Personal View

Guidelines for hospital-acquired pneumonia & health-care-associated pneumonia: a vulnerability, a pitfall, & a fatal flaw

Victor L Yu
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Health-care-associated pneumonia, was introduced that broadened the scope of the guidelines to include ambulatory p’ts who were regarded as likely to have multidrug-resistant pathogens.
Unlike guidelines for community-acquired pneumonia, confirmation of the approach & acceptance by clinicians of the 2005 hospital-acquired pneumonia guidelines has been marginal.

Shigeki Fujitani & the author pointed out that the 2005 guidelines were laudable in their intent, although poor in execution.

Ewig & colleagues issued a reasoned critique of the 2005 guidelines that was notable for its comprehension & backed by a critical & insightful review of the published work.
A prospective study

Daniel Kett & colleagues

Compliance to 2005 guidelines

use of combination broad-spectrum treatment

↑↑

Non-compliance to 2005 guidelines

a surrogate of monotherapy

↑

28-day mortality
A prospective study

Daniel Kett & colleagues

- The reason & mechanism for this surprising result is unclear, but this finding was consistent in the overall group & numerous subgroups.

- Higher mortality for combination group compared with monotherapy group could not be ascribed to adverse effects of aminoglycoside therapy.
History of pneumonia guidelines

2005 guidelines

- Problems immediately surfaced: the **classifications** were imprecise, not easily generalizable, & the **definitions** varied from country to country.

- Marginal data, cherry-picking, & small number of studies on which they were based weakened the validity of the 2005 guidelines.

included newer definitions of nosocomial, hospital-acquired, ventilator-associated, & health-care-associated pneumonia.
3 fundamental issues inherent in the definition of HAP & HCAP undermined the credibility of these guidelines & the applicability of their recommendations:
Vulnerability

- extreme heterogeneity of the population of p’ts

Fatal flaw

- failure to accurately diagnose HAP & VAP; inability to distinguish colonization from infection in respiratory-tract cultures renders the guidelines inherently unstable

Pitfall

- empiricism of antibiotic use for severely ill p’ts in whom infection might not be present

- A vicious circle of antibiotic overuse leading to emergence of resistant microflora can become established, leading to unnecessary use of empirical broad-spectrum combination antibiotics & increased mortality.
Vulnerability

of the 2005 guidelines for HCAP

- extreme heterogeneity of population

- resulted from the desire of the guidelines committee to devise a straightforward approach of broad-spectrum empirical antibiotic therapy for the largest possible group of p’ts.
Health-care-associated pneumonia

Vulnerability

of the 2005 guidelines for HCAP

- extreme heterogeneity of population

- resulted from the desire of the guidelines committee to devise a straightforward approach of broad-spectrum empirical antibiotic therapy for the largest possible group of p’ts.

- Hemodialysis p’ts were lumped together with p’ts in nursing homes.

- Functional status of p’ts ranged from ambulatory to bedridden

- Underlying diseases ranged from psychiatric problems to immunosuppressive disorders.
• The key to **selection of appropriate antibiotics** depends on *accurate identification of pathogens.*

**Fatal flaw** of any of the guidelines for nosocomial pneumonia = HAP

• traditionally difficult issue of **colonization versus pathogenicity** for microbes isolated from pts’ respiratory secretions.

**Definitive identification** of true pulmonary pathogens has always been problematic in HAP!
• **Oropharyngeal colonization** by GNB is commonplace in p’ts admitted to hospitals, especially in ICUs.

• For ICU pneumonia, the pathogens are more diverse because of **overgrowth of normal flora** by GNB.

• Intense antibiotic use promotes the emergence of resistant organisms.

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**Colonization** rather than pathogenicity remains a complex issue!
• The gold standard for definition of HAP & VAP is contentious.

• The best validated gold standard study by French investigators of pts with pneumonia in 31 ICUs.

