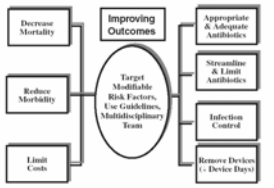
Hospital-acquired pneumonia

New guidelines and ongoing controversies



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New guidelines

- Treatment
  - *Hospital-acquired pneumonia Guideline Committee of the American Thoracic Society & Infectious Diseases Society of America. Guidelines for the management of adults with hospital-acquired pneumonia, ventilator-associated pneumonia, and healthcare-associated pneumonia – In Press.*

http://www.vhpharmsci.com/PresentationIndex.htm

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Outline

- Definitions
- Background
- Guideline Methodology
- Guideline Overview
- Controversies
  - *Pseudomonas aeruginosa*
  - *MRSA*
  - Shorter duration therapy
- Conclusions
- Future Research

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Definitions

- Healthcare-associated pneumonia (HCAP)
  - patients hospitalized in an acute care hospital ≥ 2 days within 90 days of the infection
  - patients in a nursing home or LTC facility
  - patients who have received recent IV antibiotic therapy, chemotherapy or wound care within the past 30 days, or who attended a hospital or hemodialysis clinic

Infect Dis Clin N Am 2004;18:939-962, Am J Respir Crit Care Med 2005, in press

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Definitions

- Hospital-acquired pneumonia (HAP)
  - pneumonia which occurs >48 hours after admission, which was not incubating at the time of admission
- Ventilator-associated pneumonia (VAP)
  - pneumonia that arises more than 48-72 hours after endotracheal intubation

Infect Dis Clin N Am 2004;18:939-962, Am J Respir Crit Care Med 2005, in press

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Background

- HAP is 2nd most common nosocomial infection
- Incidence of 5-10 cases/1000 admissions
- HAP accounts for 25% of ICU infections, > 50% of prescribed antibiotics
- Risk of VAP is 3% per day of intubation, occurs in 9-27% of all intubated patients
- Attributable mortality of VAP 33-50%
- Prolongs hospital stay by 7-9 days, increases costs by $40,000 per patient

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Guideline Methodology

- Clinical practice guidelines (CPGs)
  - *"Systematically developed statements to assist practitioner and patient decisions about appropriate health care for specific clinical circumstances."*

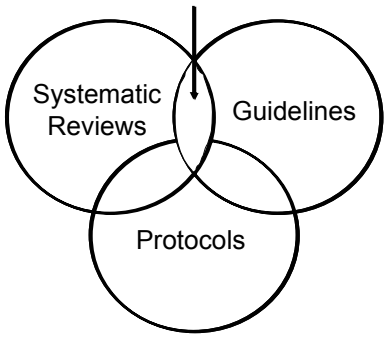
JAMA 1995;274:570-574.

Guideline Methodology

- Systematic reviews
  - "*evidence driven*", high-quality evidence
- Guidelines
  - "*necessity driven*", best available evidence
- Protocols
  - "*precise and detailed plans for the study of a medical problem or therapeutic regimen*"

Curr Opin Crit Care 2003;9:236-240.
Evidence-Based Medicine 2000. Sackett DJ.

Clinical Practice



Clinical Practice Guidelines (CPGs)

- "Authors, editors of CPGs fail to develop, adhere to, disclose potential COI relationships"
  - *BMC Med Res Methodol 2001;1:3.*
  - *JAMA 2002;287:612-617.*
  - *Sci Eng Ethics 2001;7:205-218.*
- "CPGs do not adhere well to established methodological standards"
  - *JAMA 1999;281:1900-1905.*

Clinical Practice Guidelines (CPGs)

- "CPGs often do not cite RCT evidence"
  - *J Clin Epidemiol 2002;55:545-555.*
- "Quality of CPGs from specialized societies has improved, but is still unsatisfactory"
  - *Lancet 2000;355:103-106.*
- "Quality of drug-therapy CPGs in Canada are suboptimal, no improvement from 1994-1998"
  - *CMAJ 2001;65:157-163.*

JAMA 1995;274:570-574.

Guideline Methodology

- Update to 1996 consensus statement
- Joint conference of American Thoracic Society (ATS) and the Infectious Diseases Society of America (IDSA)
- Pulmonary, critical care, and ID specialists
- Goal to provide *"framework for initial evaluation and management of immunocompetent adults with bacterial causes of HAP, VAP, HCAP"*

Infect Dis Clin N Am 2004;18:939-962, Am J Respir Crit Care Med 2005, in press

Guideline Methodology

- Each topic reviewed by >1 member
- Information presented and discussed, recommendations formulated
- Draft document prepared, reviewed, revised
- Statement *"…represents the final opinions of …majority of committee members."*
- No funding sources identified
- No potential COI declared

Infect Dis Clin N Am 2004;18:939-962, Am J Respir Crit Care Med 2005, in press

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Guideline Methodology

- Focused questions, literature search, selection, appraisal strategy not provided
- *"All available and relevant, peer-reviewed studies published until July 2004 were considered."*
- Levels of evidence

  Adapted from ATS/IDSA CAP Guidelines 2001

Infect Dis Clin N Am 2004;18:939-962, Am J Respir Crit Care Med 2005, in press

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Levels of Evidence

- Level I
  - Well-conducted randomized, controlled trials
- Level II
  - Well-designed, non-randomized controlled trials (including cohort, patient series, and case control studies)
- Level III
  - Case studies and expert opinion

Am J Respir Crit Care Med 2001;163(7):1730-54.

