De-Escalation: Do We Really Do It and If Not, Why?

Michael S. Niederman, M.D.
Chairman, Department of Medicine
Winthrop-University Hospital
Mineola, NY

Professor of Medicine
Vice-Chairman, Department of Medicine
SUNY at Stony Brook
Better To Get It Right Initially Not Change To the Right Therapy: Bacteremia

186 Patients with Bacteremia due to ESBL containing organisms. 97 given appropriate initial therapy, 89 given inappropriate therapy (47.8%). 75 then received appropriate therapy based on susceptibility data.

Mortality (%)

Switching after susceptibility results

Adequate treatment within “a few hours”

THE NEED FOR EARLY APPROPRIATE THERAPY CREATES PROBLEMS

• NEED FOR EARLY APPROPRIATE THERAPY CAN DRIVE AGGRESSIVE USE OF ANTIBIOTICS

BUT

• AGGRESSIVE USAGE MAY MEAN OVERUSE WHICH DRIVES MORE RESISTANCE AND INAPPROPRIATE THERAPY

• HOW DO WE BREAK THIS VICIOUS CYCLE ???
The Conservative Approach

Increasingly ill patients

Infection with multi-drug resistant organisms

Loss of antibiotic efficacy due to overuse

Therefore Restrict Access to Antibiotics
The Liberal Approach

Failure to treat sepsis/pneumonia rapidly

Lack of efficacy of therapy due to resistant organisms

Increased mortality due to inadequate antibiotics

Therefore Open Access and Use of More Antibiotics
THE RIGHT APPROACH IS DE-ESCALATION: RESPONSIBLE ANTIBIOTIC STEWARDSHIP

• TO AVOID INAPPROPRIATE THERAPY, NEED LIBERAL USE OF ANTIBIOTICS INITIALLY
  – Base on guidelines
  – Modify knowing local microbiologic data
  – Start therapy based on clinical diagnosis

• TO AVOID EXCESSIVE ANTIBIOTICS, MODIFY THERAPY
  – Based on clinical data and tracheal aspirate cultures

• Current Opinion Crit Care 2006; 12:452-457
• Clin Infect Dis 2006; 42: S 72-81
• Chest 2002: 122:2183-96
Antimicrobial Stewardship

- Multidisciplinary approach: ID, pharmacy, microbiology, epidemiology, (CRITICAL CARE: NOT MENTIONED)

- 2 CORE STRATEGIES
  - Prospective audit with intervention and feedback (A-I)
  - Formulary restriction and preauthorization to control resistance (B-II)

- Supplemental strategies
  - Education
  - Guidelines with local microbiology (A-I)
  - Antimicrobial cycling (C-II)
  - Antibiotic order forms (B-II), Combination therapy (C-II)
  - De-escalation (A-II)
  - Dose optimization (A-II)
  - IV to oral conversion (A-III)

- Dellit TH, et al. CID 2007; 44: 159-77
De-Escalation: A Multi-center Experience

- 398 VAP patients, 20 sites
- De-escalation is EITHER OR BOTH: fewer drugs, narrower spectrum
  - Carbapenem > cefepime > piperacillin/taz, > quinolone
  - 22.1% de-escalate, 15.3% escalate
  - 27.1% vs. 16.6% de-escalate with app rx (p=0.01)
- Highest rate of de-escalation with carbapenems: 36% (only 9% escalation)
  - De-escalation Reduced Mortality, Escalation Increased Mortality
De-Escalation: A French Experience

- 115 episodes VAP rx with broad spectrum rx if prior hospitalization or antibiotics
  - Quantitative cultures or tacheal aspirate
  - 69% given limited spectrum rx
  - 85% appropriate rx with lower mortality (20% vs. 47%, p=0.04)

- De-esclation in 26% early onset and 72% late onset (42% overall). No significant drop in mortality.

De-Escalation: Relation To Diagnostic Methods

- 143 VAP by BAL and tracheal aspirate, all with positive cultures and appropriate rx.
- 40.5% with de-escalation
  - Decreased 28 day mortality (5.1% vs. 31.7%) p<0.05
  - Shorter ICU stay (17.2 vs. 22.7 days), p<0.05
- Claim more de-escalation with BAL than tracheal aspirate (66% vs. 21%, but not by protocol, not randomized, not systematic, and retrospective analysis)

