

CAP, HAP, VAP, & HCAP

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Objectives

Following the presentation, the participant will be able to:

1. Identify typical, atypical, & hospital respiratory pathogens.
2. Identify diagnostic criteria used to establish a diagnosis of pneumonia
3. Identify differences in pathogens causing HAP vs CAP and the required differences in antibiotic coverage.
4. Identify underlying mechanisms of antibiotic resistance for typical bacterial pathogens
5. Using IDSA/ATS guidelines for CAP & HAP/VAP/HCAP identify appropriate initial antibiotic therapy

Pneumonia

- Community acquired pneumonia (CAP)
- Aspiration pneumonia
- Hospital
 - Hospital acquired pneumonia (HAP)
 - Ventilator associated pneumonia (VAP)
 - Healthcare associated pneumonia (HCAP)

2007 ATS/IDSA CAP Guidelines

Mandell, LA et al CID 44(suppl 2) 2007

Patient screening

- Determine whether to treat as outpatient or in-patient (ICU vs Ward)
- Objective scoring systems
 - Pneumonia Severity Index
 - CURB-65
 - Confusion
 - Urea > 7 mmol/L
 - Respiratory Rate \geq 30 / min
 - Blood pressure \leq 90 mm Hg & diastolic \geq 60 mm Hg
 - Age \geq 65 years
 - ICU Admit (3 minor criteria present)
 - Respiratory rate \geq 30 / min
 - $P_aO_2/FIO_2 < 250$
 - Multiobar infiltrates
 - Confusion
 - Uremia
 - Neutropenia
 - Thrombocytopenia
 - Hypothermia

Pneumonia

Diagnosis

- Fever, cough, SOB & pleuritic chest pain
- Chest x-ray infiltrate
- HAP, VAP, & HCAP
 - Sputum culture should be obtained prior to antibiotics
 - Quantitative or semiquantitative culture required
- Sputum gram stain & culture
 - <10 epithelial cells & > 25 PMN's per field
 - Appropriate cultures of blood and CSF

Bacterial Resistance in Pneumonia

Penicillin Resistant *S. pneumoniae*
Macrolide Resistant *S. pneumoniae*
Ampicillin Resistant *H. influenzae*
Beta-lactamase producing *M. catarrhalis*
MRSA & CA-MRSA
Multiple Drug Resistant Gram Negative Pathogens
P. aeruginosa
S. maltophilia
Acinetobacter spp
K. pneumoniae or *E. coli* (ESBL positive)
KPC (+) Klebsiella spp

Potential CAP Pathogens

Typical

- *S. pneumoniae*
- *H. influenzae*
- *M. catarrhalis*

Atypical

- *C. pneumoniae*
- *L. pneumophila*
- *Mycoplasma*

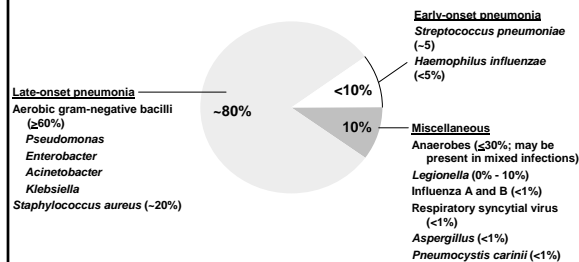
- Viruses
- Fungi
- Less Common pathogens
 - *N. meningitidis*
 - *S. pyogenes*
 - *M. tuberculosis*
 - *Chlamydia psittaci*
 - *Coxiella burnetii*
 - *B. anthracis*
 - *Y. pestis*
 - *F. tularensis*
 - CA-MRSA

Am J Med 106:385-390,1999

ATS Pathogen Risk Factors for Penicillin NS/R *S. pneumoniae*

- > 65 years
 - Multiple co-morbidities
 - Alcoholism
 - Exposure to children in day care
 - Immunosuppressed
 - Smoking
 - Use of beta-lactam within last 90 days
- Am J Respir Crit Care Med 163:1730-1754, 2001