Infect Dis Clin N Am 2004;18:939-962, Am J Respir Crit Care Med 2005, in press

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ATS Guideline - Strengths

- Peer-reviewed
- Defines focus and target population
- Identifies guideline users and clinical settings
- Links recommendations to levels of evidence
- Drug and non-drug measures provided
- Practical, clinically-important, applicable recommendations (to an extent…)
- Tables and graphical algorithms

Infect Dis Clin N Am 2004;18:939-962, Am J Respir Crit Care Med 2005, in press

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ATS Guideline - Weaknesses

- No funding sources identified
- No conflict declaration
- Not multidisciplinary
- May not account for recent developments
- No graded recommendations provided
- Review process/consensus not specified
- No implementation strategy or review criteria
- Not validated

Infect Dis Clin N Am 2004;18:939-962, Am J Respir Crit Care Med 2005, in press

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Guideline Overview

Four major principles highlighted:

- Avoid untreated or inadequately treated pneumonia…associated with increased mortality
- Recognize the variability of bacteriology…and use this information to alter the selection of an appropriate antibiotic treatment regimen
- Avoid the over-usage of antibiotics by…accurate diagnosis, tailoring therapy, and shortening duration of therapy
- Utilize prevention strategies aimed at modifiable risk factors

Infect Dis Clin N Am 2004;18:939-962, Am J Respir Crit Care Med 2005, in press

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Epidemiology

- Patients with HCAP/HAP/VAP are at increased risk for colonization and infection with MDR organisms. (II)
- Late-onset infection HAP and VAP, and patients with severe chronic underlying disease are more likely to be infected with MDR pathogens than early-onset disease, with a higher mortality. (II)
- Bacteria cause most cases of HCAP/HAP/VAP, and many are polymicrobial, especially with ARDS. (I)
- HCAP/HAP/VAP commonly caused by GNB (*P. aeruginosa, K. pneumonia, Acinetobacter spp)*, or GPC, including *MRSA*; anaerobes are uncommon. (II)
- Prevalence of MDR pathogens varies by patient population, hospital type, and ICU, underscores need for local surveillance data. (II)

Infect Dis Clin N Am 2004;18:939-962, Am J Respir Crit Care Med 2005, in press

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AJIC special article

National Nosocomial Infections Surveillance (NNIS) System Report, data summary from January 1992 through June 2004, issued October 2004

A report from the NNIS System*
Division of Healthcare Quality Promotion, National Center for Infectious Diseases, Centers for Disease Control and Prevention, Public Health Service, US Department of Health and Human Services
Atlanta, Georgia

This report is a summary of the data collected and reported by hospitals participating in the National Nosocomial Infections Surveillance (NNIS) System from January 1992 through June 2004 and updates previously published data.[1-4]

The NNIS System was established in 1970 when selected hospitals in the United States routinely began reporting their nosocomial infection surveillance data for aggregation into a national database. Hospitals participating in the NNIS System provide general medical-surgical inpatient services to adults or children requiring acute care. Identity of the nearly 300 ICUs, as well as ICU-specific denominator data. Site-specific infection rates can be calculated by using as a denominator the number of patients at risk, patient-days, and days of indwelling urinary catheterization, central vascular cannulation (central line), or ventilation.

HRN SURVEILLANCE COMPONENT

ICPs collect data on all sites of nosocomial infection in patients located in HRN, and HRN-specific denominator data. Site-specific infection rates can be calculated by using as a denominator the number of

http://www.cdc.gov/ncidod/hip/SURVEILL/NNIS.HTM

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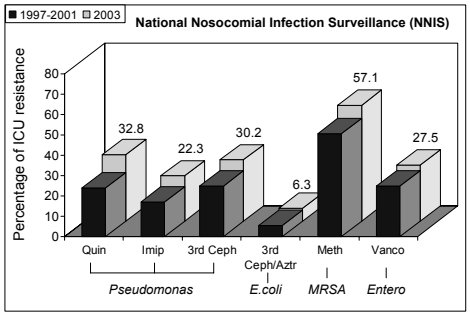
Epidemiology



Adapted from Am J Infect Control 2003;31:481-498.

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Pathogenesis

- Risk factors for HAP include healthcare devices or environment and microorganisms commonly transferred between staff, patients. (II)
- Host and treatment-related colonization factors (severity of illness, prior surgery, exposure to antibiotics, other medications, respiratory devices/equipment) important in pathogenesis of HAP and VAP. (II)
- Aspiration of oropharyngeal pathogens, or leakage of secretions containing bacteria around the endotracheal tube cuff are the primary routes of bacterial entry into the lower respiratory tract. (II)

Infect Dis Clin N Am 2004;18:939-962, Am J Respir Crit Care Med 2005, in press

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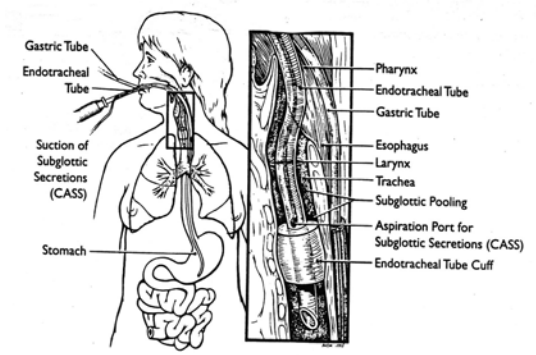

Chest 1995;108:1S-16S.