<table>
<thead>
<tr>
<th>Table 4 Study outcomes as a function of the de-escalation therapy status</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary end point</strong></td>
</tr>
<tr>
<td>------------------------</td>
</tr>
<tr>
<td>Death from all causes at 15 days, n (%)</td>
</tr>
<tr>
<td>Quantitative tracheal aspirate</td>
</tr>
<tr>
<td>Bronchoalveolar lavage</td>
</tr>
<tr>
<td>Death from all causes at 28 days, n (%)</td>
</tr>
<tr>
<td>Quantitative tracheal aspirate</td>
</tr>
<tr>
<td>Bronchoalveolar lavage</td>
</tr>
<tr>
<td>Intensive care unit duration of stay, days (SD)</td>
</tr>
<tr>
<td>Quantitative tracheal aspirate</td>
</tr>
<tr>
<td>Bronchoalveolar lavage</td>
</tr>
<tr>
<td>Hospital duration of stay, days (SD)</td>
</tr>
<tr>
<td>Quantitative tracheal aspirate</td>
</tr>
<tr>
<td>Bronchoalveolar lavage</td>
</tr>
</tbody>
</table>
De-Escalation at High Rate, Regardless of Diagnostic Method Used for VAP

- 740 patients, suspected VAP after 4 days ICU
- BAL (quantitative cultures) or EA (non-quantitative cult)
  - Initial rx with meropenem and cipro vs. meropenem
  - Try to exclude if Pseudomonas or MRSA (14% high risk organisms)
- Targeted rx: stop if cultures negative, narrow spectrum and monotherapy (except Pseudomonas) if culture +.
- 74% targeted therapy in both groups
  - Positive cults: 76% EA; 79% BAL
  - Negative cults: 73% EA; 67% BAL

How Can We De-Escalate With a Negative Culture?

• In the absence of an anticipated resistant pathogen, focus to monotherapy, using an agent known to be effective in severe VAP

• With observation and NEGATIVE CULTURE DATA, retrospective diagnosis is NOT pneumonia, so STOP therapy
  – Atelectasis
  – Congestive Heart Failure

• Use clinical data to shorten duration of therapy
Can Antibiotics Be Safely Stopped if BAL Cultures are Negative?

- Prospective observational study of 101 patients with clinical suspicion of VAP but culture negative BAL
  - 64.4% given empiric rx after BAL
    - 66.1% of these with specific non-infection dx
    - Hospital mortality similar if got or did not get initial rx (33.8% vs. 36.1%)
- All had antibiotics D/C (clinical decision) within 3 days of starting
- 6 patients got a second episode of pneumonia (4-9 days after initial BAL)
- CNBAL, even if on antibiotics when sampled, may be an indication to stop therapy if clinically stable, esp if initial CPIS is not high

De-Escalation with Negative BAL

- Retrospective study of 89 with suspected VAP and negative BAL (<$10^4$/ml)
- Early D/C within 1 day of neg cult (n=40)
- Same mortality with early vs. late discontinuation
- Fewer superinfections and MDR superinfections with early D/C

**TABLE 2. Antibiotic Utilization Categorized by Antibiotic Discontinuation Within 1 Calendar Day of Negative Culture Finalization**

<table>
<thead>
<tr>
<th>Duration of antibiotics</th>
<th>Early Discontinuation (n = 40)</th>
<th>Late Discontinuation (n = 49)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>4 (3, 4)</td>
<td>9 (6, 14)</td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>1 (1, 2)</td>
<td>6 (4, 12)</td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>3 (2, 3)</td>
<td>4 (3, 6.25)</td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>De-escalation with first change (n, %)</td>
<td>16 (40.0)</td>
<td>32 (65.3)</td>
<td>0.03</td>
</tr>
<tr>
<td>Discontinuation with first change (n, %)</td>
<td>24 (60.0)</td>
<td>12 (24.5)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

All duration data presented in days as median (interquartile range), unless otherwise specified.
De-Escalation of Empiric MRSA Therapy in The Absence of LRTI Cultures

- Examined nasal and throat cultures for MRSA if HCAP, empiric vancomycin and no LRTI cultures obtained
- 139 patients, 91 with negative cults from both sites and vanco D/C within 48h
  - 97% with CPIS \(\leq 6\)
  - Mortality 7.7%
De- Escalation of HCAP Therapy Even If Culture Negative

- 102 patients admitted with HCAP, 72% were culture negative
- De-escalation from an HCAP regimen to a narrow spectrum regimen in 75% culture negative, 77% culture positive, but one day sooner if cult neg.
  - Less de-escalation if more HCAP risks
- Most commonly de-escalate to a quinolone (moxifloxacin), and in 70% of cult neg.
- De-escalate to 2 drugs in 27% cult + and 9% cult neg.
- De-escalation with shorter LOS, and cost. Lower mortality.