• Invasive procedure (bronchoalveolar lavage or protected specimen brush) + quantitative criteria of cultures ☚ distinguish pathogenicity or colonization

• Logistics & necessity for invasive procedure before

• **Definitive identification of respiratory pathogens** involved in HAP remains elusive, despite the use of invasive diagnostic procedures & the advent of biomarkers of inflammation.
Fatal flaw in making of an accurate diagnosis of ICU pneumonia

Inability to separate uninfected colonized patients from infected patients

In Kett & colleagues’ study

- notable number of uninfected patients received unnecessary broad-spectrum combination therapy.

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- Unnecessary treatment ⇒ overtreatment ⇒ ↑ mortality
- At least 3 prospective controlled comparative studies:
  - broad-spectrum antibiotics to uninfected patients leads to significantly ↑ mortality
- special dilemmas for empirical therapy
- imbalance in antibiotic therapy

- requires Gram-positive coverage not routinely given for CAP
- traditionally covered with combination therapy (antipseudomonal β lactam + an aminoglycoside)
• Recent data suggest that *P aeruginosa* might be overestimated as a pneumonia pathogen in ICUs.

• A frequent colonizer of p’ts with COPD, *P aeruginosa* might be regarded as a pathogen when isolated from respiratory secretions of p’ts presenting with pulmonary infiltrates, even if these infiltrates are secondary to CHF.

The bitter irony is that antibiotic overprescription has led to the emergence of MRSA & multidrug-resistant *P aeruginosa*.
Administration of empirical antibiotics on the basis of “suspicion of hospital-acquired pneumonia” is a pitfall that can readily lead to antibiotic misuse.

- Such a strategy might lead to a situation in which antibiotics could be given for a non-infectious process.
- Encouraged de-escalation on the basis of serial clinical assessments & cultures.
Clinical Pulmonary Infection Score criteria as applied by Singh & colleagues identified pts who needed only 3 days of therapy (presumably because most did not really have pneumonia)

<table>
<thead>
<tr>
<th>Temperature (°C)</th>
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<tbody>
<tr>
<td>&gt; 36.5°C and &lt; 38.4°C</td>
<td>0 point</td>
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<tr>
<td>&gt; 38.5°C and &lt; 39.9°C</td>
<td>1 point</td>
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<tr>
<td>≥ 39°C or ≤ 36°C</td>
<td>2 points</td>
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<table>
<thead>
<tr>
<th>Blood leukocytes (WBC/mm³)</th>
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<tbody>
<tr>
<td>≥ 4,000 and ≤ 11,000</td>
<td>0 point</td>
</tr>
<tr>
<td>&lt; 4,000 or &gt; 11,000</td>
<td>1 point + band forms ≥ 50% = add 1 point</td>
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<table>
<thead>
<tr>
<th>Tracheal secretions</th>
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<tbody>
<tr>
<td>Absence of tracheal secretions</td>
<td>0 point</td>
</tr>
<tr>
<td>Presence of non-purulent tracheal secretions</td>
<td>1 point</td>
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<tr>
<td>Presence of purulent tracheal secretions</td>
<td>2 points</td>
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<table>
<thead>
<tr>
<th>Oxygenation (PaO₂/FI O₂, mm Hg)</th>
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<tbody>
<tr>
<td>&gt; 240 or ARDS (ARDS defined as PaO₂/FI O₂ &lt; 200, pulmonary arterial wedge pressure &lt; to 18 mm Hg and acute bilateral infiltrates)</td>
<td>0 point</td>
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<tr>
<td>≤ 240 and no ARDS</td>
<td>2 points</td>
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<table>
<thead>
<tr>
<th>Pulmonary radiography</th>
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<tbody>
<tr>
<td>No infiltrate</td>
<td>0 point</td>
</tr>
<tr>
<td>Diffuse (or patchy) infiltrate</td>
<td>1 point</td>
</tr>
<tr>
<td>Localized infiltrate</td>
<td>2 points</td>
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</table>