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Diagnosis

- In the absence of any clinical suspicion of HAP or nosocomial tracheobronchitis, no respiratory tract cultures should be obtained. (III)
- Tracheal colonization is common in intubated patients, in absence of clinical findings it is not a sign of infection, and does not require therapy or diagnostic evaluation. (II)
- Samples of lower respiratory tract secretions should be obtained from all patients with suspected HAP, and collected prior to antibiotic changes. (II)

  Endotracheal aspirate (EA)

  Bronchoalveolar lavage (BAL)

  Protected specimen brush (PSB)

Infect Dis Clin N Am 2004;18:939-962, Am J Respir Crit Care Med 2005, in press

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Clinical strategies

- A reliable tracheal aspirate Gram stain can be used to direct initial empiric antimicrobial therapy and may increase the diagnostic value of the CPIS. (II)
- A negative tracheal aspirate (absence of bacteria or inflammatory cells) in a patient without a recent (within 72 hours) change in antibiotics has a strong negative predictive value (94%) for VAP and should lead to a search for alternative sources of fever. (II)
- The presence of a new or progressive radiographic infiltrate plus at least 2 of 3 clinical features (fever > 38ºC, leukocytosis or leukopenia, and purulent secretions) is the most accurate clinical criteria for starting empiric antibiotic therapy. (II)

Infect Dis Clin N Am 2004;18:939-962, Am J Respir Crit Care Med 2005, in press

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TABLE 2. THE MODIFIED CLINICAL PULMONARY INFECTION SCORE

CPIS Points	0	1	2
Tracheal secretions	Rare	Abundant	Abundant + purulent
Chest X-ray infiltrates	No infiltrate	Diffused	Localized
Temperature, °C	⩾ 36.5 and ⩽ 38.4	⩾ 38.5 and ⩽ 38.9	⩾ 39 or ⩽ 36
Leukocytes count, per mm³	⩾ 4,000 and ⩽ 11,000	< 4,000 or > 11,000	< 4,000 or > 11,000 + band forms ⩾ 500
PaO_2/FIO_2, mm Hg	> 240 or ARDS		⩽ 240 and no evidence of ARDS
Microbiology	Negative		Positive

Definition of abbreviations: ARDS = acute respiratory distress syndrome; CPIS = clinical pulmonary infection score.

The modified CPIS at baseline was calculated from the first five variables (2). The CPIS gram and CPIS culture (Table 1) were calculated from the CPIS baseline score by adding two more points when gram stains or culture were positive. A score of more than six at baseline or after incorporating the gram stains (CPIS gram) or culture (CPIS culture) results was considered suggestive of pneumonia.

- CPIS > 6 — 60% (+) and (-) predictive value
- CPIS > 6 plus gram stain — 65% (+) predictive value; 75% (-) predictive value

Am J Resp Crit Care Med 2003;168:173-179.

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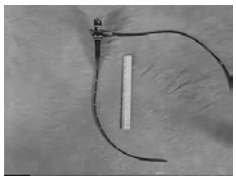
Bacteriologic strategies

- Quantitative cultures can be performed on endotracheal aspirates or samples collected either bronchoscopically and each technique has its own diagnostic threshold, and methodologic limitations. The choice of method depends on local expertise, experience, availability and cost. (II)



Infect Dis Clin N Am 2004;18:939-962, Am J Respir Crit Care Med 2005, in press

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Feature Article—Continuing Medical Education

Invasive approaches to the diagnosis of ventilator-associated pneumonia: A meta-analysis

Andrew F. Shorr, MD, MPH; John H. Sherner, MD; William L. Jackson, MD; Marin H. Kollef, MD

Overall, an invasive approach did not alter mortality (odds ratio 0.89, 95% confidence interval 0.56–1.41). Invasive testing, though, affected antibiotic utilization (odds ratio for change in antibiotic management after invasive sampling, 2.85, 95% confidence interval 1.45–5.59).

Interventions: None.

Measurements and Main Results: We identified four randomized, controlled trials that included 628 patients. The overall quality of these studies was moderate (median Jadad score of 5) and there was both clinical and statistical heterogeneity among these trials. Ventilator-associated pneumonia was confirmed bronchoscopically in 44–69% of participants, with *Pseudomonas aeruginosa* and *Staphylococcus aureus* being the most frequently isolated pathogens. Most subjects (90.3%) received adequate antibiotics; however,

Conclusions: Few trials have systematically examined the impact of diagnostic techniques on outcomes for patients suspected of suffering from ventilator-associated pneumonia. Invasive strategies do not alter mortality. Invasive approaches to ventilator-associated pneumonia affect antibiotic use and prescribing. (Crit Care Med 2005; 33:46–53)

KEY WORDS: antibiotics; bronchoscopy; diagnosis; mortality; pneumonia; ventilator

Crit Care Med 2005;33:46-53.

