BMI ≥30 2.22

Baik I, et al. *Arch Intern Med.* 2000;160:3082-3088.

High Alcoholic Intake and Risk for CAP

Independent Risk Factors	Cases (n=50)	Controls (n=50)	OR	P
High alcohol > 100 grams-men or >80 gm women for ≥ 2 years	16	7	5.33	0.008

Arch Intern Med 1995; 155:1649-54

Administrative cohort of CAP (n=22,198) in Mass.

Multivariate analyses: alcohol related D_x : risk adjusted

LOS longer by 0.6 d; ICU use greater OR 1.6;

No change in mortality

Arch Intern Med 1997; 157:1446-52

Protective Effects of Pneumococcal Vaccine

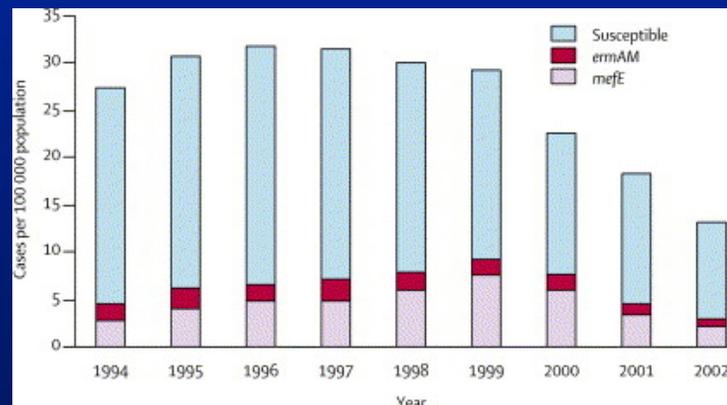
23 valent adults >65 (n=11,241)

Mortality – vaccinated 9.8% HR= .41(.23-.72)
if pneumonia no vaccine 16.3%

Pneumococcal pneumonia – HR=.55 (.34-.88)

Hospitalized for pneumonia – HR=.74 (.59-. 92)

CID 2006; 43:
860-8



Reduction: children 82%; adults >65-39%

Lancet 2005; 365:855-63

Oral Erythromycin and the Risk of Sudden Death from Cardiac Causes

Tennessee Medicaid Cohort with 1.2 Million person-years follow-up and 1476 causes of sudden death from cardiac causes

Antibiotic use	Pers-Yr	Deaths	Multivariate Rate Ratio(CI ₉₅)
Current Erythro	5305	10	2 (1.1-3.8)
Current Amox	6846	8	1.1 (.59-2.4)
Former Erythro	111,779	100	0.89(.72-1.1)
None	1,126,013	1358	1.0
Current Erythro plus CYP3A inhibitor	194	3	5.4(1.7-16.6)
Current Amox plus CYP3A Inhibitor	254	0	-

- ↑ levels of erythro cause ↑ risk ventricular arrhythmias

Fatal Interaction Between Clarithromycin and Colchicine in Patients with Renal Insufficiency

Nine (10%) of 88 pts with concomitant use died

One (4%) of 28 who received drugs sequentially died

Multivariate predictors among concomitant users:

- **longer overlap Rx - RR 2.16**
- **baseline renal impairment - RR 9.1**
- **development of pancytopenia - RR 23.4**

**Cause of death: pneumonia (5), renal failure (2), CHF - 1,
MOF - 1.**

Severe Hepatotoxicity of Telithromycin

Age/gender	Initial infection	Liver dis: day of Rx	AST/ALT/Bili	Outcome
46 WM	ear/sinus	2	948/200/3.8	good
51 WW	cough	<7	930/730/9.5	transplant
26 HM	sinus mass	2 days after 5 d course	3638/2200/13.6	died

All – previously healthy

1-2 wine/night; 1 – beer/night

FDA: 7 phase III; 10 post-market

Clay et al *AIM* 2006; 114:415-20

Three CAP Regimens Independently Associated with a Reduced 30-day Mortality

<u>Regimen</u>	<u>Adjusted mortality(CI₉₅)</u>
1) 2nd generation Cephalosporins plus macrolide	.71 (.52-.96)
2) Non-pseudomonal 3 rd generation Cephalosporin plus a macrolide	.74 (.60-.92)
3) Fluoroquinolone only	.54 (.43-.94)

Gleason et al *Arch Int Med* 1999; 2562-72

Compared to ceftriaxone monotherapy

**Four Retrospective Studies Consistently
Suggest Dual Therapy for SEVERE
Pneumococcal Bacteremic Pneumonia***

- mortality -

<u>Author</u>	<u>Mono Rx</u>	<u>Dual Rx</u>
Waterer*	18/109 (18%)	7/102 (6.9%)
Martinez	dual Rx had OR of	0.4 (.17-.92)
Weiss	11/42 (26%)	4/53 (7.5%)
Baddour	26/47 (55%)	11/47 (23%)

* >50% with a 2nd
pathogen

Arch Intern Med 2001; 161:1837-42

Clin Infect Dis 2003; 36:389-95

Chest 2005; 128:940-6

Am J Respir Crit Care Med 2004; 170:440-4

Synergy of Fluoroquinolone plus Third Generation Cephalosporin in Experimental Pneumococcal Meningitis

<u>Drugs</u>	<u>In vitro synergy</u>	<u>Synergy in animals</u>
Ceftriax + Levo	yes	significant log reduction of cfu/ml
Cefotax + Levo	yes	synergetic log reduction of cfu/ml