<table>
<thead>
<tr>
<th>Progression of pulmonary infiltrate</th>
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<tbody>
<tr>
<td>No radiographic progression</td>
<td>0 point</td>
</tr>
<tr>
<td>Radiographic progression (after CHF and ARDS excluded)</td>
<td>2 points</td>
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<table>
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<tr>
<th>Culture of tracheal aspirate</th>
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<tbody>
<tr>
<td>Pathogenic bacteria cultured in rare or light quantity or no growth</td>
<td>0 point</td>
</tr>
<tr>
<td>Pathogenic bacteria cultured in moderate or heavy quantity</td>
<td>1 point</td>
</tr>
<tr>
<td>Same pathogenic bacteria seen on Gram stain</td>
<td>add 1 point</td>
</tr>
</tbody>
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Advocates of empiricism emphasize that severe illness is an indicator of multidrug-resistant pathogens.

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- severity of illness does not directly indicate microbial cause!

- When faced with pts who might die, many doctors feel the urge to cover every scenario no matter how unlikely.

Notion: unwilling to miss anything has become a greater driving force for spiralling empiricism than has the likelihood that the pneumonia pathogen is *P. aeruginosa* or *MRSA*.
P’ts at risk for HCAP due to **multidrug-resistant (MDR) pathogens** may have been **previously hospitalized**, had **recent treatment** with antibiotics, received **care in a nursing home**, require **dialysis**, or are **immunosuppressed**.

The risk of pneumonia due to an MDR pathogen, in addition to morbidity & mortality rates, increase as one moves from **CAP** to **HCAP** & **HAP/VAP**.

**CAP** = community-acquired pneumonia; **HAP** = hospital-acquired pneumonia; **HCAP** = healthcare-associated pneumonia; **MDR** = multidrug-resistant; **VAP** = ventilator-associated pneumonia.

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2005 IDSA/ATS HOSPITAL-ACQUIRED PNEUMONIA GUIDELINES: NEW PRINCIPLES FOR IMPROVING MANAGEMENT

*Adv Stud Med. 2006;6(6C):S541-S548*
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**Figure 1. Current Concepts in Pneumonia**

CAP = community-acquired pneumonia; HAP = hospital-acquired pneumonia; HCAP = healthcare-associated pneumonia; MDR = multidrug-resistant; VAP = ventilator-associated pneumonia.

*2005 IDSA/ATS HOSPITAL-ACQUIRED PNEUMONIA GUIDELINES: NEW PRINCIPLES FOR IMPROVING MANAGEMENT*

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**High mortality** attributed to pts with HAP who received inappropriate therapy.

Clinicians who cared for a population with high mortality needed to assure themselves that everything that could be done for critically ill pts would be done.

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**Figure 5. Appropriate Antibiotic Therapy Improves Mortality Rate**

<table>
<thead>
<tr>
<th>Author(s)</th>
<th>Inappropriate</th>
<th>Appropriate</th>
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<tbody>
<tr>
<td>Dupont et al</td>
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<td>Ruiz et al</td>
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<td>Sanchez-Nieto et al</td>
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<td>Kollef</td>
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<td>Rello et al</td>
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<td>Alvarez-Lema et al</td>
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<tr>
<td>Luna et al</td>
<td></td>
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</tbody>
</table>

Crude mortality, %

*P < .05.

Data from American Thoracic Society, Infectious Diseases Society of America; Dupont et al; Ruiz et al; Sanchez-Nieto et al; Kollef; Rello et al; Alvarez-Lema et al; Luna et al.

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2005 IDSA/ATS HOSPITAL-ACQUIRED PNEUMONIA GUIDELINES: NEW PRINCIPLES FOR IMPROVING MANAGEMENT

Adv Stud Med. 2006;6(6C):S541-S548
• **30–70%** of p’ts with pulmonary infiltrates who receive antibiotics for suspected HAP or VAP do not have pneumonia.