Nosocomial Pneumonias



Adapted from Leaf HL. In: Mandell GL, Simberloff MS, eds. Atlas of Infectious Disease. Philadelphia, Pa: Current Medicine. 1996;6.VI:6.16

ATS Guidelines for HAP, VAP, & HCAP

• Risk for MDR Pathogens

- Antibiotic therapy in previous 90 days
- Current hospitalization of ≥ 5 days
- High frequency of antibiotic resistance

• Risk factors for HCAP

- Hospitalization for ≥ 2 days in previous 90 days
- Residence in nursing home or ECF
- Home infusion therapy
- Chronic dialysis within 30 days
- Home wound care
- Family member with MDR pathogen

- Immunosuppressive disease

Effect of Mechanical Ventilation and Prior Antibiotic Use on Development of Multiresistant Pathogens

Organisms	Group 1 (n=22) MV < 7 ABT = no	Group 2 (n=12) MV < 7 ABT = yes	Group 3 (n=17) MV ≥ 7 ABT = no	Group 4 (n=84) MV ≥ 7 ABT = yes
Multiresistant bacteria	0*	6 (30)	4 (12.5) [†]	89 (58.6)
<i>P. aeruginosa</i>	0	4 (20)	2 (6.3)	33 (21.7)
<i>A. baumannii</i>	0	1 (5)	1 (3.1)	20 (13.2)
<i>S. maltophilia</i>	0	0	0	6 (3.9)
MRSA	0	1 (5)	1 (3.1)	30 (19.7)
Other bacteria	41 (100)	14 (70)	28 (87.5)	63 (41.4)

Adapted from Trouillet JL, et al. Am J Respir Crit Care Med. 1998;157:531-539

* p < 0.02 versus Groups 2, 3, or 4
† p < 0.0001 versus Group 4

Diagnosis of Suspected VAP

413 patients with suspected VAP

- 32% enrolled surgical patients

Invasive management

- BAL or bronchoscopic protected specimen brush (PSB)
- Quantitative sputum cultures
 - ≥10⁴ CFU/mL BAL
 - ≥10³ CFU/mL PSB

Clinical management

- Clinical criteria
- Nonquantitative evaluation of nonbronchoscopic isolates

Fagon JY et al. Ann Intern Med. 2000;132:621-630.

Diagnosis of Suspected VAP

Intention-to-Treat Analysis

End Point	Invasive (n=204)	Clinical (n=209)	P value
Mortality at 14 days, n (%)	33 (16.2)	54 (25.8)	0.022
Mortality at 28 days, n (%)	63 (30.9)	81 (38.8)	0.099
Antibiotic-free days at 14 days	5.0 ± 5.1	2.2 ± 3.5	<0.001
Antibiotic-free days at 28 days	11.5 ± 9.0	7.5 ± 7.6	<0.001
Emergence of <i>Candida</i> spp., n (%)	23 (11.3)	47 (22.5)	0.0025

Adapted from Fagon JY et al. *Ann Intern Med.* 2000;132:621-630.

Bacteriology

Feature or Organism	Invasive (n=204)	Clinical (n=209)
Negative culture	55.9%	14.4%
Monomicrobial pneumonia	31.9%	40.2%
Polymicrobial pneumonia	12.3%	45.5%
<i>P. aeruginosa</i>	22.3%	18.3%
<i>S. aureus</i>	16.5%	12.8%
<i>H. influenzae</i>	7.4%	3.8%
<i>A. baumannii</i>	5.0%	3.5%
<i>Enterobacter</i> spp.	3.3%	3.8%

Adapted from Fagon JY et al. *Ann Intern Med.* 2000;132:621-630.

