Antibiotic Stewardship in Critically ill

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The widespread use of potent, broad-spectrum antibiotics has been paralleled by the development of resistance in bacteria.

- It is thus necessary for us to use antibiotics wisely and appropriately.
Structure of my talk

- Delayed/inappropriate therapy is problematic
- Regional susceptibilities vary from place to place and over time
- Define de-escalation & Stewardship
- How de-escalation has been reported in the literature
- How I would do it
- Duration of therapy: prolongation causes resistance
- New paradigm: broad cover, hit hard, big dose and short course
Get it right first time!

- Appropriate antibiotic treatment
- Inappropriate antibiotic treatment

Mortality rate (%)

- Micek (n=102)
- Harbarth (n=904)
- Garnacho (n=406)
- Dhainaut (n=1690)

* p<0.05
Getting therapy right first time

Cumulative survival in hospitalised patients receiving appropriate vs inappropriate antibiotic therapy

- **Appropriate**
- **Inappropriate**
- **Discharged**

Getting therapy right first time

Benefit of appropriate empiric antibiotic therapy: 30-day mortality and length of stay

- 920 patients from 3 countries (Israel, Germany, Italy)
- Inappropriate therapy in 319 cases
- All-cause 30-day mortality 20% vs 11%
  - Adjusting for medical centre and other variables
  - Odds ratio 1.58 [95% CI: 0.99–2.54; p=0.058]

Getting therapy right first time

Inadequate treatment of VAP pneumonia: risk factors and impact on outcomes

Adequate treatment n=82

Inadequate treatment n=69

Cumulative survival

Time after VAP onset (days)

Duration of hypotension prior to effective antimicrobial therapy: impact on survival in septic shock

Kumar et al. Crit Care Med 2006;34:1589–1596
Ps aeruginosa bloodstream infections: Predictors of 30-day mortality

Delay in appropriate therapy (hours)

- <12: 19%
- 12–24: 20%
- 25–52: 19%
- >52: 44%

30-day mortality (%)

p=0.03
So how do you get it right?

Regional variations in resistance

• Know your local organisms and their sensitivities
  – This will largely determine your antibiotic choices
Antibiotic susceptibility of *Klebsiella pneumoniae*, *Enterobacter cloacae* and *Pseudomonas aeruginosa* from Spain and Turkey (MYSTIC data 2006)
ESBL phenotypes among *Escherichia coli* (n=918) and *K. pneumoniae* (n=850) isolates from Asia-Pacific region

In Asian countries, ESBL phenotypes among *E. coli* and *K. pneumoniae* are mostly between 20% and 40%

![Graph showing the percentage of resistance over years](image-url)
Fluoroquinolone-resistant *P. aeruginosa* among ICU patients (1995–2004)
Know your ‘local’ pathogens: *E. coli*

Prevalence of ciprofloxacin non-susceptible *E. coli* (1999–2001)

<table>
<thead>
<tr>
<th>Institution</th>
<th>No. of Isolates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Australia</td>
<td>1098</td>
</tr>
<tr>
<td>Japan</td>
<td>270</td>
</tr>
<tr>
<td>Taiwan</td>
<td>271</td>
</tr>
<tr>
<td>Mainland China</td>
<td>163</td>
</tr>
<tr>
<td>Hong Kong</td>
<td>493</td>
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<td>South Africa</td>
<td>190</td>
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<tr>
<td>Philippines</td>
<td>298</td>
</tr>
<tr>
<td>Singapore</td>
<td>260</td>
</tr>
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</table>

Bell, Turnidge. Commun Dis Intell 2003;27 (Suppl.):S61–S66
## Know your ‘local’ pathogens

Note variability across regions (and over time)