Fig. 3 Antibiotic utilization for de-escalation therapy in patients with HCAP. Gray-shaded column Culture-negative patients (n = 55), open column culture-positive patients (n = 22), black-shaded column combined groups (culture-positive + culture-negative) patients.
De-Escalation: Benefits

• **Benefits** of De-Escalation:
  
  – Fewer drugs:
    
    • Ibrahim et al; Crit Care Med 2001
  
  – Use narrower spectrum of drugs
  
  – Shorter course of antibiotics: Duration of therapy of 5.8 days for VAP even with resistant GNB, using de-escalation
    
    • Micek et al; Crit Care Med 2004
  
  – No evidence of harm: BUT is reduced mortality an effect or a marker of those able to de-escalate??
    
  
  – Accurate and aggressive empiric therapy can lead to shorter duration of therapy, more focused therapy:
    
    MORE CAN BE LESS
Benefits of De-Escalation in ICUAP: Lower Mortality (؟ As A Marker)

- 137 with ICUAP. 44 De-escalate (32.1%), 93 not
- Lower pneumonia related mortality with de-escalation (DE) (2.3 vs 10.8%)
- Mortality predictors: Day 5 APACHE II and CPIS score. BOTH higher in non de-escalation group. OK to DE if clinically stable at day 5, even if negative cultures.
  - App rx in 72.7% DE, 67.7% non-DE
  - 43% of the 20% with negative cultures had de-escalation

<table>
<thead>
<tr>
<th>Severity index</th>
<th>De-escalation</th>
<th>Non-de-escalation</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean APACHE II score (±SD)</td>
<td>13.6 ± 1.4</td>
<td>15.8 ± 6.0</td>
<td>0.003</td>
</tr>
<tr>
<td>APACHE II score, n (%)</td>
<td></td>
<td></td>
<td>0.04</td>
</tr>
<tr>
<td>&lt;19</td>
<td>34 (87.2%)</td>
<td>55 (72.4%)</td>
<td></td>
</tr>
<tr>
<td>19 to 23</td>
<td>4 (10.3%)</td>
<td>11 (14.5%)</td>
<td></td>
</tr>
<tr>
<td>&gt;23</td>
<td>1 (2.6%)</td>
<td>10 (13.2%)</td>
<td></td>
</tr>
<tr>
<td>Mean CPIS (±SD)</td>
<td>6.5 ± 1.2</td>
<td>7.5 ± 1.4</td>
<td>0.002</td>
</tr>
<tr>
<td>CPIS category, n (%)</td>
<td></td>
<td></td>
<td>0.009</td>
</tr>
<tr>
<td>4 to 6</td>
<td>21 (48.8%)</td>
<td>25 (27.8%)</td>
<td></td>
</tr>
<tr>
<td>7 to 9</td>
<td>22 (51.2%)</td>
<td>61 (67.8%)</td>
<td></td>
</tr>
<tr>
<td>≥10</td>
<td>0 (0%)</td>
<td>4 (2.7%)</td>
<td></td>
</tr>
</tbody>
</table>

aAPACHE II, Acute Physiology and Chronic Health Evaluation II; CPIS, Clinical Pulmonary Infection Score.
Benefits of De-Escalation in Septic Shock: Mortality as an Effect

- 712 with sepsis or septic shock, 628 evaluable (no early death)
- 34.9% de-escalation
- Mortality predictors: septic shock, SOFA score, inadequate rx. De-escalation was PROTECTIVE.
- De-escalation also protective if apply propensity score or if only look at those with appropriate rx.
De-Escalation in Surgical Patients: No Mortality Impact

- 138/1596 SICU patients with VAP diagnosed by BAL. De escalate by protocol with initial rx for MRSA and *P. aeruginosa*
- VAP mortality 37%. Same DE and not.
- 93% appropriate initial rx
  - 9% had *P. aeruginosa*, 14% MRSA
- 55% had de-escalation. Less with monotherapy
  - 66/77 fewer drugs, 16 narrower spectrum
- De escalation with no increase in recurrent pneumonia
De-Escalation in Neutropenic Sepsis: No Mortality Impact

- 101 neutropenic cancer patients in ICU with severe sepsis
- 44% de-escalation. More if adequate rx or follow local rx guideline
- Most within 12 days
- No adverse mortality impact
Correlates of De-Escalation Frequency

• Reported rates in VAP vary from 22% to 74%
  – Highest rates with a protocol vs. usual care
  – Higher rates if initial therapy appropriate
  – Unclear if diagnostic method has any impact on de-escalation
  – Rates are often higher if cultures are positive vs. negative
  – Lower rates of de-escalation with initial monotherapy/limited spectrum/early onset vs. broad spectrum / multidrug/late onset
  – Lower rates of de-escalation if high frequency of MDR pathogens