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Initial Antibiotic Therapy

- Select an initial empiric therapy based on the absence or presence of risk factors for MDR pathogens. (III)
- Risk factors for MDR pathogens include prolonged duration of hospitalization (> 5 days), admission from a healthcare related facility, and recent prolonged antibiotic therapy. (II)
- Choice of specific agents should be dictated by local microbiology, cost, availability, and formulary restrictions. (II)

Infect Dis Clin N Am 2004;18:939-962, Am J Respir Crit Care Med 2005, in press

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Initial Antibiotic Therapy

- Inappropriate therapy… is a major risk factor for excess mortality and length of stay in patients with HAP, and antibiotic resistant organisms are the pathogens most commonly associated with inappropriate therapy. (II)
- In selecting empiric therapy for patients who have recently received an antibiotic… use an agent from a different antibiotic class, since recent therapy increases the probability of inappropriate therapy and can predispose to resistance to that same class of antibiotics. (III)

Infect Dis Clin N Am 2004;18:939-962, Am J Respir Crit Care Med 2005, in press

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Initial Antibiotic Therapy

- Initial antibiotic therapy should be given promptly since delays in administration may add to excess mortality in VAP. (II)
- Initial empiric therapy is more likely to be appropriate if a protocol for antibiotic selection is developed…but adapted to local patterns of antibiotic resistance, with each ICU collecting this information, and updating it on a regular basis. (II)

Infect Dis Clin N Am 2004;18:939-962, Am J Respir Crit Care Med 2005, in press

[A46] [Poster: E23] Antibiotic Susceptibility of Respiratory Tract Pathogens Isolated from Critically Ill Patients: Towards More Rational Choice of Empiric Antibiotics

D.M. Forrest, H. Parwana, R. Slavik, S. Gorman, D.R. Chittock, V.K. Dhingra, J. de Lemos Critical Care Medicine, UBC, Vancouver, BC, Canada; Pharmaceutical Sciences, UBC, Vancouver, BC, Canada

Introduction: Prompt initiation of empiric antibiotics for ventilator associated pneumonia (VAP) is essential. But inadequate therapy worsens outcome, while unnecessarily broad spectrum antibiotics increase resistance. Appropriate antibiotic selection requires knowledge of local flora and resistance patterns.
Objectives: Describe the incidence and antibiotic susceptibilities of
1. respiratory tract pathogens (RTPs) early (EVAP, <72h) or late (LVAP, >=72h) after ICU admission
2. RTPs with changing sensitivity over time (emergent resistance, ER)
Methods: Retrospective review of microbiology records of patients admitted April 1 to August 31, 2002 to a 24 bed medical-surgical ICU.
Results: 143/310 patients grew RT pathogens. 97 had no growth or normal flora only. 71% were in hospital before ICU.
1. EVAP RTPs included methicillin sensitive S. aureus (25%), H. influenzae (22%), Klebsiella spp. (11%) and Streptococcus spp. (10%); all sensitive to cefuroxime. Methicillin resistant S. aureus (MRSA; 6%) and more resistant Gram negative (G-ve) RTPs (11%; >90% sensitive to quinolones) were grown primarily from patients hospitalized before ICU.
2. LVAP RTPs included Acinetobacter spp. (16%), Enterobacter spp. (14%), Klebsiella spp. (14%), MRSA (13%) and other G-ve RTPs (9%). Sensitivity patterns were more variable. Klebsiella spp. isolated initially as LVAP RTPs were more resistant than those isolated as EVAP RTPs.
3. ER occurred in =<12% of G-ve RTPs (especially Acinetobacter and Enterobacter spp.) a median of 13 days after initial isolation.
Conclusion: Identity and resistance patterns of local RTPs isolated from patients with EVAP, LVAP and of RTPs prone to ER allows more rational empiric therapy targeted to specific patient groups. This will facilitate development of local guidelines for empiric VAP therapy adaptable to changing RTPs and resistance patterns.

Sunday, May 23, 2004 8:15 AM

[**] Thematic Poster Session (Abstract Page: A129) Session: 8:15 am-4:15 pm, TREATMENT OF PULMONARY INFECTIONS

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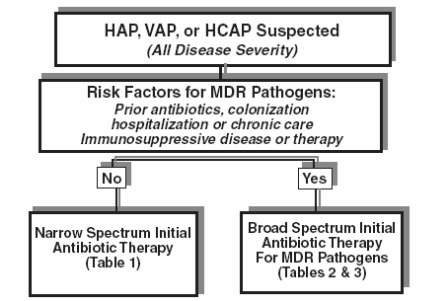

Infect Dis Clin N Am 2004;18:939-962, Am J Respir Crit Care Med 2005, in press

Box 1. Summary of risk factors for multidrug-resistant pathogens causing healthcare-associated pneumonia, including hospital-acquired pneumonia, and ventilator-associated pneumonia

- Prior antimicrobial therapy in preceding 3 months
- Current hospitalization for at least 5 days
- High frequency of antibiotic resistance in the community or in the specific hospital unit
- Presence of risk factors for health-care related pneumonia
  - Hospitalization for at least 2 days in the preceding 90 days
  - Residence in a nursing home or extended care facility
  - Home infusion therapy (including antibiotics)
  - Chronic dialysis within 30 days
  - Home wound care
  - Family member with infection involving MDR pathogen
- Immunosuppressive disease or therapy

Infect Dis Clin N Am 2004;18:939-962, Am J Respir Crit Care Med 2005, in press

Table 1
Initial empiric antibiotic therapy for healthcare-associated pneumonia or hospital-acquired pneumonia in patients with no known risk factors for multi-drug resistant pathogens, early onset, and any disease severity

Common pathogens	Possible initial, empiric, antibiotic regimens[a]
Streptococcus pneumoniae	Third-generation cephalosporin
Haemophilus influenza	eg, ceftriaxone
Methicillin-sensitive *S aureus*	OR
Antibiotic-sensitive enteric Gram-negative bacilli	Extended-spectrum fluouroquinolone
Escherichia coli	eg, levofloxacin, gatifloxacin, moxifloxacin
Klebsiella pneumoniae (ESBL−)	or gemifloxacin
Enterobacter spp	OR
Proteus spp	Amino-penicillins
Serratia marcescens	eg, ampicillin/sulbactam
	OR
	Narrow-spectrum carbapenem
	eg, ertapenem

Abbreviation: ESBL, extended spectrum β-lactamase producer.
[a] Based on normal renal function; see Table 3 for proper initial doses of antibiotics.

