Community Acquired Pneumonia

Background & Rationale to North American Guidelines

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Consider

• Impact of the disease

Issues to reflect upon

Impact of the Disease

- 3-4 million cases annually
- 10 million physician visits
- 600,000 hospitalizations
- 45,000 deaths
- 64 million days of restricted activity
- most common cause of death from infection
- 6th most common cause of death overall

Issues to Reflect Upon

- Significance of the disease
- Limitations of current diagnostic methods
- Copathogens
- Resistance
- Inappropriate therapy predicts poor outcome

What Are The Important Etiologic Pathogens?



- CAP is not a homogeneous entity
- Must consider
 - 1. whether acquired in community or N.H.
 - 2. severity of illness
- Pathogen not found in 1/2 of cases
- Copathogens

S. pneumoniae

- meta-analysis of CAP 1966 – 1995

S. pneumoniae – 66% of 7000 cases
- 66% of fatalities

Fine JAMA 1996:275;134

Atypical Pathogens

M. pneumoniae, C. pneumoniae and Legionella sp. ranked 2nd 3rd and 4th of over 2700 hospitalized CAP patients with a definite etiologic diagnosis.

> Marston et al Arch Intern Med 157:1709,1997

<u>Outpatients</u>	<u>Inpatients</u>	<u>Nursing Home</u>
S. pneumoniae	S. pneumoniae	S. pneumoniae
Atypicals (2)	Atypicals (3)	Atypicals (2)
H. influenzae	H. influenzae	S. aureus
	GNR	GNR



HAP - well established - Bartlett '86 CAP - 2.7%-10% Fang - Medicine '90 Marrie - CID '94 Marston - Arch Int Med '97 What's Happening With Resistance?

S. PNEUMONIAE - 225 CENTRES ACROSS U.S. Jan '00-July '00



S. PNEUMONIAE Jan '00-July '00

<u>Blood</u>	<u>% R to Erythro</u>
Pen S.	4.3
Pen R.	58.9

Respiratory

Pen S. Pen R. 5.9 74.5

Impact of Resistance

- [↑] LOS Plouffe JAMA 1996
 - Einarsson SJID 1998
- [↑] Mortality Pallares NEJM 1995

- Einarsson SJID 1998

- Feikin Am J Pub Health 2000

 Cost - OTA 1995 - total annual direct cost of resistance - \$4 billion or 0.5% of total U.S. health care costs What Are The Limitations of Current Diagnostic Methods?

Test characteristics of sputum Gram staining for patients with community-acquired pneumonia (CAP), according to different diagnostic criteria.

Diagnostic criterion	Sensitivity	Specificity
	%	%
Any gram-positive diplococci, any shape	100	0
Any gram-positive lancet-shaped diplococci	83	38
>10 gram-positive diplococci per OIF, any shape	83	31
Preponderance of gram-positive cocci, any shape	86	31
Preponderance of gram-positive diplococci, any sha	ape 86	46
>10 gram-positive lancet-shaped diplococci per C	DIF 55	85
Preponderance of >10 gram-positive lancet shaped		
diplococci per OIF	62	85
Preponderance of gram-positive lancet-shaped		
diplococci	48	100

Sputum Gram's Stain & Culture

- Up to 30% of CAP pts unable to produce sputum
- Prior use of antibiotics \downarrow usefulness
- With use of "grading" systems only 25%-40% sputum samples are of good quality
- Even good quality specimens have been negative despite positive blood cultures
- Gram's stain unable to detect atypicals

What Are the Treatment Options?

Is Initial Antimicrobial Therapy Important?