Flatz et al *JAC* 2004; 53:305-10

Kuhn et al *AAC* 2003; 47:2487-91

Empirical Antibiotics for CAP

Site of delivery	In vitro data favoring specific Rx	Clin Trials favoring specific Rx
Outpatient	FQ active vs. pneumococcus	No
Inpatient wards	FQ active vs. pneumococcus or ceftriaxone plus macrolide	No
Inpatient ICU	FQ active vs. pneumococcus plus ceftriaxone PLUS Rx or R/O <i>P. aeruginosa</i> CA-MRSA (vanco plus linezolid or clinda plus IVIG); influenza	No * 4 retrospective studies suggest dual Rx better for bacteremic pneumococcal pneumonia

** ketolides have rare, severe hepatotoxicity of great concern

Community Acquired Pneumonia

- Leading cause of death
 - Pneumococcus overrepresented in mortality
- 2009 – without PCR - Understand etiology in ~50% cases
- Careful history - social Hx! – physical exam, may give clues to etiology, appropriate empirical Rx
- Empirical therapy impacted by: demographics, exposures, resistance patterns, toxicity-allergies-other meds, underlying disease

Hepatotoxicity of Telithromycin

- **Phase III data from Sanofi-Aventis:**
 - 7 cases of hepatitis or hepatocellular damage**
 - 1/7 recurrent hepatitis; confounders in 4**
- **FDA adverse reporting system**
 - 10 cases postmarketing of hepatic events**
 - 2/10 died; confounders in 8**

Clay et al *AIM* 2006; 114:415-20

Age and Lifestyle: Risk Factors for CAP

- A prospective study of risk factors for CAP in general population
- Study cohort:
 - Health Professionals Follow-up Study
(26,429 men aged 44 to 79)
 - Nurses, Health Study II
(78,062 women aged 27 to 44)
- 290 cases among men (6 years of follow-up)
- 305 cases among women (2 years of follow-up)

Case History

A 45 year African American male from Mississippi with no underlying disease presents with 7 days of progressive dypnea, cough and fever. He has no exposures and on admission is found to have ARDS

Cultures for bacteria and viruses are negative

Four Patients with CA-MRSA Causing Severe Necrotizing CAP

Patient	Age	Hemop	Shock	Cavities
1	31	+	+	+
2	52	+	+	+
3	20	-	+	+
4	33	+	+	+

All suscept to clinda, trm-sulfa, gent, vanc.

Consider also linezolid, rifampin.

All isolates PVL genes and SCC mec type IV element

Timing of Antibiotic Administration and Outcomes for Medicare Patients with Community-Acquired Pneumonia

Retrospective Study – Random sample of 18,209 Medicare patients over age 65.

No prior outpatient therapy

<u>Rx group</u>	<u>In hospital mortality</u>	<u>Adjusted OR (CI₉₅)</u>
< 4 hours* vs > 4 hours	6.8%	.85 (.74-.98)
	<u>30-day mortality</u>	<u>Adjusted OR (CI₉₅)</u>
	11.6%	.85 (.76-.95)

* 61% of patients had documented receipt of antibiotics < 4 h

Panton Valentine Leukocidin (PVL)

Q: Will protein synthesis inhibiting antibiotics help in therapy of CA-MRSA?

PVL: 2-protein component toxin

=> pores in cell membrane of polys releasing IL-8, Leukotriene B (chemotactic)

=> inflammatory tissue necrosis

α toxin: Vanco – no effect on production

Clinda reduced expression 98%

Linezolid: subinhib concentration reduced secretion of enterotoxin A, autolysin, Protein A, α and β hemolysin

CID 2002; 35:819-24

Intens Care Med 2003; 29: 1840-3

AAC 1998; 42: 2817-23

AAC 2004; 48: 546-55

Four Patients with CA-MRSA PVL-positive, Necrotizing Pneumonia

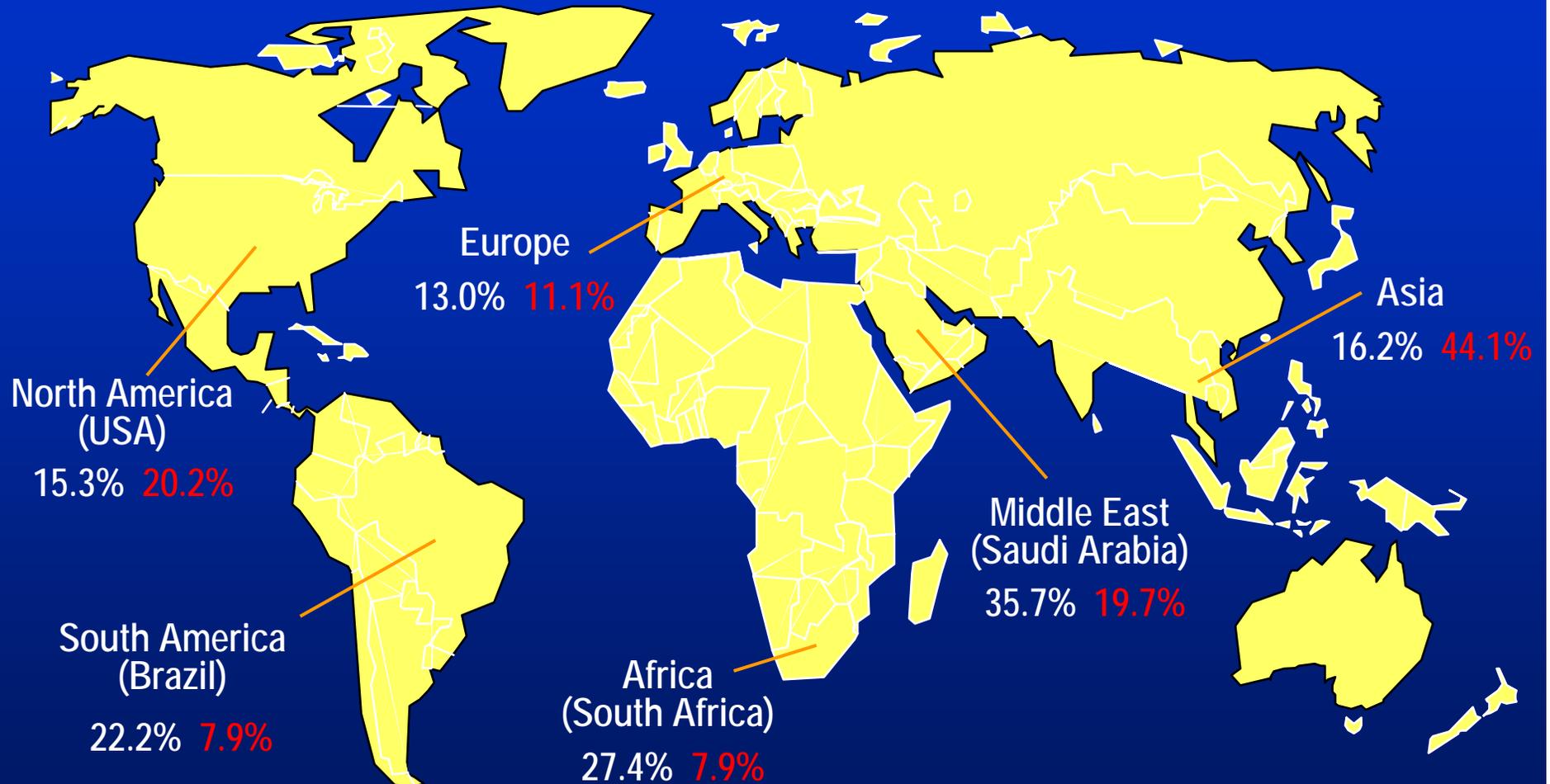
Age	Sex	Prodrome(d)	(+) Cult	Late AB	Lived
45	M	5	Blood Sputum	Linezolid Rifampin	Y
40	F	1	Pl fluid Sputum	Vanco	Y
34	M	3	Blood/Bal	Vanco, Clinda Linezolid	Y
40	M	?	Blood/Bal* Nasal- on admission	Linezolid, Rifampin	Y