Infect Dis Clin N Am 2004;18:939-962, Am J Respir Crit Care Med 2005, in press

Table 2
Initial empiric therapy for hospital-acquired pneumonia in patients with late-onset disease or risk factors for multidrug resistant pathogens and all disease severity

Potential pathogens	Initial, broad-spectrum, combination antibiotic therapy[a]
MDR Gram-negative bacilli	Anti-pseudomonal cephalosporin
P aeruginosa	eg, cefepime, ceftazidime
K pneumoniae (ESBL+)[b]	OR
Acinetobacter spp[b]	Anti-pseudomonal carbepenem
Non-MDR Gram-negative bacilli	eg, imipenem or meropenem
L pneumophila[c]	OR
MDR Gram-positive cocci	Anti-pseudomonal Penicillin
Methicillin-resistant *S aureus*	eg, piperacillin-tazobactam
	PLUS
	Anti-pseudomonal fluoroquinolone[c]
	eg, ciprofloxacin or levofloxacin
	OR
	Aminoglycoside[c]
	eg, amikacin, gentamicin, or tobramycin
	PLUS
	Linezolid or vancomycin
	(if MRSA is suspected or there is a high incidence locally)

[a] See Table 3 for adequate initial dosing of antibiotics.
[b] If an ESBL+ strain *K pneumoniae* or MDR *Acinetobacter* sp is suspected, a carbepenem is suggested for initial therapy.
[c] If *L pneumophila* is suspected, the combination antibiotic regimen should include a fluoroquinolone rather than an aminoglycoside.

Infect Dis Clin N Am 2004;18:939-962, Am J Respir Crit Care Med 2005, in press

Optimal Antibiotic Therapy

- Empiric therapy of patients with severe HAP or VAP requires the use of antibiotics at optimal doses… to assure maximum efficacy. (III)
- Initial therapy should be administered to all patients intravenously, with a switch to oral/enteral therapy in selected patients with a good clinical response and a functioning intestinal tract. Highly bioavailable agents, such as the quinolones and linezolid, may be easily switched to oral therapy in such patients. (II)
- Aerosolized antibiotics have not been proven to have value in the therapy of VAP. (I)

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Table 3
Initial intravenous, adult doses of antibiotics for empiric therapy of healthcare-associated pneumonia, including hospital-acquired pneumonia, and ventilator-associated pneumonia in patients with late onset disease or risk factors for multidrug resistant pathogens

Antibiotic	Dose
Antipseudomonal cephalosporins	
Cefepime	2 g every 8–12 hours
Ceftazidime	2 g every 8 hours
Carbepenems	
Imipenem	500 mg every 6 hours or 1 g every 8 hours
Meropenem	1 g every 8 hours
Anti-pseudomonal pencillins	
Piperacillin–tazobactam	4.5 g every 6 hours
Aminoglycosides[a]	
Gentamicin	7 mg/kg/d
Tobramycin	7 mg/kg/d
Amikacin	20 mg/kg/d
Antipseudomonal quinolones	
Levofloxacin	750 mg every day
Ciprofloxacin	400 mg every 8 hours
Antibiotics for MRSA	
Vancomycin[b]	15 mg/kg every 12 hours
Linezolid	600 mg every 12 hours

Doses are based on normal renal and hepatic function.
[a] Trough levels for gentamicin and tobramycin should be <1 μg/mL; trough level for amikacin should be <4–5 μg/mL.
[b] Trough levels should be maintained at high levels (15 μg/mL).

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Optimal Antibiotic Therapy

- Combination therapy should be used if patients are likely to be infected with MDR pathogens. (II) No data have documented the superiority of this approach to monotherapy, except to enhance the likelihood of initially appropriate empiric therapy. (I)
- If patients receive combination therapy with an aminoglycoside containing regimen, the aminoglycoside can be stopped after 5-7 days in responding patients. (III)
- Monotherapy with selected agents can be used for patients with severe HAP and VAP in the absence of resistant pathogens. (I) Patients in this risk group should initially receive combination therapy until the results of lower respiratory tract cultures are known and confirm that a single agent can be used. (II)

Infect Dis Clin N Am 2004;18:939-962, Am J Respir Crit Care Med 2005, in press

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Response to Therapy

- A serial assessment of clinical parameters should be used to define the response to initial empiric therapy. (II) Modifications of empiric therapy should be made based on this information, in conjunction with microbiologic data. (III)
- Clinical improvement usually takes 48-72 hours, and thus therapy should not be changed during this time unless there is rapid clinical decline. (III) Non-response to therapy is usually evident by day 3, using an assessment of clinical parameters. (II)

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Response to Therapy

- The responding patient should have de-escalation of antibiotics, narrowing therapy to the most focused regimen possible, based on culture data. (II)
- The non-responding patient should be evaluated for non-infectious mimics of pneumonia, unsuspected or drug-resistant organisms, extra-pulmonary sites of infection, and complications of pneumonia and its therapy. (III)