<table>
<thead>
<tr>
<th>Country</th>
<th>1998</th>
<th>1999</th>
<th>2000</th>
<th>2001</th>
<th>4-year totals</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of strains</td>
<td>% ESBL positive</td>
<td>No. of strains</td>
<td>% ESBL positive</td>
<td>No. of strains</td>
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<tr>
<td>Australia</td>
<td>33</td>
<td>6</td>
<td>45</td>
<td>2</td>
<td>55</td>
</tr>
<tr>
<td>Hong Kong</td>
<td>8</td>
<td>25</td>
<td>9</td>
<td>0</td>
<td>10</td>
</tr>
<tr>
<td>Japan</td>
<td>22</td>
<td>5</td>
<td>32</td>
<td>0</td>
<td>33</td>
</tr>
<tr>
<td>Mainland China</td>
<td>25</td>
<td>28</td>
<td>13</td>
<td>54</td>
<td>0</td>
</tr>
<tr>
<td>Philippines</td>
<td>19</td>
<td>37</td>
<td>27</td>
<td>33</td>
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<tr>
<td>Singapore</td>
<td>14</td>
<td>29</td>
<td>2</td>
<td>0</td>
<td>9</td>
</tr>
<tr>
<td>South Africa</td>
<td>7</td>
<td>14</td>
<td>6</td>
<td>0</td>
<td>18</td>
</tr>
<tr>
<td>Taiwan</td>
<td>8</td>
<td>38</td>
<td>2</td>
<td>0</td>
<td>10</td>
</tr>
<tr>
<td>Total</td>
<td>136</td>
<td>20</td>
<td>136</td>
<td>13</td>
<td>172</td>
</tr>
</tbody>
</table>
Know your ‘local’ pathogens

- Methicillin
- Vancomycin
- Imipenem
- Ceftazidime
- Enterococcus spp.
- Acinetobacter spp.
- P. aeruginosa

Susceptibility (%)

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Medical ICU</th>
<th>Surgical ICU</th>
<th>Trauma ICU</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methicillin</td>
<td>*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vancomycin</td>
<td>*</td>
<td>*</td>
<td></td>
</tr>
<tr>
<td>Imipenem</td>
<td>*</td>
<td>*</td>
<td></td>
</tr>
<tr>
<td>Ceftazidime</td>
<td>*</td>
<td>*</td>
<td>*</td>
</tr>
</tbody>
</table>

*Significant difference between ICUs

Impact of antibiotic resistance

• Infections are more commonly caused by multidrug-resistant (MDR) pathogens

• It is increasingly difficult to be sure that initial therapy will be appropriate unless it is extremely broad spectrum

• Awareness of the need for early and appropriate therapy means the use of broad-spectrum antibiotics at the first sign of infection

• In turn, overuse of antibiotics could drive more resistance
TO COVER POTENTIAL ORGANISMS MEANS...

BROAD COVER UP FRONT
Ensuring adequate antibiotic therapy: Local resistance patterns

- **Paris**: 
  - P. aeruginosa: 70%
  - MRSA: 20%
  - Acinetobacter spp.: 10%
  - S. maltophilia: 5%

- **Sevilla**: 
  - P. aeruginosa: 85%
  - MRSA: 10%
  - Acinetobacter spp.: 5%
  - S. maltophilia: 0%

- **Montev.**: 
  - P. aeruginosa: 80%
  - MRSA: 20%
  - Acinetobacter spp.: 0%
  - S. maltophilia: 5%

- **Sabadell**: 
  - P. aeruginosa: 90%
  - MRSA: 10%
  - Acinetobacter spp.: 5%
  - S. maltophilia: 0%

- **Tarragona**: 
  - P. aeruginosa: 75%
  - MRSA: 25%
  - Acinetobacter spp.: 10%
  - S. maltophilia: 5%
Problem

RESISTANCE    ADEQUATE THERAPY
What are the Goals of Antibiotic Stewardship?

- Optimize clinical outcomes while minimizing unintended consequences of antibiotic use
- Toxicty
- Selection of pathogenic organisms
- Emergence of resistance

Comprehensive infection control to limit emergence and transmission of resistance

Reduce healthcare costs without adversely impacting quality of care

Two Core Antimicrobial Stewardship Strategies

- Prospective audit of antimicrobial use with intervention and feedback to the prescriber
  - Rating: A-I

- Formulary restriction and preauthorization requirements for specific agents

Possible Outcome Measurements

- Mortality
- Discharge location
- Re-admission
- Length of stay
- Resistance
- Adverse events
- Collateral damage
- Drug cost

Important for patients

Important for hospitals
De-escalation, a significant strategy of stewardship

- De-escalation involves the practice of:
  - Starting with a broad-spectrum empiric therapy regimen designed to avoid inappropriate therapy, combined with a commitment to:
    - Change from broad- to narrow-spectrum therapy
    - Reduce the duration of therapy
    - Stop therapy in selected patients, as dictated by the patient’s clinical response and by culture results
  - Culture data are used to narrow, focus or even stop therapy
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\textsuperscript{a} and Jordi Rello\textsuperscript{b}
Why cultures to de-escalate?