• As many as **50%** of p’ts in some emergency rooms who receive empirical antibiotics for such infection will not have pneumonia.
Management of Adults with HAP, VAP, HCAP
ATS Guidelines 2005

Definitions:
HAP: Hospital Acquired Pneumonia
VAP: Ventilator Associated Pneumonia
HCAP: Healthcare-associated Pneumonia

Broad Spectrum Indicated if:
- Late onset (>5 days)
- Risk Factors for MDR Pathogens
  - Antimicrobial therapy in preceding 90 d
  - Current hospitalization of 5 d or more
  - High frequency of antibiotic resistance in the community or in the specific hospital unit
- Presence of risk factors for HCAP:
  - Hospitalization for 2 d or more in the preceding 90 d
  - Residence in a nursing home or extended care facility
  - Home infusion therapy (including antibiotics)
  - Chronic dialysis within 30 d
  - Home wound care
  - Family member with MDR pathogen
- Immunosuppressive disease and/or therapy
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### Initial Empiric Therapy for HAP, VAP, HCAP in patients without MDR Risk factors with early onset

<table>
<thead>
<tr>
<th>Potential Pathogen</th>
<th>Recommended Antibiotic</th>
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<tbody>
<tr>
<td>S. pneumoniae</td>
<td>Ceftriaxone OR</td>
</tr>
<tr>
<td>H. influenzae</td>
<td>Levo or Moxi OR</td>
</tr>
<tr>
<td>MRSA</td>
<td>Ampicillin/sulbacam OR</td>
</tr>
<tr>
<td>E. coli</td>
<td></td>
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<tr>
<td>K. pneumoniae</td>
<td></td>
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<tr>
<td>Enterobacter spp</td>
<td></td>
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<tr>
<td>Proteus spp</td>
<td></td>
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<tr>
<td>Serratia marcescens</td>
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</tbody>
</table>

### Initial Empiric Therapy for HAP, VAP, HCAP in patients with Late Onset Disease of Risk Factors for MDR Pathogens

<table>
<thead>
<tr>
<th>Potential Pathogen</th>
<th>Recommended Antibiotic</th>
</tr>
</thead>
<tbody>
<tr>
<td>MDR Organisms</td>
<td></td>
</tr>
<tr>
<td>- Pseudomonas aeruginosa</td>
<td>• Antipseudomonal cephalosporin (cefepime, ceftazidime) OR</td>
</tr>
<tr>
<td>- Klebsiella pneumoniae</td>
<td>• Antipseudomonal carbopenem (imipenem or meropenem) OR</td>
</tr>
<tr>
<td>(ESBL+)</td>
<td>• B-Lactam/B-lactamase inhibitor (piperacillin–tazobactam)</td>
</tr>
<tr>
<td>- Acinetobacter species</td>
<td>PLUS</td>
</tr>
<tr>
<td>MRSA</td>
<td>• Antipseudomonal fluoroquinolone (ciprofloxacin or levofloxacin) OR</td>
</tr>
<tr>
<td></td>
<td>• Aminoglycoside (amikacin, gentamicin, or tobramycin)</td>
</tr>
<tr>
<td></td>
<td>PLUS</td>
</tr>
<tr>
<td></td>
<td>Linezolide OR Vancomycin</td>
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Proposed solutions

- The heterogeneity of the population for which the 2005 guidelines were intended & the elusiveness of a gold standard for establishment of microbial cause render them inherently unstable.

Main objective of guidelines:

- to ensure **empirical antibiotic therapy** would cover multidrug-resistant pathogens.
Precipitating factor:

- Emergence of multidrug-resistant pathogens including MRSA ➞ prior antibiotic therapy (unnecessary broad-spectrum antibiotic therapy)

2 studies by guideline committee (ICU pneumonia)

- Restriction of the common practice of broad-spectrum antibiotic was more important to improving outcomes than was use of the broader coverage

- **Monotherapy** was effective in many p’ts with HCAP who were ambulatory & not severely ill.
• In an attempt to rectify the shortcomings of the guidelines, revisionists proposed to use the concept of risk factors for multidrug-resistant pathogens.