TRUST 12 (2008) National Antibigram: Susceptibility of *S. pneumoniae* (N=2858)

Antimicrobial Agent	% S	% I	% R
Levofloxacin	99.4	0.0	0.6
Moxifloxacin	99.4	0.4	0.2
Ceftriaxone (nonmeningitis)	94.0	4.6	1.4
Amox-clav (nonmeningitis)	86.7	3.1	10.2
Tetracycline	79.8	0.3	19.9
Cefuroxime (oral)	77.4	3.4	19.2
Cefdinir	77.0	2.8	20.2
Trimethoprim-sulfa	73.7	7.9	18.4
Azithromycin	66.5	0.1	33.4
Clarithromycin	66.7	0.4	32.9
Penicillin (oral)	62.7	21.6	15.7

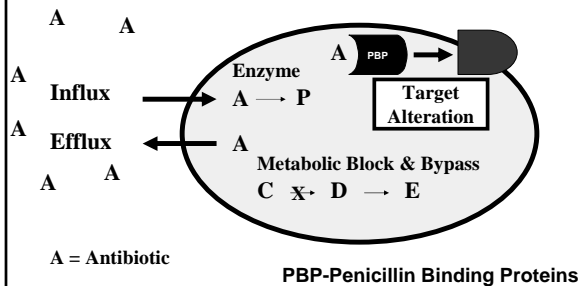
In vitro activity does not necessarily correlate with clinical results. All isolates were vancomycin susceptible. Breakpoints (S/I/R) for other antimicrobials are CLSI.

New FDA Pneumonia Breakpoints for *S. pneumoniae* (2008)

- Sensitive
 - PCN MIC ≤ 2 (Previously 0.06 mg/L)
- Non-susceptible
 - PCN MIC = 4 (Previously 0.12 to 1.0 mg/L)
- Resistant
 - PCN MIC ≥ 8 mg/L (Previously ≥ 2 mg/L)
- Meningitis breakpoint for penicillin sensitive remains at ≤ 0.06mg/L
- Mechanism of resistance is alteration of penicillin binding proteins not beta-lactamase production

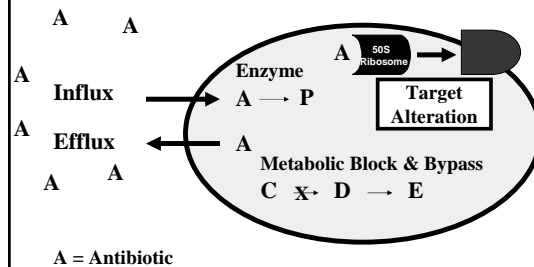
S. pneumoniae Penicillin Resistance

- Influx-Block Porin Channel
- Efflux- Pump (mefA)
- Enzyme Inactivation
- Target Alteration(PBP)
- Environment Factors
- Metabolic Bypass



S. pneumoniae Macrolide Resistance

- Influx-Block Porin Channel
- Efflux- Pump (mefA)
- Enzyme Inactivation
- Target Alteration(ermB)
- Environment Factors
- Metabolic Bypass



Pneumonia Treatment Guidelines 1993-Present

- American Thoracic Society (ATS)
 - First published 1993
 - Revision – *Am J Respir Crit Care Med* 163:1730-1754, 2001
- Infectious Diseases Society of America (IDSA)
 - First published April 1998
 - Revision – *Clin Infect Dis* 31:347-382, 2000
 - Revision – *Clin Infect Dis* 37:1405-1433, 2003
- New Joint IDSA/ATS CAP Guidelines 2007
 - Mandell, LA et al *Clin Infect Dis* 44(suppl 2) 2007
- Joint IDSA/ATS HAP/ VAP / HCAP Guidelines 2005

2007 ATS/IDSA CAP Guidelines

Mandell, LA et al *CID* 44(suppl 2) 2007

- **Healthy & no risk factors for DRSP**
 - Macrolide or Doxycycline
- **Comorbidities present** – Antibiotic Use in last 90 days, heart, lung, or renal disease, diabetes, DRSP risk factors...
 - Respiratory fluoroquinolone
 - Moxifloxacin, Levofloxacin, or Gemifloxacin
 - Macrolide (or doxycycline) & beta-lactam
 - Ampicillin ± Clavulanate, Ceftriaxone, Cefpodoxime, or Cefuroxime
- **Note:** gatifloxacin has been removed from guidelines & no recommendation is offered for telithromycin