- The vicious cycle created by the need for aggressive, broad-spectrum antibiotic therapy to achieve appropriate therapy, which creates more resistance and more overuse of antibiotics, can only be broken by
  - De-escalation

- Culture data are used to narrow, focus or even stop therapy
De-escalation in clinical practice
Changes in antibiotic therapy based on microbiological results

121 episodes

Aetiology

UNKNOWN
n=10

Change n=3
Poor clinical resolution

KNOWN
n=111

Change n=65

Appropriate treatment

Inappropriate treatment

Poor clinical resolution n=12
De-escalation n=38
Adverse events n=4
Resistant pathogens n=11

De-escalation and outcome

- De-escalation: 10%
- Unchanged: 50%

p < 0.05
De-escalation in clinical practice

ALARM study

P. aeruginosa

MRSA

Kollef et al. Chest 2006;129:1210–1218
Avoiding antibiotic overuse

• Conclusions:
  
  “A rational empirical antimicrobial therapy for ventilator-associated pneumonia using limited-spectrum antibiotics is possible if local ecology and patient medical history and clinical status are considered. In addition, de-escalation is feasible in 42% of patients. This integrative approach may reduce the emergence of resistant bacteria …”
The bottom line/what I do

- Get it right first time
  - Cover all likely organisms but be reasonable
- Send off cultures
- De-escalate according to culture results
- If nothing grows, re-evaluate
Duration of antibiotic therapy
Predictor of response

Serial Clinical Pulmonary Infection Score (CPIS) measurements to determine outcome in VAP therapy

- Evolution of the CPIS correlated with mortality
- PaO₂:FiO₂ ratio was the best correlate of clinical response and outcome

Luna et al. Crit Care Med 2003;31:969−970
Duration of antibiotic therapy
Clinical resolution

VAP resolution (non-ARDS)

Patients (%)

Days (n)

- Fever <38°C
- PaO₂:FiO₂ >250
- WBC count <10,000
- Clearance of secretions

Duration of antibiotic therapy
8 vs 15 days of antibiotic therapy for VAP

No difference in survival

Chastre et al. JAMA 2003;290:2588–2598
Key point: Duration

• There is an international trend to use shorter courses of antibiotics

• *P. aeruginosa* VAP probably needs 7–10 days

• In my unit, we seldom use more than a 7-day course – more often a 5-day course
## Overcoming Barriers to Stewardship

<table>
<thead>
<tr>
<th>Issue</th>
<th>What is Lacking?</th>
<th>What can be Done?</th>
</tr>
</thead>
</table>
| Strategic | • Physician participation  
• Cooperation from colleagues  
• Network between hospitals and regional bodies  
• Community center participation | • Acknowledge effort  
Provide information  
Improve communication |
| Operational| • Emphasis on diagnostic procedures in guidelines  
• De-escalation | • Incorporate community centers in the hospital ASPs  
• Emphasis on diagnosis  
• Incorporate de-escalation as a tool |
| Support   | • Education                                                                      | • Formalize training in antimicrobial use                                          |

In the context of your hospital’s resistance patterns

**NEW TREATMENT PARADIGM**

<table>
<thead>
<tr>
<th>Old</th>
<th>New</th>
</tr>
</thead>
<tbody>
<tr>
<td>Start with penicillin</td>
<td>Get it right first time</td>
</tr>
<tr>
<td>Cost-efficient low dose</td>
<td>De-escalate</td>
</tr>
<tr>
<td>Low doses = fewer side</td>
<td>Hit hard up front</td>
</tr>
<tr>
<td>effects</td>
<td>Low dose → resistance</td>
</tr>
<tr>
<td>Long courses ≥2 weeks</td>
<td>Seldom &gt;7-days</td>
</tr>
</tbody>
</table>
“A ‘postantibiotic era’ is difficult to contemplate but might become a reality unless the threat of progressive antibiotic resistance is taken seriously.” SM Opal & T Calandra, JAMA 2009;302:2367-8.
We need a new way of prescribing antibiotics in sick patients

- The old way doesn’t work
- Using fewer antibiotics is better than more
- Restriction & prioritization leads to resistance
- Appropriate empiric therapy is better