* Ventilator associated

Micek et al *Chest* 2005; 128:2732-8

Q: did exotoxin-inhibiting antibiotic effect outcome?

Penicillin-nonsusceptible *S. pneumoniae*



Penicillin-intermediate (MIC 0.12 – 1 µg/ml)

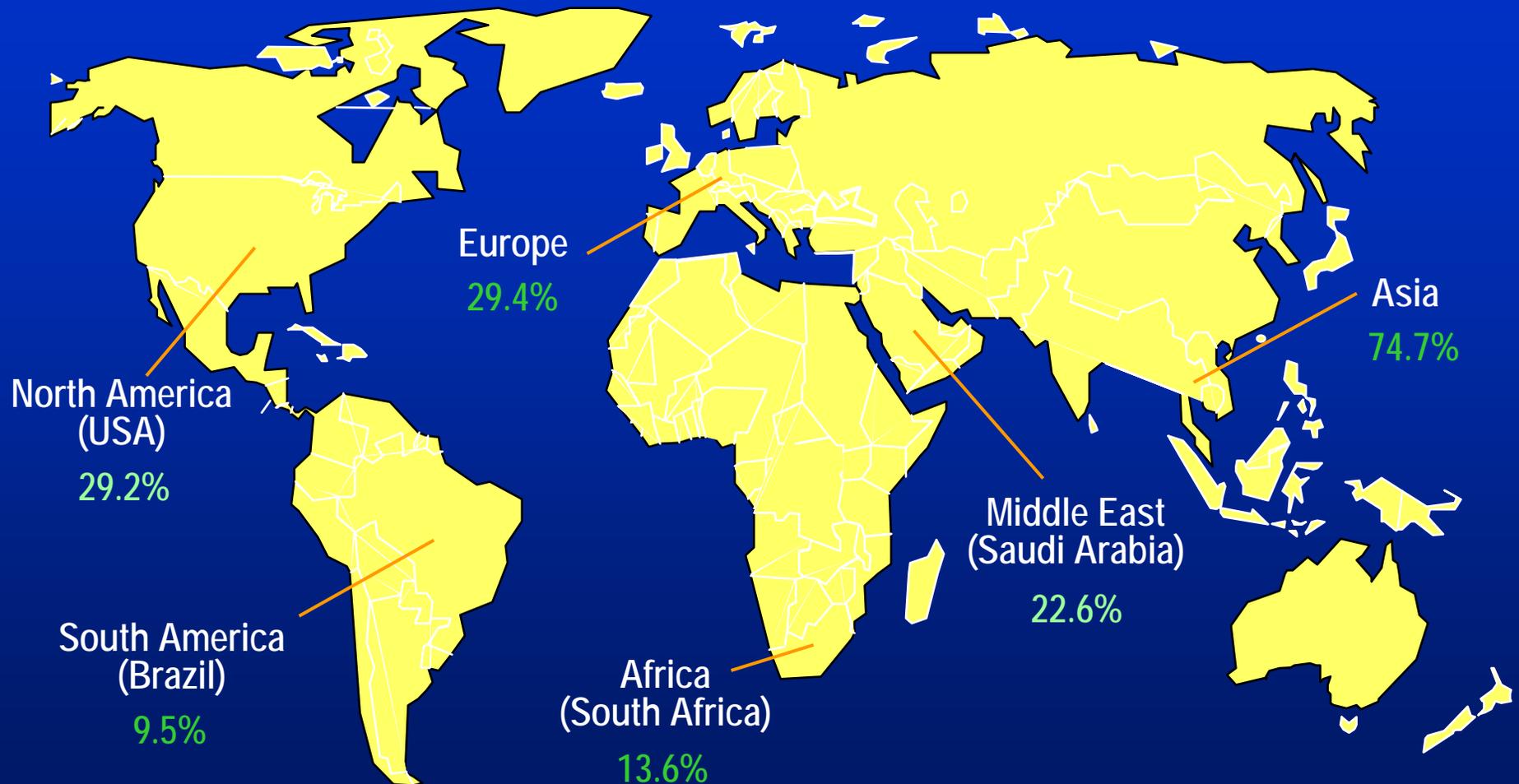
Penicillin-resistant (MIC ≥ 2 µg/ml)

Jones *et al* (2003). *Diagn Microbiol Infect Dis* 47(4):579-86.