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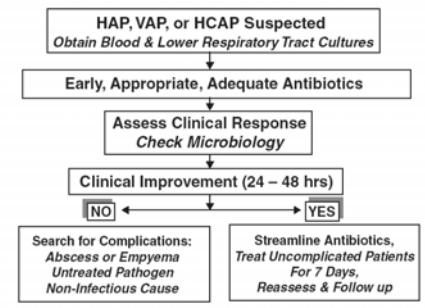

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Pseudomonas aeruginosa

- If *P. aeruginosa* pneumonia is documented, combination therapy is recommended. The principal justification is the high frequency of development of resistance on monotherapy. While combination therapy will not necessarily prevent the development of resistance, combination therapy is more likely to avoid patients receiving inappropriate and ineffective treatment. (II)
- Monotherapy or double-coverage…?

Infect Dis Clin N Am 2004;18:939-962, Am J Respir Crit Care Med 2005, in press

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Pseudomonas aeruginosa

Limitations of evidence

- Industry author consultant/employees
- Small subgroups of *P. aeruginosa*
- Open-label design
- Varied comparator ("apples vs. oranges")
- AMG dosing not well reported
- Not always an ITT analysis
- Not powered for ADE comparison
- Not powered for "non-inferiority"
- Threat of history

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Pseudomonas aeruginosa

Study	Population	Intervention	Endpoint	Outcome (*p<0.05)
[1]Rubinstein 1995	HAP, UTI, sepsis (n=297)	Ceftazidime vs. CTX/tobramycin	Clinical	CTZ – 73.0 % CTX/TB – 65.2 %
[2]Cometta 1994	HAP, IA, sepsis (n=177)	Imipenem vs. Imipenem/netilmicin	Clinical -Nephrotoxicity	Imip – 82.4 % Imip/net – 83.7 % *ARI – 3.1 %#
[3]Sieger 1997	HAP (n=211)	Meropenem vs. Ceftazidime+Tobra	Clinical Microbiological	Mero – 71.7 % CTZ/TB – 59.0 % *Mero – 54.7% CTZ/Tobr – 36.2 %
[4]Alvarez 2001	VAP (n=140)	Meropenem vs. Ceftazidime+Amik	Clinical Microbiological	$Mero – 68.1 % CTZ/Amik – 54.9 % *Mero – 74.5% CTZ/Amik – 53.3 %

 # - Scr increase of 45 µmmol/L, calculate p = 0.059, $ - calculated p = 0.153

Source: [1]Clin Infect Dis 1995;20:1217-28, [2] Antimicrob Agents Chemother 1994; 38:1309-1313, [3] Crit Care Med 1997;25:1663-70, [4]J Chemother 2001;13:70-81.

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Pseudomonas aeruginosa

- Provide empiric double-coverage in areas with high incidence of *Pseudomonas spp*, de-escalate therapy as appropriate
- Continue targeted, individualized double-coverage for critically-ill patients, MDR isolates, or those not responding to monotherapy
- Consider targeted monotherapy only for lower acuity patients with sensitive isolates in patients with possible ADEs from double-coverage regimens

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MRSA pneumonia

- Linezolid is an alternative to vancomycin for the treatment of MRSA VAP and may be preferred, based on a subset analysis of two prospective randomized trials. (II) This agent may also be preferred if patients have renal insufficiency or are receiving other nephrotoxic agents, but more data are needed. (III)
- Alternatives to consider…?

Infect Dis Clin N Am 2004;18:939-962, Am J Respir Crit Care Med 2005, in press

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MRSA pneumonia

- *Limited* high-quality evidence from RCTs
- No RCT data for vancomycin/rifampin
- No RCT data for vancomycin/gentamicin
- 1 RCT vancomycin vs. quinupristin/dalfopristin
- 2 RCTs vancomycin vs. linezolid
- PKPD issues for vancomycin dosing

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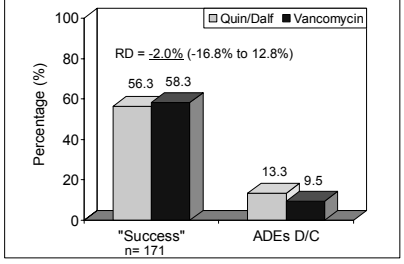
MRSA Pneumonia

Limitations of evidence

- Industry author consultants/employees
- Small subgroups of *MRSA*
- Open-label design
- "Equivalence" trials
- Vanco dosing?, co-interventions?
- Clinical efficacy
  - Evaluable patients (~50-60%)
- Bacteriologic response
  - Evaluable patients (~20-30%)
- Not powered for ADE comparison

MRSA pneumonia

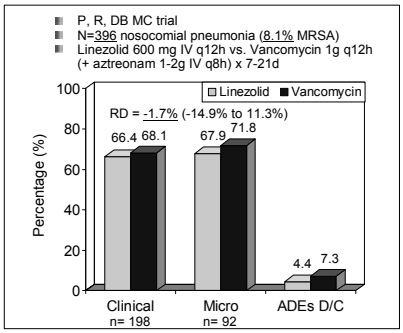
- P, R, open-label MC trial
- N=298 nosocomial pneumonia (17.1% MRSA)
- Quinupristin/dalfopristin 7.5 mg/kg q8h vs. Vanco 1g q12h (+/- aztreonam 2g IV q8h) x 5-14d



Am J Respir Crit Care Med 2000;181:753-762.

