Monotherapy or Combination Therapy for HCAP?
Hey Teacher! Leave Them Quinolones!

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Pharmacy Grand Rounds
February 9th, 2016
Objectives

• Review American Thoracic Society (ATS) / Infectious Diseases Society of America (IDSA) guidelines of health-care associated pneumonia for empiric antimicrobial therapy of gram negative pathogens

• Describe advantages and disadvantages surrounding empiric monotherapy versus combination antimicrobial therapy for gram negative coverage

• Discuss how the 2015 Mayo Clinic (Rochester) combination antibiogram can guide empiric treatment regimens
Poll

*Pseudomonas aeruginosa* (PSA) is a “two drug bug”

1. Yes
2. No
Epidemiology

- CDC indicates that pneumonia is the leading cause of infectious disease-related deaths in the United States
  - 1.2 million of 35 million annual hospitalizations
- PSA accounts for 20-60% mortality
- Increasing prevalence of MDR Gram-negative infections leads to increase utilization of broad spectrum antibiotics
Evolution of Pneumonia Classifications

1996 IDSA / ATS Guidelines

- CAP
- HAP
- VAP

2005 IDSA / ATS Guidelines

- HCAP

Criteria:
- Hospitalization for ≥ 2 days within 90 days
- Nursing home or long-term care facility residence
- IV antibiotics, chemotherapy or wound care within the past 30 days
- Hemodialysis clinic

References:
- Am J Respir Crit Care Med 1996
- Am J Respir Crit Care Med 2005
Kollef, et al. *CHEST*. 2005

Mortality rate, % patients

- CAP (n = 2221): 10%
- HCAP (n = 988): 19.8%
- HAP (n = 835): 18.8%
- VAP (n = 499): 29.3%
Empiric HCAP Coverage

- Anti-PSA β-lactam/β-lactamase inhibitor
- Anti-PSA Cephalosporin
- Anti-PSA Carbapenem

PLUS

- Anti-PSA Fluoroquinolone
- Aminoglycosides

As mentioned, the benefits of combination therapy are unclear, with the only data supporting this practice coming from a study of \textit{P. aeruginosa} bacteremia (few of which were due to pneumonia) which showed that patients receiving combination therapy were less likely to die (258). A prospective...

- 200 patients with *P. aeruginosa* bacteremia
  - PNA as primary source in 10%
- Primary Outcome: Mortality (Death at Day 10)
  - Combination therapy
    - Piperacillin or Ticarcillin + Aminoglycoside
    - Mortality: 27%
  - Monotherapy
    - Aminoglycoside
    - Mortality: 47%
Time to reevaluate HCAP criteria?

• Gross et al found that MDROs were uncommon in HCAP (5.9%) in a US tertiary medical center

• Chen et al found no difference in clinical outcomes treating HCAP patients with CAP guidelines

• Jones et al found increased prescribing of broad-spectrum agents with no increase in cultures for PSA

Hospitalization for ≥ 2 days within 90 days
Nursing home or long-term care facility residence
IV antibiotics, chemotherapy or wound care within the past 30 days
Hemodialysis clinic

Sensitivity: 52.2%
Specificity: 67.7%


Proportion of Hospitalized Patients, %

- **Single Pseudomonas Coverage**
- **Double Pseudomonas Coverage**

<table>
<thead>
<tr>
<th>Year</th>
<th>Single Pseudomonas Coverage</th>
<th>Double Pseudomonas Coverage</th>
</tr>
</thead>
<tbody>
<tr>
<td>2006</td>
<td>25</td>
<td>4</td>
</tr>
<tr>
<td>2007</td>
<td>28</td>
<td>5</td>
</tr>
<tr>
<td>2008</td>
<td>30</td>
<td>8</td>
</tr>
<tr>
<td>2009</td>
<td>33</td>
<td>10</td>
</tr>
<tr>
<td>2010</td>
<td>35</td>
<td>12</td>
</tr>
</tbody>
</table>

![Graph showing the percentage of patients with positive cultures for Pseudomonas from 2006 to 2010.](image-url)
FQ and Resistance Among Gram Negatives


Graph showing the trend of Fluoroquinolone Use (kg x 1000) and the percentage of strains resistant to Ciprofloxacin (%) from 1993 to 2000 for P. aeruginosa and GNR. The use of Fluoroquinolones increases over time, while the percentage of resistant strains also increases.
Preserving the β-lactam Backbone

β-lactamases
Double coverage
Efflux pumps
Target site modifications

Antimicrobial Stewardship
Double coverage
Rapid detection
Optimize PK/PD

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Hesitation of Double-Coverage

• Increased drug toxicity
• Increased costs
• Increased risk of superinfection with MDR bacteria
• *Clostridium difficile* incidence

Yu VL. *Lancet Infect Dis.* 2011
Justification of Combination Therapy

1) Synergistic effect of two anti-pseudomonal antibiotics

2) Prevent emergence of resistance

3) Increase likelihood that at least one drug is active against a MDR pathogen
Synergy: β-lactams and Aminoglycosides/FQ

• First PK/PK analysis to compare β-lactam with aminoglycoside versus FQ against *P. aeruginosa*

• In vitro
  • AG: 79%
  • FQ: 57%

• In vivo data
  • Meta-analysis showing no difference in clinical outcomes in septic patients with combination vs. monotherapy

Prevent Resistance

• FQ associated with selecting for mutant *P. aeruginosa* that overproduce multidrug efflux pumps
  • Confer β-lactam/AG cross resistance

• Development of resistant phenotypes during therapy has been documented
Increase Odds of Covering Your Bug

