Meeting Today’s Challenges in VAP & Serious Infections by MDR Gram Negative

Jordi Rello, MD, PhD
Chief of the Critical Care Department
Joan XXIII University Hospital
Professor of Medicine. Rovira & Virgili Medical School
Director, Research Group, CIBER Respiratory Diseases
Tarragona, Spain
Structure of my talk

- Delayed/inappropriate therapy is problematic
- Regional susceptibilities vary from place to place and over time
- Considerations for Nosocomial pneumonia
- New paradigm: broad cover, hit hard, big dose and short course
Mortality Rates

Resistance in the ICU is Increasing

<table>
<thead>
<tr>
<th>Bacterium</th>
<th>Ceftazidime Resistant (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>S. aureus</td>
<td>59.5</td>
</tr>
<tr>
<td>P. aeruginosa</td>
<td>31.9</td>
</tr>
<tr>
<td>Enterobacter spp.</td>
<td>31.1</td>
</tr>
<tr>
<td>Klebsiella spp.</td>
<td>20.2</td>
</tr>
</tbody>
</table>

EPIC2 Study -- Latinamerica

- 28% Pseudomonas
- 20% Klebsiella
- 19% Acinetobacter
ESBL-producing Gram-negative bacilli

Data from SMART study 2004

Increasing Antibiotic Resistance Requires a New Approach

- What has been the traditional approach?
  - Start narrow-spectrum antibiotic
  - Reserve the most potent drugs for patients who:
    • Are severely immunocompromised
    • Do not respond to treatment
    • Have a resistant organism

- Why the traditional approach?
  - A desire to avoid using antibiotics when infection is not confirmed
  - Concerns about the development of resistance
  - Concerns about cost
Hmmmm...wrong bottle. I guess THIS one must’ve been the Elixir of Death...
Determinants of Mortality in Pneumonia and Sepsis: Appropriate Versus Adequate Therapy

Pathogen coverage

Correct dose

Optimal therapy

Timely initiation

Adjuvant therapy

Increased survival

P. aeruginosa in VAP

- The leading cause of VAP in ICUs
- Risk factors
  - Extended ICU stay
  - Intubated for >8 days
  - Acute respiratory distress syndrome (ARDS)
  - Severe COPD
  - Previous exposure to antimicrobials
- Initial therapy should include an antipseudomonal β-lactam (piperacillin-tazobactam, carbapenem, third- or fourth-generation cephalosporin) plus an aminoglycoside

A. baumannii in VAP

- Prospective study of 707 mechanically ventilated patients in 3 medical ICUs in teaching hospitals in Uruguay and Spain
- Intubated patients who develop pneumonia and have any of the following factors are at increased risk of infection with A. baumannii
  - Neurosurgery
  - ARDS
  - Head trauma
  - Large-volume pulmonary aspiration
- Treatment options include: carbapenems, aminoglycosides, or ampicillin/sulbactam

Why Are Cephalosporins Increasingly Inappropriate?

- The most common etiological agents for nosocomial pneumonia are often resistant
  - *P. aeruginosa*
  - *S. aureus*
  - *Enterobacter* spp.
  - *Klebsiella* spp.
  - *Acinetobacter* spp.
  - *H. influenzae*
  - *S. pneumoniae*

- Even if pathogen appears susceptible, third-generation cephalosporins select for resistant mutants
ESBLs

- ESBLs lead to increased MICs to third-generation cephalosporins, aztreonam, and sometimes cefepime/cefpirome
- Genes encoding ESBLs are carried on plasmids that also confer resistance to aminoglycosides and fluoroquinolones
- 18-56% of ESBL-producing *Klebsiella* spp. are quinolone-resistant

## Adequate Therapy for β-Lactamase Producers

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>ESBLs</th>
<th>AmpC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Third-generation cephalosporins</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Cefepime</td>
<td>-</td>
<td>+++</td>
</tr>
<tr>
<td>Quinolones</td>
<td>+/-</td>
<td>+</td>
</tr>
<tr>
<td>Tigecycline</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Piperacillin/tazobactam</td>
<td>+/-</td>
<td>+/-</td>
</tr>
<tr>
<td>Carbapenems</td>
<td>+++</td>
<td>+++</td>
</tr>
</tbody>
</table>
Do we need a new Carbapenem?

**Carbapenems for NP due to *P. aeruginosa***

**Clinical Success**
- First Author
  - West et al.
  - Zanetti et al.
  - Torres et al.
  - Jaccard et al.
  - Jaspers et al.
  - Norrby et al.
  - Combined

**Eradication of *P. aeruginosa***
- First Author
  - Joshi et al.
  - West et al.
  - Alvarez Lerma et al.
  - Torres et al.
  - Sieger et al.
  - Mouton and Beuscart
  - Norrby et al.
  - Combined

Treatment Decision Tree for VAP

Suspected VAP

Microbiological investigation

Cultures and Gram stain

Empiric antibiotics based on risk factors

Gram +ve stain: if MRSA, start anti-MRSA coverage
Gram -ve stain: if A. baumannii, start carbapenem, but if Pseudomonas spp., start 2 antipseudomonal agents
If none of above, start antibiotics and consider local epidemiology

Reassess at 48-72 h

Therapy for VAP Should Be Tailored to the Individual Institution

- Retrospective study comparing VAP etiology in ICUs in France, Spain, and Uruguay
- In an attempt to develop generalized empiric therapy guidelines, patients were stratified according to:
  - Number of ventilation days and previous antibiotic use
- VAP etiology varied markedly across centers
- Empiric therapy should be based on:
  - Up-to-date information on pathogen etiology and antibiotic resistance patterns
  - A variation of general recommendations

Predicting the causative organism: Know your ‘local’ pathogens

(>7 days + prior antibiotic)

Causative organism (%)

Stenotrophomonas maltophilia
Acinetobacter spp.
MRSA
P. aeruginosa

Paris
Seville
Montevideo
Sabadell
Tarragona

A Patient-based Antibiotic Management Program: The Tarragona Strategy for VAP

- “Hit hard” with a high dose of broad-spectrum antibiotic
- “Get to the point”: take pharmacodynamics into account
- “Focus, focus, focus”: tailor or stop therapy according to microbiological results
- “Listen to your hospital”: tailor antibiotic policy regularly
- “Look at your patient”: administer antibiotics according to comorbidities, intubation period, and previous antibiotic exposure

Top Five Frequent Mistakes

- Delay appropriate start of therapy
- Lack of Dosing Flexibility in Severe Sepsis
- Ignore tisular penetration and haemodynamics.
- Choices ignoring local organisms variability
- Prolonged atb courses.
Open up your eyes when filling in the death certificate pal! You entered your own name into the column 'cause of death' again!
Summary: Appropriate Antibiotic Therapy Improves Efficacy and Limits Resistance

- Inappropriate initial therapy is associated with higher mortality, length of stay, and cost.
- Broad-spectrum antibiotics are an optimal initial choice for NP and severe sepsis.
- Select the best antibiotic depending on the patient, risk factors, suspected infection, and resistance.
Reviews of de-escalation

*Current Opinion in Critical Care*
Volume 12(5), October 2006, p 452-457

De-escalation therapy in ventilator-associated pneumonia
Michael S. Niederman

*Current Opinion in Pulmonary Medicine*
Volume 12(5), September 2006, p 364-368

De-escalation in lower respiratory tract infections
Thiago Lisboa\(^a\) and Jordi Rello\(^b\)
Thank you

Jrello.hj23.ics@gencat.cat

www.grig.es