MRSA pneumonia

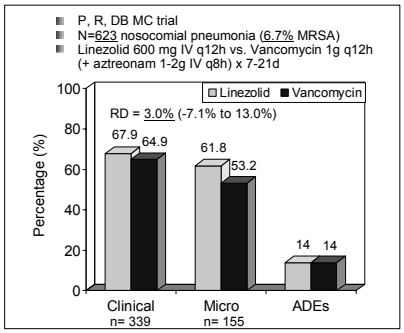
- P, R, DB MC trial
- N=396 nosocomial pneumonia (8.1% MRSA)
- Linezolid 600 mg IV q12h vs. Vancomycin 1g q12h (+ aztreonam 1-2g IV q8h) x 7-21d



Clin Infect Dis 2001;32:402-412.

MRSA pneumonia

- P, R, DB MC trial
- N=623 nosocomial pneumonia (6.7% MRSA)
- Linezolid 600 mg IV q12h vs. Vancomycin 1g q12h (+ aztreonam 1-2g IV q8h) x 7-21d



Clin Therap 2003;25:980-992.

MRSA pneumonia

- *Post hoc retrospective* logistic regression analysis of MRSA subgroup suggested higher clinical cures NNT = 3 [2-16], and *"trend toward survival advantage associated with linezolid"*
- *Post hoc retrospective* logistic regression analysis of MRSA subgroup suggested shorter duration of IV therapy, no reduction in LOS *associated* with linezolid

Chest 2003;124:1789-1797.
Pharmacotherapy 2001;263-274.

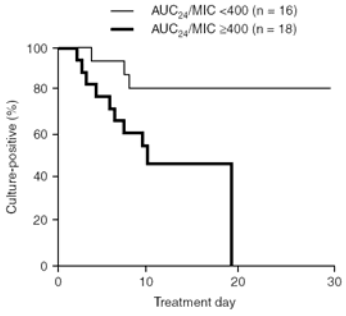
Vancomycin – PKPD Issues

Moise-Broder PA, et al *Clin Pharmacokinet 2004;43:925-942.*

- N = 108 patients with MSSA/MRSA pneumonia
- PK modeling of [Vanco], and MIC obtained
- Clinical and bacteriologic success
  - AUC/MIC > 350 vs. AUC/MIC ≤ 350
  - OR = 7.19 (1.91 to 27.3)
- Faster time to bacterial eradication
- Authors recommend AUC/MIC ~ 400

Clin Pharmacokinet 2004;43:925-942.

Vancomycin – PKPD Issues



Clin Pharmacokinet 2004;43:925-942.

MRSA pneumonia

- Vancomycin still agent of choice
- Consider selected PK monitoring to ensure "optimal exposure" in critically-ill patients (Cmin ≥ 15mg/L, AUC/MIC ≥ 400)
- Linezolid may be best alternative
- Combination therapy not proven to improve outcomes, may provide synergy, consider in patients that fail to respond, individualize Rx

Shorter Duration of Therapy

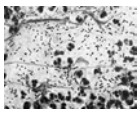
- If a clinical strategy is used, re-evaluation of the decision to use antibiotics based on the results of semi-quantitative lower respiratory tract cultures and serial clinical evaluations, by day 3 or sooner, is necessary (II)
- A modified CPIS score < 6 proposed by Singh et al is an objective criterion to select patients at low risk for discontinuing empiric treatment of HAP, but still requires validation in patients with more severe forms of VAP (I)
- If patients receive an initially appropriate antibiotic regimen, efforts should be made to shorten duration of therapy from the traditional 14 to 21 days to periods as short as 7 days, provided that the etiologic pathogen is not *P. aeruginosa*, and that the patient has a good clinical response with resolution of clinical features of infection. (I)

Infect Dis Clin N Am 2004;18:939-962, Am J Respir Crit Care Med 2005, in press

Short Duration of Therapy

Paradox…

- Desire to prescribe empiric broad antimicrobial therapy versus trying to minimize emergence of antimicrobial resistance



J Clin Pharmacol Therap 2003;28:123-129.

Shorter Duration of Therapy

Potential Benefits

- ↓ Overall antibiotic use
- ↓ Resistance rates
- ↓ Super-infection
- ↓ Drug costs
- ↓ Adverse events

Potential Risks

- ↑ Treatment failures
- ↑ Relapse rates
- ↑ Re-infection rates
- ↑ Complications

J Clin Pharmacol Therap 2003;28:123-129.

Shorter Duration of Therapy

Strategies

- Discontinue antibiotics in patients with a low likelihood of pneumonia
- Use invasive diagnostic methods to accurately diagnose VAP, enable shorter antibiotic courses
- Use a clinical antibiotic discontinuation policy to enable shorter antibiotic courses

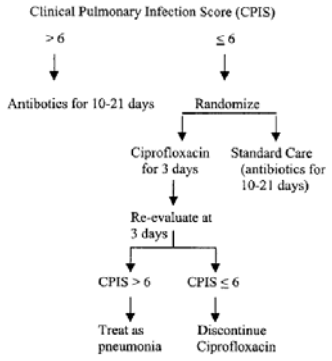
J Clin Pharmacol Therap 2003;28:123-129.

Shorter Duration of Therapy

Singh N *et al*, 2000

- P, R, open-label MC trial
- N=81 nosocomial pneumonia in ICU
- Low likelihood of pneumonia (CPIS ≤ 6)
- "Standard care" (Discretionary choice) vs. "CPIS-guided" (Ciprofloxacin 400 mg IV q8h x 3 days)
- Endpoints: Antibiotic duration, cost, resistance or super-infection, ICU length of stay, mortality

Am J Respir Crit Care Med 2000;162:505-511.