• No benefit of de-escalation in an open-label randomized trial. Difficult to understand since more appropriate therapy (76% vs. 48%) but no impact on mortality or LOS.
POSSIBLE REASONS FOR NOT DOING DE-ESCALATION MORE BROADLY

- Want to start narrow and then broaden therapy only if needed
  - An “ecologic” policy that puts patients at risk
- Cultures were negative
  - Still can de-escalate
- Afraid to change a “winning hand”
  - Not justified as a concern
- Unable to reduce number of drugs
  - May need continued combination therapy for Pseudomonal bacteremia, not for non-bacteremic infection
- Unable to reduce spectrum of activity of drugs
  - Occasionally, when certain MDR pathogens are present
- Unable to reduce duration of therapy
  - Rarely, eg. S. aureus bacteremia and/or endocarditis
Why Do We Not De-Escalate More Often?

- 1 Year study of 216 episodes of severe sepsis in 169 patients with broad spectrum B-lactam, alone or combo
- 4 groups: de-escalation (stop or narrow spectrum), escalation, no change, mixed change
- 77% micro data: 44% lung infxn, 38% abdomen
- 43% de-escalation, 36% no change (only 5% missed chance to de-escalate), 10% escalation
- 77 with no change: unable to narrow (46%), no cultures (32%), inconclusive cults (13%), MDR pathogen (4%)
Barriers to Implementing De-Escalation

- 229 ICU patients, de-escalation in 51%, mean 3.8 days
  - No protocol for DE
  - 94% fewer drugs, 6% reduced spectrum, 9.4% stopped
- DE: more if appropriate therapy, less if inappropriate rx, MDR pathogens
- No impact of DE on mortality

<table>
<thead>
<tr>
<th>Variable</th>
<th>Coefficient</th>
<th>Standard error</th>
<th>Chi-squared</th>
<th>P value</th>
<th>Odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>-0.32</td>
<td>0.34</td>
<td>0.9</td>
<td>0.33</td>
<td>0.7 (0.4-1.4)</td>
</tr>
<tr>
<td>Coma</td>
<td>-0.21</td>
<td>0.47</td>
<td>0.2</td>
<td>0.66</td>
<td>0.8 (0.3-2.0)</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>0.24</td>
<td>0.61</td>
<td>0.2</td>
<td>0.68</td>
<td>1.3 (0.4-4.2)</td>
</tr>
<tr>
<td>Previous antibiotic therapy</td>
<td>0.63</td>
<td>0.41</td>
<td>2.3</td>
<td>0.13</td>
<td>1.9 (0.8-4.2)</td>
</tr>
<tr>
<td>Appropriate initial antibiotic</td>
<td>1.08</td>
<td>0.34</td>
<td>9.9</td>
<td>0.002</td>
<td>2.9 (1.5-5.7)</td>
</tr>
<tr>
<td>Narrow-spectrum antibiotic</td>
<td>-4.51</td>
<td>1.04</td>
<td>18.6</td>
<td>&lt;0.001</td>
<td>0.1 (0.0-0.1)</td>
</tr>
<tr>
<td>MDR bacterial infection</td>
<td>-1.41</td>
<td>0.52</td>
<td>7.4</td>
<td>0.006</td>
<td>0.2 (0.1-0.7)</td>
</tr>
</tbody>
</table>

CI, confidence interval; MDR, multidrug resistant.
Using Procalcitonin To Reduce Duration of VAP Therapy

• PRORATA trial: Prospective, multicenter, open label trial of PCT to guide duration of therapy for infection in the ICU
  – 307 PCT with algorithm: <0.25, <0.5, <1.0, >1.0 mcg/L
  – 314 control. Recommended 15 days Rx. for VAP due to P. aeruginosa or if inappropriate initial therapy or immune suppressed

• PCT with similar mortality but more days without antibiotics. Absolute difference of 2.7 days.
Suspicion Of VAP

Collect Lower Respiratory Tract Sample for Culture

Start Empiric Antibiotic Therapy Using Local Protocol Based On Local Microbiologic Data and Resistance Patterns

Days 2-3: Evaluate Culture Data and Clinical Course

Define If There Is Clinical Improvement

YES

Culture +

Consider De-Escalation Using One or All of:
Narrower Spectrum Agent,
Fewer Antimicrobials,
Short Duration of Therapy

NO

Culture -

Consider De-Escalation By Stopping Antibiotics If Findings Resolving

De-Escalation NOT Possible

De-Escalation NOT Possible

Niederman. Semin Respir Crit Care Med. 2006;27:45-50