Fouda *et al* (2004). *J Chemother* 16(6):517-23.

Jenkins *et al* (2005). *J Infect* 51(5):355-63.

Macrolide-resistant *S. pneumoniae*



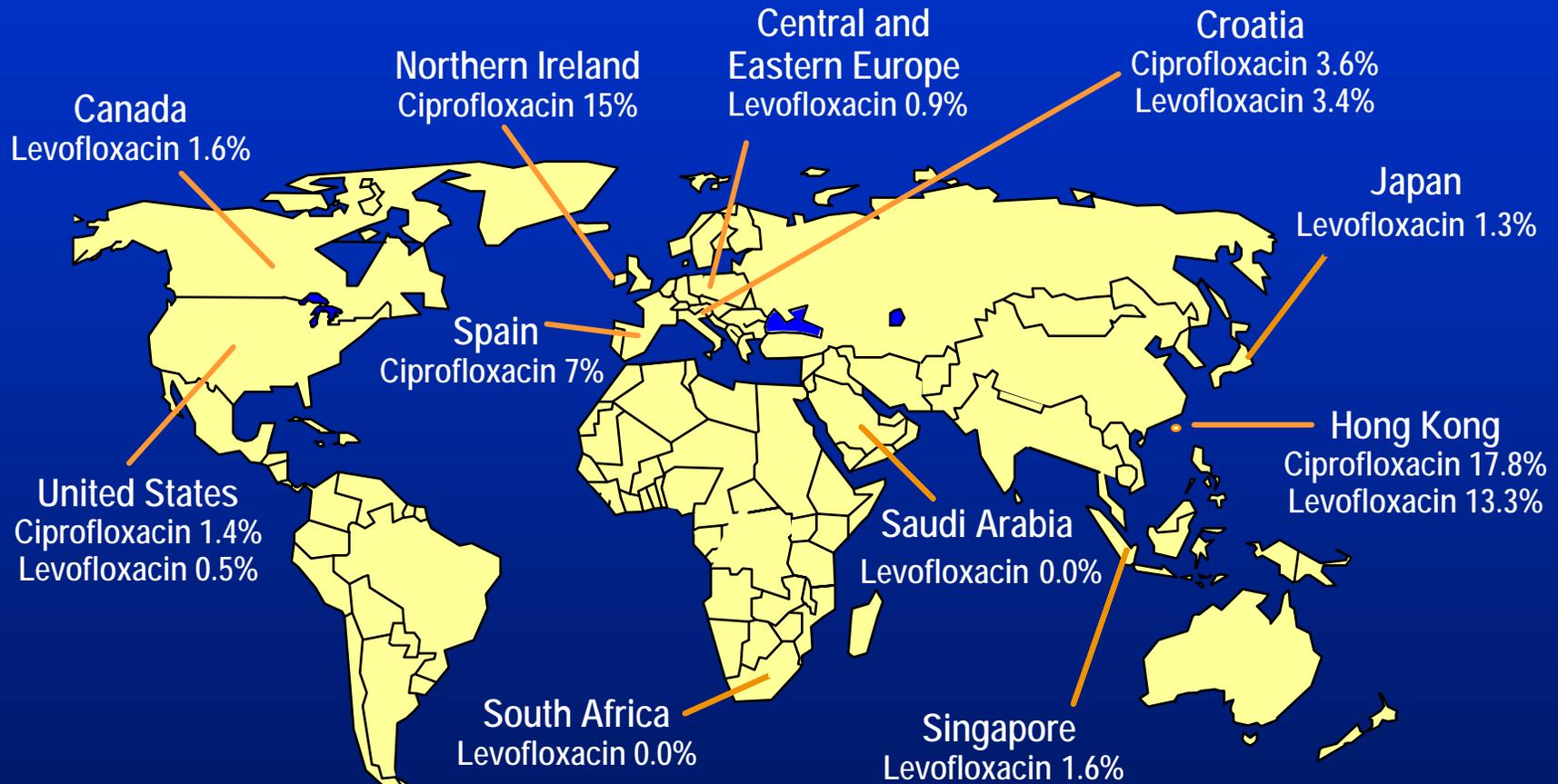
Azithromycin-resistant (MIC > 1 µg/ml)
Erythromycin-resistant (MIC > 0.5 µg/ml)

Jones *et al* (2003). *Diagn Microbiol Infect Dis* 47(4):579-86.

Fouda *et al* (2004). *J Chemother* 16(6):517-23.