A 5 Year Study of Severe CAP With Emphasis on Prognosis in Patients Admitted to an ICU

Leroy O. Intensive Care Med 1995;21:24-31

Factors Selected by Multivariate Analysis Independently Related to Mortality

Variable	Relative O.R.	<u>P value</u>
Underlying Disease	3.09	.0007
(UF + RF)		
Shock	2.85	0.016
Bacteremia	2.63	0.019
Ineffective Initial	4.71	.0001
Therapy		

Choosing Among the Options

FQ vs. Comparators

4 Studies Showing Statistically Significant Improvement For FQ vs. Comparators

- 1. Ortqvist: Sparflox vs. Roxi Chest '96
- 2. File: Levo vs. CTX ± erythro AAC '97
- Tremolieres: Trova vs. Amox Eur. J. Clin M & ID '98
- 4. O'Doherty: Grepa vs. Amox JAC '97

Clinical Success Rates

Investigator	Regimen	Success Rate	95%CI
Ortqvist	sparflox	94%	1.9 to 10.8
	roxithro	79%	
File	levo	96%	-10.7 to -1.3
	CTX ± erythro	90%	
Tremolieres	trova	91%	1.6 to 17.6
	amox	81%	
O'Doherty	grepa	78%	2 to 43
ITT with	amox	58%	
Proven Pathogen			

CLINICAL TRIAL

Moxifloxacin vs. Amox-clav ±

clari

Sequential IV to PO in 538 patients

Demographics

	Moxi (n=258)	Control (n=280)
Mean age	55 yrs	55 yrs
Mild-mod	129 (50%)	143 (51%)
Severe	129 (50%)	137 (49%)

Clinical Response

Moxi Comparator 95%CI

Cure241 (93.4%)239 (85.4%)2.9 to 13.2

Failure17 (6.6%)41 (14.69%)

Same Response with ITT Analysis

Bacteriologic Response

Moxi	Comparator	95%CI
(n=64)	(n=71)	

Eradication60(94%)58(82%)1.2 to 22.9

Persistence 4 (6.3%) 13(18.3%)

Median Time to Defervescence

Moxi Comparator P

Day 2	40%	35%	.02
Day 3	80%	65%	

Other Outcomes

Comnarat	nr

Mean IV	4.1	4.9
duration (days)		

Mean hospitalization9.510.4Duration (days)

Deaths $9^{x}(3.5\%)$ $17^{xx}(6\%)$

^x6 due to pneumonia ^{xx}10 due to pneumonia

New Guidelines For CAP

Timelines **1993 - CIDS** 1993 - ATS **1998 - IDSA 2000 - CDC** <u>2000 - IDSA</u> **CIDS-CTS 2001- ATS**



OUTPATIENT





- <u>a.</u> No Modifiers Macro
- **<u>b.</u>** Modifiers
 - **<u>I.</u>** COLD No recent antibx New Macro
 - **II.** COLD Recent antibx
 - FQ
- **<u>c.</u>** Aspiration Amox/Clav

±

Macro



WARD



In contrast with IDSA & CIDS No 1st line role for FQ in outpts. hospitalized ward pts

INPATIENT ICU

β-lactam +FQ/ Macro

Pseudo – β-lactam + FQ/Macro Pseudo + APA + FQ

Pseudo – β-lactam + FQ/Macro Pseudo + APA + Cipro

NURSING HOME

Nursing Home

Hospital

FQ or Am/Clav + Macro Similar to other hospitalized patients **Main Differences Outpatient <u>CDC</u>** - suggests β -lactam without "atypical" coverage - no 1st line role for FQ **CIDS - splitters vs lumpers** Inpatient **CDC** - no 1st line role for FQ for ward patients - pseudomonas not mentioned **Nursing Home CIDS** - separate category

ATS Guidelines

AM J Respi Crit Care Med 163:1730, 2001

Main difference among CIDS-CTS IDSA ATS

ATS – only document to allow monotherapy with macrolide for hospitalized CAP

Are the Guidelines Validated?

Yes:

- Guglielmo ICAAC 1997 K146 Gordon - Am J Resp Crit Care Med 1995 Bateman - Chest 1996 Gleason - Arch Int Med 1999
- Stahl Arch Int Med 1999
- Dean Am J Med 2001

LOS Mortality