Am J Resp Crit Care Med 2000;162:505-511.

Shorter Duration of Therapy

Results

Outcome	'CPIS' n = 39	Standard n = 42	p-value
Antibiotics > 3 days	28 %	97 %	0.01
Days of antibiotics	3.0	9.8	0.0001
Antibiotic cost	$259	$640	0.0001
Resistance/super-infection	14 %	38 %	0.017
ICU Length of stay (days)	9.4	14.7	0.04
30-day mortality	13 %	31 %	0.06

Am J Resp Crit Care Med 2000;162:505-511.

Shorter Duration of Therapy

Fagon J *et al*, 2000

- P, R, open-label MC trial
- N=413 intubated patients with suspected VAP
- "Clinical management" (clinical and gram stain) vs. "invasive management" (bronchoscopic BAL or PSB)
- Treatment algorithms from ATS guideline, 14d therapy
- Endpoints: Antibiotic use, organ failure, mortality assessed at 14 and 28 days

Ann Intern Med 2000;132:621-630.

Shorter Duration of Therapy

Results

Outcome	'Invasive' n = 204	'Clinical' n = 209	Difference (95% CI)
Antibiotics free days (14d)	5.0	2.2	2.8 (1.9 to 3.6)
Antibiotics free days (28d)	11.5	7.5	3.9 (5.5 to 2.3)
Resistance	61.3 %	59.8 %	1.5 (-7.9 to 10.9)
ICU Length of stay	19.3	17.6	1.5 (-0.3 to 3.2)
Mortality (14d)	16.2 %	25.8%	-9.6 (-17.4 to -8.1)
Mortality (28d)	30.9	38.8	-7.9 (-17.0 to 1.2)

Ann Intern Med 2000;132:621-630.

Shorter Duration of Therapy

Chastre J *et al*, 2003

- P, R, DB* MC "non-inferiority" trial (10%)
- N=401 VAP patients diagnosed by bronchoscopy
- Onset > 5 days, antibiotics within 15 days
- "8-day" versus "15-day" course 3 days after bronchoscopy if initial therapy "appropriate"
- Discretionary regimens, suggested broad-spectrum beta-lactam plus AMG or FQ
- Endpoints: Antibiotic-free days, pulmonary infection recurrence, mortality

JAMA 2003;290:2588-2598.

Shorter Duration of Therapy

Results

Outcome	'8-day' n = 197	'15-day' n = 204	Difference (95% CI)*
Antibiotics free days	13.1	8.7	4.4 (3.1 to 5.6)
Pulmonary infection recurrence	28.9 %	26.0 %	2.9 (-3.2 to 9.1)
Pulmonary infection 'relapse' subgroup	16.8 %	11.3 %	5.5 (0.7 to 10.3)
Pulmonary infection recurrence (NLF) n=127	40.6 %	25.4 %	15.2 (3.9 to to 26.6)
Mortality	18.8 %	17.2 %	1.6 (-3.7 to 6.9)

*Criteria for non-inferiority of 10% for upper limit of 90% CI

JAMA 2003;290:2588-2598.

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Shorter Duration of Therapy

Micek ST *et al*, 2004

- P, R, un-blinded single centre trial
- N=290 medical ICU patients treated for VAP
- Antibiotic treatment for VAP determined by "discontinuation policy" (pharmacist) or "conventional" (physician teams)
- Vancomycin/linezolid plus cefepime plus gent/cipro
- Endpoints: Duration of antibiotics, secondary episodes of VAP, ICU length of stay, mortality

Chest 2004;125:1791-11799.

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Shorter Duration of Therapy

Results

Outcome	Discontinue n = 150	Conventional n = 140	p-value
Days of antibiotics	6.0	8.0	0.001
Secondary VAP	17.3 %	19.3 %	0.667
ICU length of stay (days)	6.8	7.0	0.798
Hospital length of stay (days)	15.7	15.4	0.865
Hospital mortality	32.0 %	37.1 %	0.357

Chest 2004;125:1791-11799.

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Shorter Duration of Therapy

- HAP/VAP patients with a low likelihood pneumonia based on modified CPIS score (≤ 6) at baseline and after 3 days of therapy can have antibiotics stopped
- VAP patients diagnosed invasively who receive initially appropriate antibiotic therapy and are not infected with NLF gram(-) organisms or MRSA can have antibiotics stopped after 8 days
- VAP patients diagnosed clinically who receive initially appropriate antibiotic therapy and either fail to have pneumonia or have responded clinically after 7 days of treatment can have antibiotics discontinued

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Conclusions

- Evaluate strengths/weaknesses of new ATS guidelines for HCAP/HAP/VAP
- Apply *principles* and recommendations based on higher-quality evidence, be wary of expert opinion
- Individualize therapy by integrating local resistance patterns and resources into treatment protocols applicable to *your* hospital
- Evaluate effectiveness of local protocols
- Use "best" available evidence for controversies

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Future Challenges

- More studies to resolve controversies
- Validate effect of ATS treatment recommendations on clinical outcomes
- Develop and disseminate current, local antibiograms to optimize empiric therapy
- Re-evaluate local resistance patterns and treatment protocols
- Implement proven, effective, preventative strategies for HCAP/HAP/VAP

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