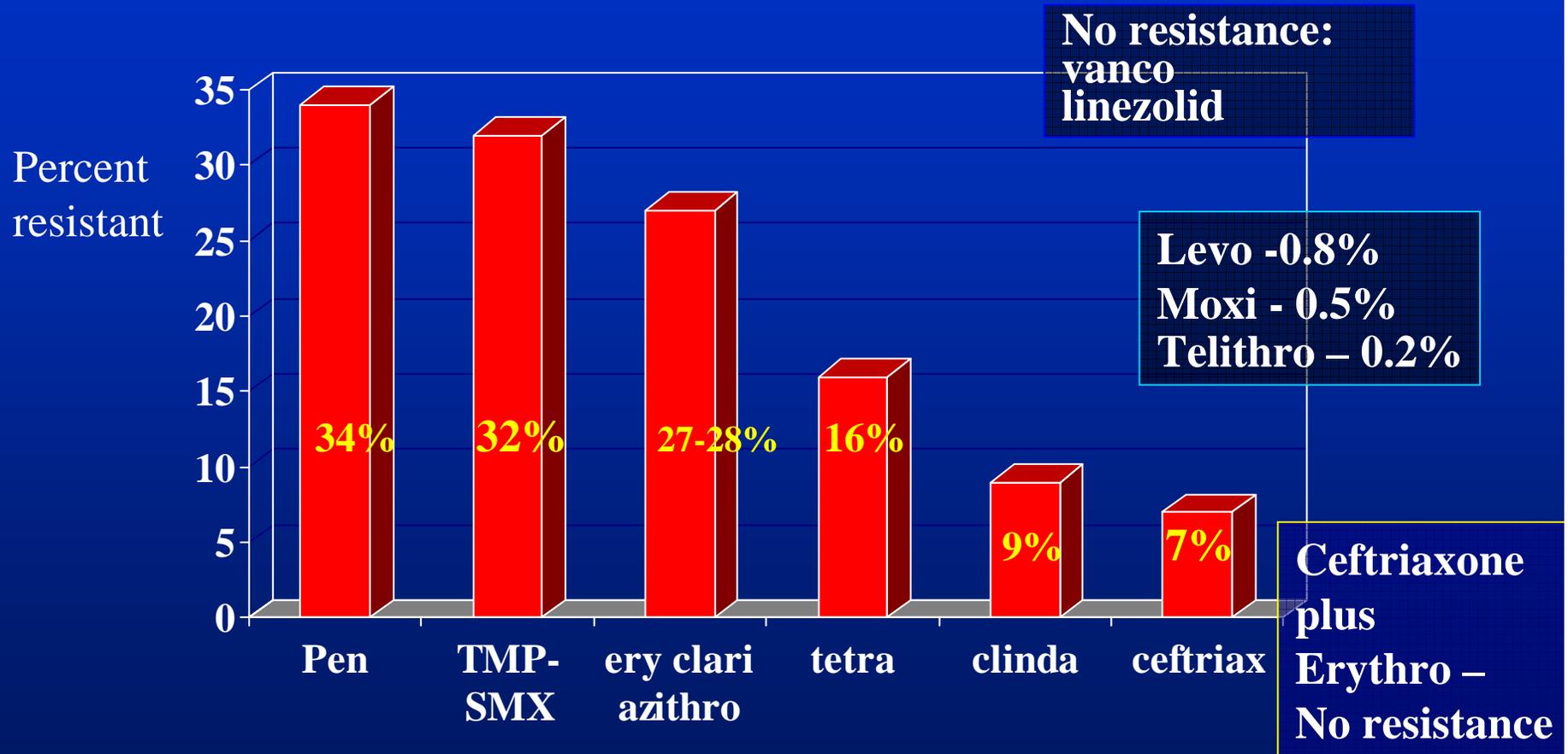
Jenkins *et al* (2005). *J Infect* 51(5):355-63.

Worldwide rates of *S. pneumoniae* non-susceptible to fluoroquinolones



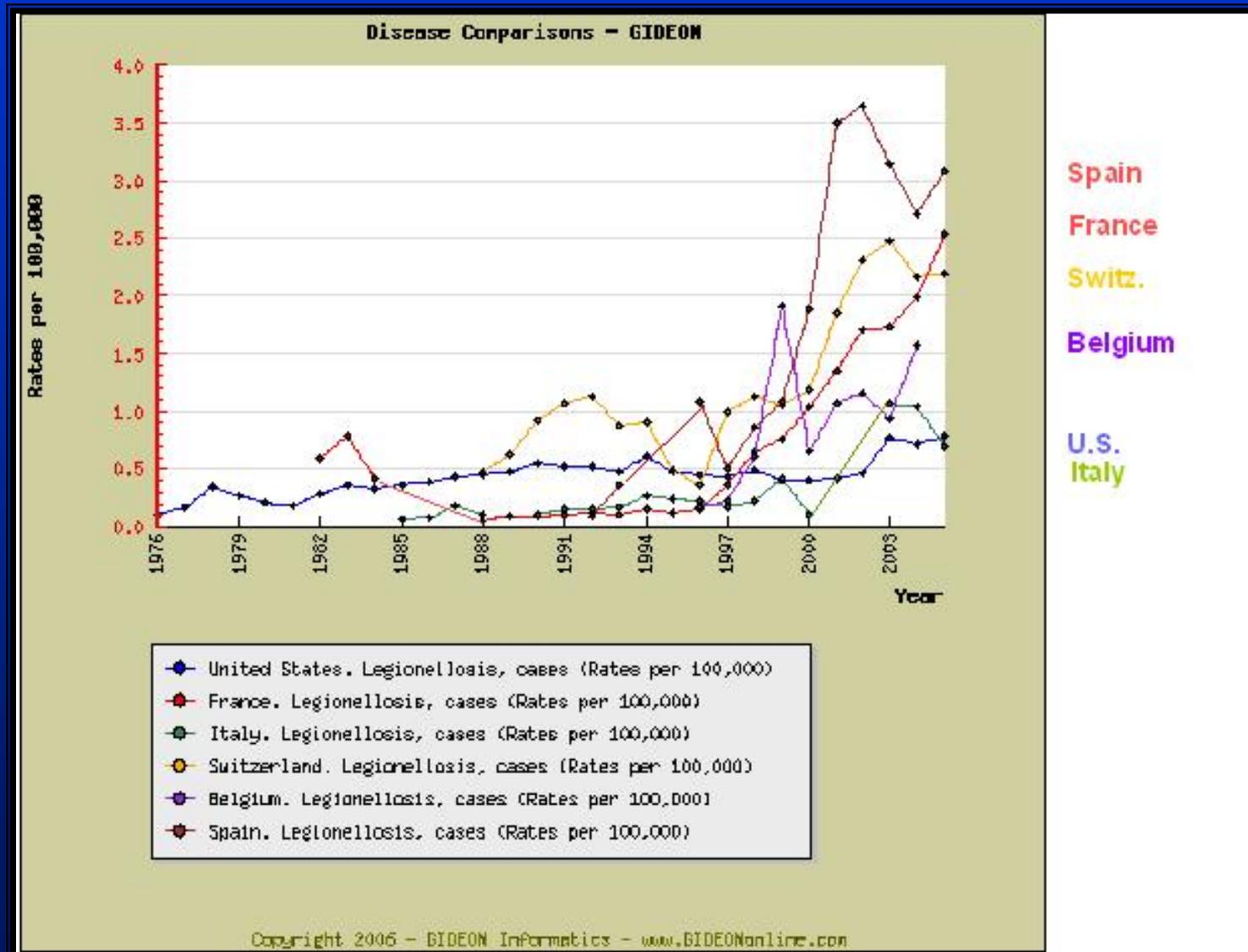
Doern *et al. Antimicrob Agents Chemother* 2001; **45**:1721–1729; Ho *et al. J Antimicrob Chemother* 2000; **48**:659–665; Nagai *et al. Antimicrob Agents Chemother* 2002; **46**:371–377; Thornsberry *et al. Clin Infect Dis* 2002; **34**:S4–S16; Goldsmith *et al. J Antimicrob Chemother* 1998; **41**:420–421; Pankuch *et al. Antimicrob Agents Chemother* 2002; **46**:2671–2675; Perez-Trallero *et al. Antimicrob Agents Chemother* 2001; **45**:3334–3340; Low *et al. Canadian Bacterial Diseases Network*, 2002; Alexander Project 2001, GSK data on file

