Antibiotic Prescribing in Severe Sepsis - From Good to Great

Robert G Masterton
NHS Ayrshire & Arran

“Good to Great”
- Antibiotic stewardship
- Maximising existing antibiotic efficacy
  - PK/PD
  - New dosing approaches
    - Increased drug doses
    - Increased duration of administration
    - Continuous infusion

Traditional Treatment Paradigm

Conservative start with ‘workhorse’ antibiotics

Reserve more potent drugs for non-responders

Does initial under treatment matter?

- 612 patients with Gram-negative bacilli bloodstream infections
- Appropriate antibiotic therapy reduced mortality rate by 50% across all severities of underlying disease
- Early appropriate antibiotics reduced frequency of septic shock by 50%

The Effect of the Traditional Approach

Inappropriate therapy (%)

<table>
<thead>
<tr>
<th>Community-acquired infection</th>
<th>Hospital-acquired infection after initial therapy for community-acquired infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>50</td>
<td>40</td>
</tr>
<tr>
<td>40</td>
<td>30</td>
</tr>
<tr>
<td>30</td>
<td>20</td>
</tr>
<tr>
<td>20</td>
<td>10</td>
</tr>
<tr>
<td>10</td>
<td>0</td>
</tr>
</tbody>
</table>

Mortality Impact of Inadequate Therapy

Mortality Impact of Inadequate Therapy

<table>
<thead>
<tr>
<th>Appropriate</th>
<th>Inappropriate</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td>20</td>
<td>80</td>
</tr>
<tr>
<td>40</td>
<td>60</td>
</tr>
<tr>
<td>60</td>
<td>40</td>
</tr>
<tr>
<td>80</td>
<td>20</td>
</tr>
<tr>
<td>100</td>
<td>0</td>
</tr>
</tbody>
</table>

Morbidity Impact of Inadequate Therapy

Impact of appropriate antibiotic therapy on survival

Pathogens associated with inadequate VAP antimicrobial therapy

Delay versus Outcome

Delay versus Outcome
Outcome Predictors in ESBL Enterobacteriaceae Bacteraemia

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall 21-day mortality rate (MR)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MR for patients (89 of 186 [47.6%]) with initial inadequate treated</td>
<td>59.5% versus 18.5%; OR 2.38; 95% CI 1.76 to 3.22; P &lt; 0.001</td>
<td></td>
</tr>
<tr>
<td>Multivariate analysis of MR in inadequate initial antimicrobial therapy</td>
<td>OR 6.28; 95% CI 3.18 to 12.42; P &lt; 0.001</td>
<td></td>
</tr>
<tr>
<td>Multivariate analysis of MR in unidentified primary infection site</td>
<td>(OR 2.69; 95% CI 1.38 to 5.27; P &lt; 0.004)</td>
<td></td>
</tr>
</tbody>
</table>

New Treatment Paradigm

- Hit hard and early with appropriate antibiotic
- Short treatment duration
- De-escalate where possible

The New Treatment Paradigm

- Getting therapy right first time
- Broad-spectrum initial empiric treatment
- Optimise antibiotic dosing and administration using PK/PD principles
- Knowledge of local patterns
- Tailor antibiotic therapy based on microbiological results (de-escalation)
- Correct duration

New Paradigm – recognising the risks!

Risk factors for inadequate treatment of VAP = Multidrug-resistant bacteria (OR = 2.93), polymicrobial infection (OR = 3.67) and late-onset VAP (OR = 2.38; 95% CI 1.76 to 3.22; P < 0.001)

Adequate treatment n=82 Inadequate treatment n=69

New Paradigm – “right” and resistance

Frequency of the appropriateness of empiric-antibiotic therapy (a) and proportion of deaths (b) in relation to the number of antibiotics to which the E. coli isolated from blood cultures was non-susceptible
Mortality in ESBL vs. non-ESBL Enterobacteriaceae bacteraemia

New Paradigm – ESBL Sepsis
Clinical impact of bacteraemia with ESBL-producing Enterobacteriaceae

Mortality in ESBL-producing K. pneumonia

Outcome by Class v. Active Antimicrobial

Carbapenems v. other beta-lactams in severe infections

- Systematic review of ICU RCTs 265 papers, 12 in meta-analysis (four 4GC and eight APP).
- Carbapenems showed significant reduction in all-cause mortality (RR 0.62, 95% CI: 0.41 to 0.95; p=0.03).
- Carbapenems showed significant reduction in withdrawals from adverse events (RR 0.65, 95% CI: 0.45 to 0.96; p=0.03).
- In febrile neutropaenia carbapenems showed significant increase in:
  - clinical response in first 72 h treatment (RR 1.37, 95% CI: 1.09 to 1.74; p=0.008)
  - bacteriologic response (RR 1.73, 95% CI: 1.03 to 2.89; p=0.04).
Definition of De-escalation

“De-escalation of antibiotic therapy can be thought of as a strategy to balance the need to provide adequate initial antibiotic treatment of high-risk patients with the avoidance of unnecessary antibiotic utilization, which promotes resistance.”