*Figure: The vicious circle within the hospital-acquired pneumonia and health-care-associated pneumonia guidelines*

The key decision point is that of risk factors for multidrug-resistant pathogens, but the most important risk factor is previous administration of antibiotics (red arrows; thickness denotes relative risk). This classification can lead to widespread overuse of broad-spectrum antibiotics. MDR=multidrug-resistant.
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Victor L Yu believe the solution is straightforward—**individualization**

- If individualization is applied to **antibiotic selection**, the regional differences in antibiotic use, unique characteristics of the population, & special situations can be taken into consideration.

- Every pt’s can be assessed with respect to their **individual risk factors**.

**Individualization is useful when the pt’s history is sufficiently complex that a one-size-fits-all approach is no longer feasible**
The **vulnerability of heterogeneity** can be resolved by explicitly accepting that certain subgroups of p’ts have their own distinctive epidemiology & risk factors.

Proposed solutions

- **Individualization**

Provision of empirical MRSA coverage to a select population of drug addicts in Los Angeles, CA, USA who have a high prevalence of community-acquired MRSA would be rational, but blanket MRSA coverage might not be in Scandinavia, which has a low prevalence of such infections.

If a p’t on hemodialysis is a known MRSA nasal carrier with a past history of MRSA infection or if *Legionella spp* are present in drinking water of hospital, such knowledge can improve antibiotic selection.
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Recommend guidelines be tailored to those specific settings that provide clues to the most likely pathogens.

- Extended-care facilities & nursing homes (stratified by functional status)
- Immunosuppressed hosts (stratified by p’ts with neutropenia, HIV status, or transplanted organ)
- Pneumonia in ICUs (stratified by VAP & postoperative pneumonia)

P’ts receiving home intravenous therapy should not be included in the guidelines but their immunosuppressed status is pertinent.
Molecular-based diagnostic tests are being introduced to the clinical setting at the point of care.

The emphasis on empirical therapy can be reduced if the microbial pathogens of pneumonia can be identified before antibiotic initiation.

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- suggest that a worthy effort of pneumonia investigators would be to apply, assess, & validate these new innovative diagnostic tests, including those for inflammatory biomarkers (especially procalcitonin).
- A solution, if one exists, must focus on accurate identification of the pathogens of HCAP.
More studies as a way of improving the 2005 guidelines is a safe recommendation, but not an easy solution.

Retrospective databases are **unreliable** for formulation of guidelines for antibiotic therapy.

- As an example, MRSA was the most common cause of CAP (25%) & HCAP followed by S pneumoniae (20·3%) in one such retrospective study—a surprising finding that is unlikely to be replicated elsewhere.

For maximum effectiveness,

**New, large-scale, prospective studies (strict design) need to be commissioned.**

- **Standardized microbiological methods** should be used, which must be applied to all p’ts.
The net effect of selective testing of a pathogen rather than universal testing is **underestimation** for that particular pathogen in the population because the diagnostic test is not ordered, or **overestimation** of the virulence of the pathogen when tests are targeted for p’ts not responding to therapy or those who are severely ill.

- Such studies would also provide the opportunity to also assess **molecular diagnostic tests & biomarkers**.

- A series of smaller studies with a **well-defined population** with HCAP (eg, patients in a nursing home) is preferable to one large study with a heterogeneous study population.
Conclusion

- The 2005 ATS–IDSA guidelines lead to potential overtreatment.
- Because of the results of the study by Kett & colleagues, doctors caring for p’ts in intensive-care should exercise restraint in antibiotic use.

- If point-of-care microbiological tests are not revealing, then monotherapy should be used for only 3 days in non-severely ill p’ts in ICUs.

Antibiotic therapy should be stopped when culture evidence suggests absence of infection.
Because of the irremediable weakness of present data, the fundamental principles of infectious diseases need to be applied for HAP & HCAP until newer, more rigorous studies are done.

- Determine microbial etiology & use empirical therapy only if necessary.

- A rational solution for effective management of pneumonia will ultimately rely on these principles.
Thanks for your attention!