National Multicenter Surveillance for *S.pneumoniae* Resistance



Doern et al *CID* 2005; 41:139-48

Legionella



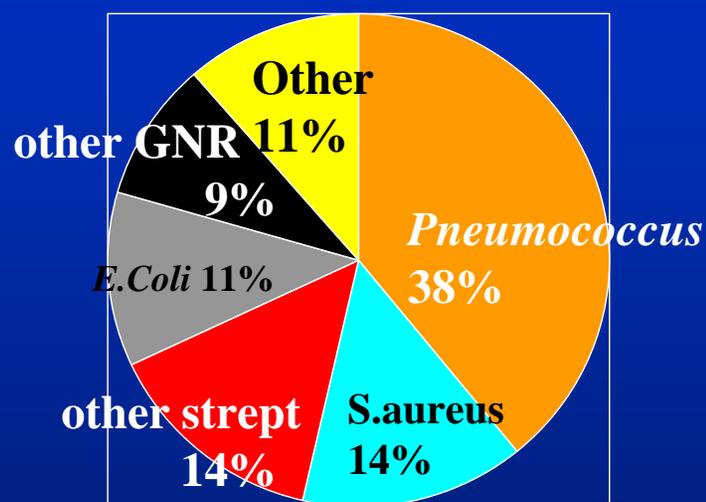
Critique of Metersky et al Manuscript on Bacteremic CAP

Possible confounding not accounted for in retrospective analyses

Those patients receiving therapy for atypicals also more likely to have received concordant R_x within 24 hours and also within 8 hours;

Smaller proportion (12%) receiving levofloxacin vs macrolides (23%) may have caused an issue with statistical power.

Bacteremic Pneumonia: Value of Therapy for Atypical Organisms (n=2209 Medicare patients)



Independent Predictors of 30-day Mortality

Variable	OR	P
PSI I, II, III vs.V	0.10	<0.001
Concordant R _x on 1 st day	0.75	0.021
Initial R _x for atypicals	0.76	0.034

(only macrolide significant)

-THERAPY -

	Mono (n=855)	Dual (n=1324)
Macrolide	-	23% (always with 3 rd gen ceph)
Levo	34%	12% (25% w/clinda or vanco)
3 rd Gen Ceph	39%	32%

Metersky et al
Chest 2007; 131:
466-73

Independent Predictors of Mortality with Pneumococcal Bacteremia (ORs)

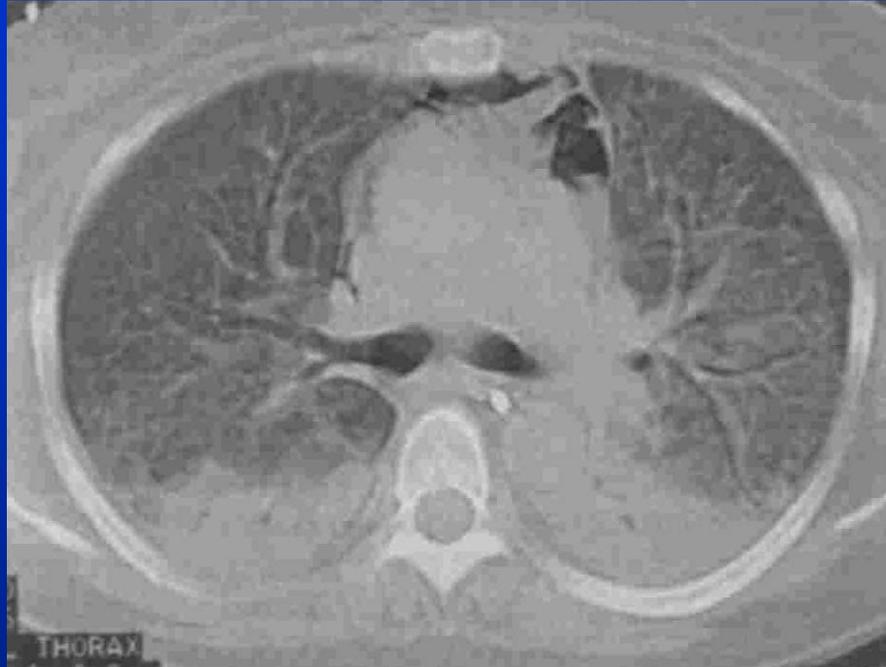
Variable	all pts (n=421) (p)	HIV pts (n=212)
pO ₂ < 50	33.8 (<0.001)	47.5 (<0.001)
Hi-level Pen [®]	6.0 (<0.02)	7.8 (<0.01)
Hispanic	2.4 (<0.02)	3.1 (<0.03)
Multilobe/Effusions	2.4 (<0.02)	(.07)
Age	<0.02	(.09)
CD4 <122	-	(.051)