P. aeruginosa

Ciprofloxacin
78 %

Pip/Tazo
86 %

How many times do they miss?
The Misleading Antibiogram

Piperacillin/Tazobactam: 86%
Ciprofloxacin: 78%

<table>
<thead>
<tr>
<th>Microorganism (number tested)</th>
<th>Amp &lt;8</th>
<th>Cefaz &lt;2</th>
<th>Ceftriaxone&lt;1</th>
<th>Cefaz &lt;8</th>
<th>Cefep&lt;8</th>
<th>Mero&lt;1</th>
<th>Ertal &lt;0.5</th>
<th>Amp/ Sulb &lt;8/4</th>
<th>Pip/ Tazo &lt;16/4</th>
<th>Gent ≤4</th>
<th>Tobra ≤4</th>
<th>Amik &lt;16</th>
<th>Cipro &lt;1</th>
<th>Levo &lt;2</th>
<th>TMP/ SMX &lt;2/38</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Pseudomonas aeruginosa</em>&lt;sup&gt;1&lt;/sup&gt; (531)</td>
<td></td>
<td></td>
<td></td>
<td>87</td>
<td>83</td>
<td>83&lt;sup&gt;1&lt;/sup&gt;</td>
<td>86</td>
<td>85</td>
<td>94</td>
<td>93</td>
<td>78</td>
<td>76</td>
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</tr>
</tbody>
</table>

100% - 86% = 14%
100% - 78% = 22%

Pip/Tazo Resistant = 14% → 0.14 × 0.22 = 3%
Cipro Resistant = 22% → 0.03/97%
### 2015 Mayo Clinic (Rochester) PSA Isolates

<table>
<thead>
<tr>
<th></th>
<th>% Susceptible</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>N=489</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Monotherapy</strong></td>
<td></td>
</tr>
<tr>
<td>Pip/Tazo</td>
<td>86%</td>
</tr>
<tr>
<td>Cefepime</td>
<td>79%</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>73%</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>78%</td>
</tr>
<tr>
<td>Tobramycin</td>
<td>93%</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>83%</td>
</tr>
<tr>
<td>Amikacin</td>
<td>91%</td>
</tr>
<tr>
<td><strong>Combo with Ciprofloxacin</strong></td>
<td>92% 97%</td>
</tr>
<tr>
<td><strong>Combo with Tobramycin</strong></td>
<td>96% 98%</td>
</tr>
<tr>
<td><strong>Combo with Amikacin</strong></td>
<td>99% 95%</td>
</tr>
</tbody>
</table>

Resistance ≠ Statistical Independence
What About Just ICU’s?

### Pseudomonas isolates ICU 2015, % Susceptible

<table>
<thead>
<tr>
<th></th>
<th>N=126</th>
<th>Monotherapy</th>
<th>Combo with Levofloxacin</th>
<th>Combo with Tobramycin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pip/Tazo</td>
<td>77%</td>
<td>86%</td>
<td>93%</td>
<td>94%</td>
</tr>
<tr>
<td>Cefepime</td>
<td>72%</td>
<td>80%</td>
<td></td>
<td>87%</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>70%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tobramycin</td>
<td>96%</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**P. aeruginosa % susceptible**
- Pip/Tazo 77%  
  - 93%  
- Levofloxacin 70%
Empiric Coverage of ICU Patients for Infections Due to β-lactam Resistant *Pseudomonas aeruginosa* with Combination Therapy: A Needs Assessment

- Clinical question
  - Should an aminoglycoside be administered in combination with an anti-pseudomonal β-lactam as routine empiric therapy in critically ill patients at risk for infection with β-lactam resistant PSA?

- Retrospective study

- Adult ICU patients (2013) with at least one *P. aeruginosa* isolate resistant to one anti-pseudomonal β-lactam
Results

15,113 ICU admissions

n = 61 patients (100 isolates)

- 19/61 (31.2%) had PSA recovered within previous year
- 38/61 (62.3%) had structural respiratory tract changes and/or depressed CNS function
- 10/61 (16.4%) had diagnosis of sepsis
- 21/61 (34.4%) died during the hospitalization or shortly thereafter
- 8/21 who died received “mismatch therapy”
  - Drug administered ≠ in vitro susceptibility
  - Only 1 death was possibly related to “mismatch therapy”

Data courtesy of LM Baddour, MD, FIDSA, FAHA
Summary

15,113
61
21
8
1
Impact of Combination Antibiogram on FQ prescribing patterns for HCAP

- Retrospective pre/post provider education intervention study evaluating antibiotic prescribing patterns (FQ DOT*) and patient outcomes
  - FQ DOT decreased post-intervention: 3.7 vs 1.4 days (p<0.001)
  - Double coverage reduced by 2.1 days (p<0.001)
  - No difference on clinical outcomes
  - Concluded double coverage would benefit <1% of patients with HCAP

Question

Which of the following is not a common rationale for “double coverage”? 

1) Synergy of two antibiotics 
2) Prevent resistance 
3) Increase odds that you’ll cover the organism 
4) Achieve steady state quicker
Question

Utilizing a unit-specific combination antibiogram will improve empiric therapy for Gram-negative infections.

1) True
2) False
Conclusion

• 2005 ATS / IDSA guidelines for empiric HCAP coverage recommend combination antimicrobials targeted at gram negatives, specifically *Pseudomonas aeruginosa*

• Array of literature supports both advantages and disadvantages surrounding empiric monotherapy versus combination antimicrobial therapy

• Using the 2015 Mayo Clinic (Rochester) combination antibiogram may help optimize empiric treatment regimens
Questions?
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2016 ATS / IDSA HCAP Guidelines Update:
Spring 2016!