What De-escalation means

- Start with broad spectrum appropriate agent
- Stop if infection unlikely
- Change to a narrower spectrum agent
- Use single rather than multiple agents
- Shorten the course of therapy as much as possible


De-escalation in VAP

- Change of therapy was documented in 56.2%
- De-escalation = 31.4% (increasing to 38% if isolates were sensitive)
- De-escalation mortality rate lower than those who continued initial regimen (18% vs 43%; p<0.05)
- Inappropriate antibiotic therapy = 9% of cases and associated with 14.4% excess mortality
- De-escalation lower (p < .05) with nonfermenting Gram-negative bacilli (2.7% vs. 49.3%) and in late-onset pneumonia (12.5% vs. 40.7%)
- When the pathogen remained unknown, half of the patients died and de-escalation was not performed


Guidelines and De-escalation

- ICU imipenem-based regimen
- After D3, therapy based on susceptibility results
- Better empirical cover (81 vs 46%; p<0.01)
- No change in imipenem resistance rates


De-escalation in Practice

- De-escalated (n=88)
- No change (n=245)
- Escalated (n=81)

De-escalation in VAP (Surgical patients with septic shock)

<table>
<thead>
<tr>
<th></th>
<th>De-escalation</th>
<th>No de-escalation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrent pneumonia</td>
<td>27.3%</td>
<td>35.1%</td>
</tr>
<tr>
<td>Overall mortality</td>
<td>33.8%</td>
<td>42.1%</td>
</tr>
</tbody>
</table>

- 138 Patients
- Appropriate initial therapy (AIT) in 93%
- De-escalation in 55% of AIT patients
- Escalation in 8% of AIT patients


Kollef MH. Chest 2006; 129: 1210–1218

De-escalation Dilemmas

- When to de-escalate to a "stop"
  - Day 3 and Microbiology negative
  - No Systemic Inflammatory Response Syndrome (SIRS)
  - White blood cell count and temperature not markedly and increasingly abnormal

- When not to de-escalate and to consider escalation
  - Day 3 and Microbiology negative
  - Patient clinically septic
  - Systemic Inflammatory Response Syndrome (SIRS)
  - Markedly abnormal temperature
  - Markedly abnormal white blood cell count

How to improve de-escalation?

<table>
<thead>
<tr>
<th>Tracheal Aspirate (n = 81)</th>
<th>BAL (n=62)</th>
</tr>
</thead>
<tbody>
<tr>
<td>De-escal (21%)</td>
<td>No De-escal (66%)</td>
</tr>
<tr>
<td>1SD Mortality</td>
<td>5.6%</td>
</tr>
<tr>
<td>2SD Mortality</td>
<td>11.6%</td>
</tr>
<tr>
<td>LOS ICU</td>
<td>17.2 +/- 1.6</td>
</tr>
<tr>
<td>LOS Hospital</td>
<td>23.1 +/- 4.4*</td>
</tr>
</tbody>
</table>

* = p < 0.05

Do you practice ‘de-escalation’ therapy?

1. Yes 82%
2. No 18%

In my unit, most of my colleagues practice de-escalation:

1. True 42%
2. False 58%

Sepsis pathophysiology v. Antibiotic pharmacology

- Increased Cardiac Index
- Leaky Capillaries
- High Serum Concentrations
- Low Serum Concentrations
- End Organ Dysfunction
- Increased clearances
- Decreased clearances
- Increased volume of distribution
- Decreased volume of distribution

Antibiotic dosing in severe sepsis

- Provided:
  - There is acceptance that the ratio of serum antibiotic concentration to MIC has a definite impact on clinical outcome
  - That the exact target values to be reached are known
  - Both the MIC and the serum concentration of an antibiotic can be determined

The dosing of critically ill patients should be adapted in order to achieve target values based on serum antibiotic concentrations and MICs.
**Target Attainment: An Aid to Clinicians**

- **Ensure maximal bacterial killing**
- **Offers another indicator of clinical success**
- **Complements MIC/susceptibility data**