2007 ATS/IDSA CAP Guidelines

Mandell, LA et al *CID* 44(suppl 2) 2007

Inpatient Non-ICU

- Respiratory fluoroquinolone
- Macrolide (or Doxycycline) plus beta-lactam
 - Cefotaxime, Ceftriaxone, Ampicillin, or Ertapenem

Inpatient ICU

- Azithromycin or respiratory fluoroquinolone plus beta-lactam
 - Cefotaxime, Ceftriaxone, or Ampicillin/Sulbactam

2007 ATS/IDSA CAP Guidelines

Community Acquired MRSA (CA-MRSA)

- Common following a viral infection
 - Check Gram stain & Check X-ray for cavitary infiltrates
- CA-MRSA prolific toxin producer
- Treatment (No preference given)
 - Vancomycin
 - Possible issues with lung penetration, slow kill rate, failure to shut down toxin production, & cell lysis upon death
 - Linezolid
 - Antibiotic recommendations for pneumonia different than S/STI recommendations
 - Daptomycin binds to surfactant & can't be used for pneumonia

Possible Tip Offs for Patients with CA-MRSA Pneumonia

Patients tend to be younger
 Contact with CA-MRSA carrier or infection
 Previous or concomitant influenza
 Not current on influenza vaccination
 Gram positive cocci on Gram stain
 Multi-lobar involvement
 Cavitory pneumonia
 Evidence of airway hemorrhage

CAP Prevention

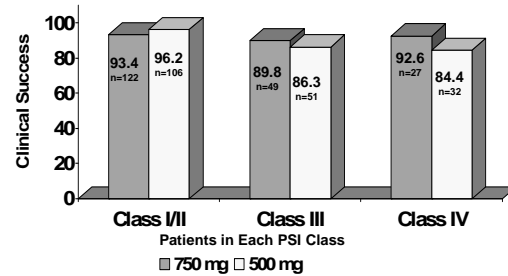
Mandell, LA et al *CID* 44(suppl 2) 2007
 MMWR December 15, 2006 Vol 55

- Persons \geq 50yrs, healthcare workers, risk patients should receive annual influenza vaccination
- Persons \geq 65 yrs or at risk should receive pneumococcal vaccine
- CDC recommends T_{dap} for adults 19-64 years
- Vaccination status should be evaluated at time of admission
- Patients should be offered influenza vaccination at discharge or outpatient treatment in the fall and winter
- Smoking cessation should be offered to patients who smoke
 - Smokers should be vaccinated against pneumococci & influenza
- Suggest appropriate respiratory hygiene & IC practices to patients with a cough

CAP Hospital Quality Standards

- Document
 - Influenza vaccination
 - Pneumococcal vaccination
 - Offer of smoking cessation therapy (if patient a smoker)
- Appropriate diagnostics & monitoring used
- Initial antibiotics consistent with CAP guidelines
- Antibiotics started at site of CAP diagnosis (ED) for hospitalized patients (Old standard 4 hours)
 - May initially need broad spectrum coverage
 - May be able to de-escalate after pathogen known
 - Duration
- Prophylaxis for thromboembolic disease

750-mg, Short-Course Levofloxacin for CAP: Clinical Success by PSI Class



Dunbar et al Clin Infect Dis. 2003;37:752-760

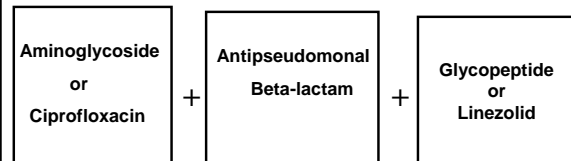
CAP Antibiotic Overview

Pathogen	BL	MAC	FQ	DOX	Ket
S. pneumoniae	+	+	+	+	+
PCN-R	±	±	+	±	+
Macro-R	±	-	+	±	+
H. influenzae	±	±	+	+	±
M. catarrhalis	±	+	+	+	+
Atypicals	0	+	+	+	+

Antibiotic choice highly dependent on specific agent selected
 For *S. pneumoniae* with PCN MIC ≥ 2 mg/L, vancomycin, FQ, or ketolide probably best choice depending on circumstances
 BL-beta-lactam, MAC-macrolide, FQ-fluoroquinolone, DOX-doxycycline, & Ket-ketolide

Antibiotic Treatment Presence of MDR bacteria?