(CD 4 count did not predict Pen[®])

Case History

A previously healthy 64 year old male presents with a 7-day history of progressive SOB. He has mild cough, severe exertional dyspnea. No exposures to ill people, animals, travel, toxins, cigarettes.

He has fever to 102°, tachycardia, R=36/min and BP 122/82. Diffuse rales. CXR bilat alveolar infiltrates. PO₂ 70, and he is intubated with progressive bilat alveolar infiltrates.



High-resolution computed tomography scan performed at the middle level. Bilateral areas of alveolar opacification are evident in the pending areas of the lungs.

Eur Respir J 2003; 21:187-91

Acute Interstitial Pneumonitis - Hamman Rich Syndrome -

Most patients > 50

No underlying lung diseases

Progressive dyspnea over weeks

Usually fatal - 75% mortality!

X-ray/Physical exam: resembles ARDS

Bx: Organizing form of diffuse alveolar damage

BAL: huge neutrophilia and scattered

Type - II pneumocytes

Acute Interstitial Lung Disease

- Acute interstitial pneumonitis
- Acute respiratory distress syndrome:
sepsis, transfusion, trauma, no left atrial HTN,
 $pO_2/FIO_2 < 200$
- Bronchiolitis Obliterans Organizing Pneumonia:
infection, transplant, collagen vasc dis, mean age 53
- Acute Eosinophilic Pneumonia:
mean age 28, symptoms < 1 wk, 38.6°
- Acute hypersensitivity pneumonitis

Neoplasms Mimic CAP

Bronchial neoplasm/obstruction

Small cell or squamous

**occasionally mets:melanoma, CA breast, GI
hypernephroma, kaposis**

Alveolar cell Carcinoma

Profuse bronchorrhea (33%0

Females>> Males

Present with consolidation (30%)

Lymphangitic Carcinomatosis

Stomach (44%), bronchos 23%

Breast (9%), Pancreas 5%

Lymphomatoid Granulomatosis

Males >> Females

Bilat nodules - middle, lower lobes.

Ceftriaxone

3rd generation cephalosporin

Usual dose: 1 gram q 12 h

AE: PDR

Rash (2.0 %), GI (3%), ↑ liver enzymes (3%)

↑ BUN (1%) gall bladder sludge (0.1%)

Levofloxacin (quinolone)

Dose: 500 mg/d

Reduced bioavailability if given with
Ca⁺ antacids, aluminum, magnesium,
sucralfate

(no Δ with H-2 blockers)

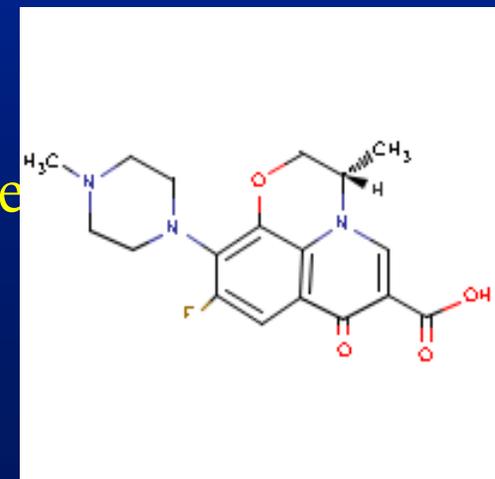
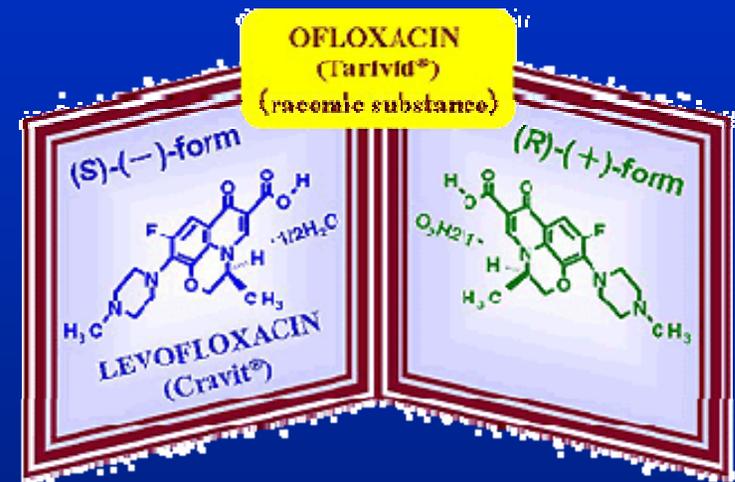
AE: GI – 3-17%

Headache/dizziness 0.9-11%

Arthropathy (Achilles)

[Seizures reported with NSAIDs (displace

Enoxacin only)]



