Hospital-acquired pneumonia
New guidelines and ongoing controversies

New guidelines

Treatment

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

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

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

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
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"

JAMA 1995;274:570-574.

Clinical Practice

Systematic Reviews

Guidelines

Protocols

Clinical Practice Guidelines (CPGs)

- "Authors, editors of CPGs fail to develop, adhere to, disclose potential COI relationships"


- CPGs do not adhere well to established methodological standards"


Clinical Practice Guidelines (CPGs)

- "CPGs often do not cite RCT evidence"


- "Quality of CPGs from specialized societies has improved, but is still unsatisfactory"


- "Quality of drug-therapy CPGs in Canada are suboptimal, no improvement from 1994-1998"


JAMA 1995;274:570-574.
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

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

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

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

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 modifying risk factors
**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)

**Pathogenesis**

- Risk factors for HAP include healthcare devices or environment and microorganisms commonly transferred between staff and 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)

**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)
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 (95%) 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 > 38°C, leukocytosis or leukopenia, and purulent secretions) is the most accurate clinical criteria for starting empiric antibiotic therapy. (II)

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)

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)
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)

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 3 days
- High frequency of antibiotic resistance in the community or in the specific hospital unit
- Presence of risk factors for healthcare-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

Table 1

<table>
<thead>
<tr>
<th>Risk Factors for MDR Pathogens: Prior antibiotic, colonization hospitalization or chronic care</th>
<th>Immunosuppressive disease or therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Narrow Spectrum Initial Antibiotic Therapy (Table 1)</td>
<td>Broad Spectrum Initial Antibiotic Therapy For MDR Pathogens (Tables 2 &amp; 3)</td>
</tr>
</tbody>
</table>

Table 2

| Initial empiric therapy for hospital-acquired pneumonia in patients with no known risk factors for multidrug-resistant pathogens, only empiric and you choose MLIU. |
|---|---|
| Acinetobacter baumannii | Pseudomonas aeruginosa, and other antibiotic-resistant bacterial pathogens |
| Methicillin-resistant Staphylococcus aureus (MRSA) | Third-generation cephalosporins, or alternative |
| Antibiotic-resistant oral Gram-negative bacteria | Second- or third-generation cephalosporins, or other Gram-negative bacterium |
| Carbapenem-resistant Enterobacteriaceae (CRE) | Antimicrobial agents, including carbapenems, or other Gram-negative bacterium |
| Vancomycin-resistant enterococci (VRE) | Second- or third-generation cephalosporins, or other Gram-negative bacterium |
| Antibiotic-resistant respiratory pathogens | Non-methicillin-resistant Staphylococcus aureus (NMSA) |

Abbreviations: MLIU, extended-spectrum β-lactamase producer.
* Based on second and third-generation cephalosporins for initial class of antibiotics.
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)

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)

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)

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)

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)

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Dose</th>
<th>Route</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cephalosporin</td>
<td>2 g every 6-12 hours</td>
<td>Intravenous</td>
</tr>
<tr>
<td>Carbapenem</td>
<td>2 g every 8 hours</td>
<td>Intravenous</td>
</tr>
<tr>
<td>Imipenem</td>
<td>500 mg every 6 hours or 1 g every 8 hours</td>
<td>Intravenous</td>
</tr>
<tr>
<td>Piperacillin/tazobactam</td>
<td>4.5 g every 6 hours</td>
<td>Intravenous</td>
</tr>
<tr>
<td>Linezolid</td>
<td>600 mg every 12 hours</td>
<td>Oral</td>
</tr>
</tbody>
</table>

Doses are based on normal renal and hepatic function. The usual initial loading dose of ciprofloxacin should be 400 mg, though levels for aminoglycosides should be 6-8 μg/mL and linezolid should be maintained at high levels (15 μg/mL).

HAP, VAP, or HCAP Suspected

Obtain Blood & Lower Respiratory Tract Cultures

Assess Clinical Response

Check Microbiology

Evaluation for Complications:
- Abscess or Empyema
- Untreated Pathogen
- Non-Infectious Cause

Streamline Antibiotics:
- Treat Uncomplicated Patients
  - For 7 Days, Reassess & Follow up

Clinical Improvement (24 - 48 hrs)

Yes

No

Yes
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…?

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

Pseudomonas aeruginosa

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Intervention</th>
<th>Endpoint</th>
<th>Outcome (p&lt;.05)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Robienst 1995</td>
<td>HAP, UTI, IIS (n=297)</td>
<td>Cefazidime vs. CTX/Tobramycin</td>
<td>Clinical</td>
<td>C/TZ 73.9%  CTX/TB 65.2%</td>
</tr>
<tr>
<td>Cometas 1994</td>
<td>HAP, IIS (n=177)</td>
<td>Imipenem vs. Imipenem/Netilmicin</td>
<td>Clinical</td>
<td>Imp 52.4% Imp/Net 63.7% APP 3.1%</td>
</tr>
<tr>
<td>Sieger 1997</td>
<td>HAP (n=211)</td>
<td>Meropenem vs. Ceftazidime/Tobramycin</td>
<td>Clinical</td>
<td>Microbiological</td>
</tr>
<tr>
<td>Alvarez 2001</td>
<td>VAP (n=140)</td>
<td>Meropenem vs. Ceftazidime/Amikacin</td>
<td>Clinical</td>
<td>Microbiological</td>
</tr>
</tbody>
</table>

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


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

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…?

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
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

Clinical Micro ADEs
- Vancomycin
- Linezolid

Vancomycin – PKPD Issues

- *Vancomycin – PKPD Issues*
- 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
Vancomycin – PKPD Issues

- AUC\textsubscript{0-4}\textsuperscript{MIC} ≥ 400
- C\textsubscript{min} ≥ 15 mg/L
- AUC/MIC ≥ 400

MRSA pneumonia

- Vancomycin still agent of choice
- Consider selected PK monitoring to ensure “optimal exposure” in critically-ill patients
- 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
- 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
- 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

Potential Benefits

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

Potential Risks

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

Shorter Duration of Therapy

Paradox...

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

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
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

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

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
**Shorter Duration of Therapy**

**Results**

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

*Criteria for non-inferiority of 10% for upper limit of 95% CI

JAMA 2003;290:2588-2598.

**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


**Shorter Duration of Therapy**

**Results**

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


**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

**Conclusions**

- **Evaluate** strengths/weaknesses of new ATS guidelines for HCAP/HAP/VAP
- **Apply principles** and recommendations based on higher-evidence quality, 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

**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