Combination Therapy



Höffken G, Niederman MS. Chest. 2002;122:2183-2196.

ATS Guidelines for HAP, VAP, & HCAP

Initial empiric therapy for HAP, VAP, & HCAP in patients with late onset or risk for MDR

- Cefepime (1-2Gm Q8-12H) or Ceftazidime (2Gm Q8H)
- Imipenem (500mg Q6H) or Meropenem (1Gm Q8H)
- Piperacillin/Tazobactam (4.5Gm Q6H)
- One of the above plus
- Gentamicin or Tobramycin 7 mg/Kg/Day
- Amikacin 20 mg/Kg/Day
- Levofloxacin 750 mg QD or Ciprofloxacin 400 mg Q8H
- One of the above plus
- Vancomycin 15 mg/Kg Q12H or Linezolid 600 mg Q12H
- Daptomycin binds to lung surfactant & should not be used

Vancomycin Treatment Guidelines

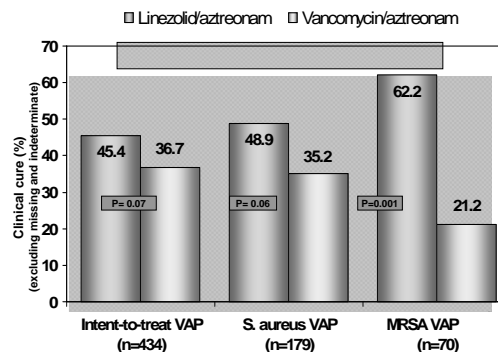
Guideline	Organ	Dose	Trough (mg/L)
HAP/VAP	ATS	15 mg/KgQ12H	15-20
Meningitis	IDSA		15-20*
Endocarditis	BSAC	1GmQ12H	10-15
Endocarditis	AHA	15 mg/KgQ12H	10-15*

* Graded Recommendation

Vancomycin Trough Recommendations from Treatment Guidelines

- Guidelines recommending vancomycin trough concentration of 10-20 mg/L based on expert opinion not clinical trial data
- No data that empiric doses will produce desired vancomycin trough concentrations
- No data that higher vancomycin trough concentrations are safe &/or more effective
- Would FDA allow a change in the vancomycin product insert?

Superior results for linezolid vs vancomycin in ventilator-associated pneumonia (VAP)



ATS Guidelines for HAP, VAP, & HCAP

- Combination vs Monotherapy
 - Synergy only documented in-vitro, in patients with neutropenia, or bacteremic patients
 - Clinical relevance is unclear
 - Preventing the emergence of resistance during therapy not well documented
 - Meta-analysis of >1200/7586 patients with HAP/VAP beta-lactam monotherapy vs combination beta-lactam plus aminoglycoside, clinical failure more common with combination therapy
 - No advantage for *P. aeruginosa*
 - Combination therapy did not prevent emergence of resistance
 - More nephrotoxicity with combination

Summary

- LRTI/URTI's remain a serious and expensive problem
- Level of antibiotic resistance among common respiratory pathogens is concerning & could grow
- Need better diagnostic methods
- Antibiotics often over utilized in URTI & LRTI
 - Need to be more responsible with antibiotic resources
 - Increase the rate of vaccination for *S. pneumoniae*
 - Use oral therapy whenever possible
 - Use antibiotics for as short a time as possible
 - Remain watchful for antibiotic resistance & ADR's

Summary

Optimizing Therapy:

- Get in quick with appropriate empiric antibiotics
- Hit hard with definitive therapy once pathogen is identified and dose appropriately
- Get out ASAP limiting collateral damage
 - 5 days of therapy for CAP
 - 7 days of therapy for HAP, VAP, & HCAP for non- MDR pathogens
 - Streamline therapy per culture results