PPID 2005

Vancomycin

Glycopeptide: workhorse for MRSA Rx

Usual dose 1 gm q 12

Key AE: renal insufficiency

Efficacy limited by ↑ MICs, poor tissue penetration

Slow killing rates

CID 2006; 42:S51-7

Failure in 19/25 (76%) of serious

Infection with MICs 2-4 µg/ml

CID 2004; 38:521-8

Accessory gene regulator

II polymorphism linked to

Vancomycin failure

CID 2004; 38:1700-5

Linezolid

Inhibit bacterial protein synthesis (early step in tRNA binding to ribosome)

Dose: 600 mg q 12h

AE: Thrombocytopenia after 2-3 weeks

Peripheral + optic neuropathy reported

Lactic acidosis reported

May ↑ [] of serotonergic drugs

Clinical Trials – SSTI:

Equivalent to weekly Dalbavancin

CID 2005; 41: 1407-15

Equivalent to vancomycin

AAC 2005; 49:2260-6

S. aureus pneumonia:

current data suggest equivalence to vanco

Tigecycline

Activity: HA and CA-MRSA

Vanco[®] and [®]*E. faecium* and *E. faecalis*

Skin-soft tissue infection: Clinical end point

100 mg IV => 50 mg q 12 h

Vs Vanco 1 gm q 12/aztreonam 2 q 12

Cure rates 87% and 89%, respectively

AE: No EOF. n/v 35% and 20% vs 8% and 4% (vanc/aztreo)

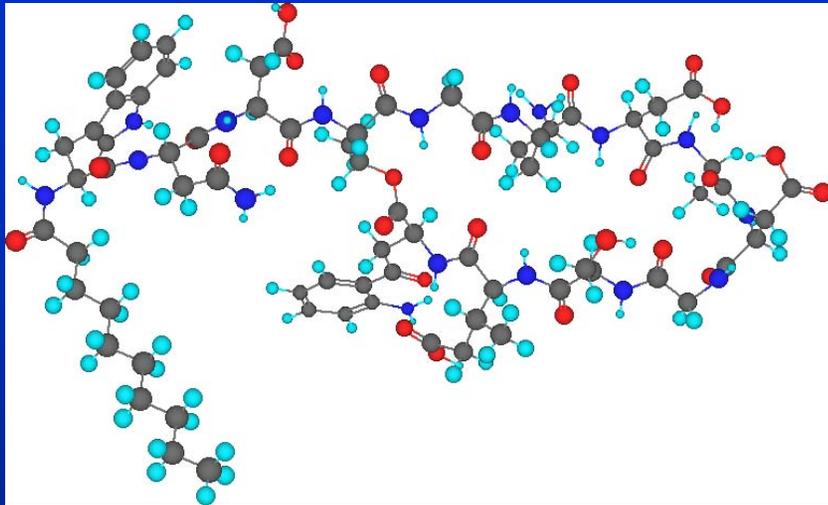
www.FDA.gov/cder/foi/label/2005

Reviewed by Wenzel et al

Nat Rev Drug Disc 2005; 4:809-10

No FDA approval for CAP

Daptomycin (Cyclic Lipopeptide)



Active Vs MRSA, VISA,
VRSA and Vanco[®]

E. faecalis and
E. faecium

Syndman et al *ECCMID* 2002:1165
Adler, *Drugs of Today* 2005; 41:81-90

Binds to cell membrane → efflux of K⁺ ions
→ depolarization → destroy ion [] gradient
→ inability to synthesize ATP → cell death

Complicated skin, skin structure infections:
two randomized controlled studies
(n=1092)

Daptomycin: 4 mg/kg/day once
Vs either Vanco (1 gm q 12) or
Semisynthetic PCN (4-12 gm/day)

	Dapto	Vanco semisynth PCN
Clinical Cure	83.4%	84.2%

NOT RECOMMENDED FOR PNEUMONIA
Since low levels in alveolar spaces

Liver Damage After a Drug

Drug
Rx



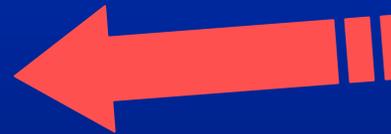
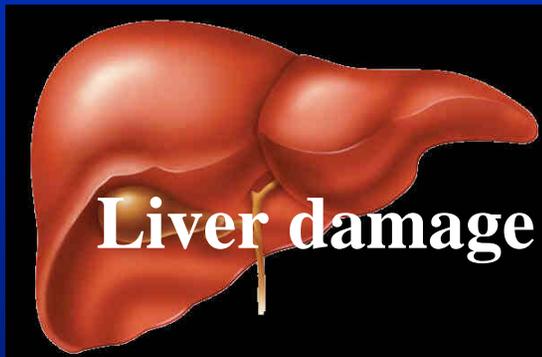
metabolized
by P450
in unusual way
(genetically programmed)



one of the
metabolites



stimulates a
T-lymphocyte
immune reaction
to the cleaved
metabolite



Questions:

- Definition of *toxicity* if rare event occurs that is genetically determined?
- Is the damaging metabolite useful in treating the infection as well?
- Who are *especially susceptible*?

Rare Liver Events and Outcomes

1) If the attack rate of a rare event is 1:1000, how many people need to be observed to have a 95% chance of finding ≥ 1 ?

Binomial answer: 3 (incidence) or ~ 3000

2) "Hy's Law": If both hepatocellular injury and jaundice occur, mortality will be $\geq 10\%$

FDA/CDER-AASLD – Pharma
Hep tox steering group

-Telithromycin – New Antibiotic with AE: Three Perspectives

EPIDEMIOLOGY

- Low AR in populations
- Risk-benefit analysis?
- Available alternatives exist

CLINICIAN

- No predictive risk factors
- Severe AE if occur
- Available alternatives
- Informed consent?

INDUSTRY

- Good drug with rare AE
- Huge investment
- Need: define risk factors
pharmacogenomics
- Legal, ethical challenges