**TA provides insight into the appropriate antibiotic options for empiric therapy.**

**Target Attainment rates for a 2000-subject Monte Carlo simulation of q 8 h dose at steady state.**

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>0.5 h Inf (%)</th>
<th>0.8 h Inf (%)</th>
<th>2.0 h Inf (%)</th>
<th>3.0 h Inf (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>S. marcescens</strong></td>
<td>98.5</td>
<td>98.0</td>
<td>99.4</td>
<td>99.6</td>
</tr>
<tr>
<td>A. baumannii</td>
<td>89.7</td>
<td>91.4</td>
<td>94.1</td>
<td>95.8</td>
</tr>
<tr>
<td>P. aeruginosa</td>
<td>89.4</td>
<td>91.2</td>
<td>94.4</td>
<td>96.7</td>
</tr>
<tr>
<td><strong>S. marcescens</strong></td>
<td>94.5</td>
<td>96.2</td>
<td>98.1</td>
<td>98.9</td>
</tr>
<tr>
<td>A. baumannii</td>
<td>72.7</td>
<td>76.4</td>
<td>83.7</td>
<td>89.2</td>
</tr>
<tr>
<td>P. aeruginosa</td>
<td>72.5</td>
<td>76.0</td>
<td>82.6</td>
<td>87.9</td>
</tr>
</tbody>
</table>

**Prolonged Infusion and Dose - making the best of both worlds**

**Target Attainment for maximum bactericidal effect**

- **Commonly accepted maximum targets are:**
  - Carbapenems: 40% of time >MIC
  - β-Lactams: 50% of time >MIC
  - Quinolones: AUC:MIC ratio >125

**Improving TA by prolonging infusion time**

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>30 min (%)</th>
<th>3 hr (%)</th>
<th>4 hr (%)</th>
<th>Increase (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meropenem 1 g q8h</td>
<td>77.1</td>
<td>82.8</td>
<td>—</td>
<td>+6.7</td>
</tr>
<tr>
<td>2 g q8h</td>
<td>84.1</td>
<td>88.1</td>
<td>—</td>
<td>+4.7</td>
</tr>
<tr>
<td>Pip/tazo 4.5 g q8h</td>
<td>56.4</td>
<td>—</td>
<td>80.7</td>
<td>+24.3</td>
</tr>
</tbody>
</table>

**Calculated probability of TA vs clinical cure and microbiological outcome**

- **Cure rate (%)**
  - Clinical: 92% (Bacteriostatic T>MIC 40%)
  - Microbiological: 83% (Bacteriostatic T>MIC 20%)
- **Predicted response (%)**
  - Clinical: 92% (Bacteriostatic T>MIC 40%)
  - Microbiological: 83% (Bacteriostatic T>MIC 20%)

*The use of Monte Carlo simulation to predict the clinical response of meropenem in complicated skin and skin structure infections is accurate.*

**Target Attainment**

- **TA: Shifting the Paradigm**
  - **Input variables**
    - Microbiology data
    - Pharmacokinetic data
  - **Simulation**
    - Monte Carlo simulation using defined bactericidal target values
  - **Probability calculation**
    - Probability of TARGET ATTAINMENT

- **Drusano G. Personal Communication.**

- **Carbapenems**
  - AUC:MIC ratio >125


**Prolonged infusion - making the most of dose**

Meropenem 1000 mg - Percent target attainment for maximal kill

- 0.5 h infusion
- 1.0 h infusion
- 2.0 h infusion
- 3.0 h infusion

**Distribution of P. aeruginosa MICs to meropenem**

**Beta-lactam Continuous Infusion in Severe Infections**

- 12 evaluable trials
  - 2 fourth generation cephalosporin
  - 4 third generation cephalosporin
  - 1 second generation cephalosporin
  - 3 beta-lactam/BL inhibitor
  - 2 meropenem

- Clinical indications
  - 7 Severe Sepsis/Critically ill
  - 3 VAP
  - 1 intra-abdominal sepsis
  - 1 P. aeruginosa infection

**Beta-lactam Continuous Infusion in Severe Infections**

- Role of continuous infusion beta-lactams unclear.
- Increasing evidence suggests potential benefits.
- Superior C"ss of continuous administration v. C min of bolus dosing translates into better pharmacodynamic target attainment.
- More reliable pharmacokinetic parameters expected from continuous infusion especially in seriously ill patients
- When MIC of pathogen ≥4 mg/L continuous administration provides pharmacodynamic advantages even at lower doses.

**Carbapenem by Infusion**

- Meropenem by continuous infusion (1 g over 360 min every 6 h), v. intermittent infusion (1 g over 30 min every 6 h). (Plus tobramycin; 14 days)
  - Continuous infusion greater clinical cure rate (36 of 42, 86.05%, vs 26 of 39, 65.39%, respectively, with OR 2.03 [95% CI 1.27 to 3.24]; p < 0.001).

**Beta-lactam Continuous Infusion in Severe Infections**

- Meropenem by continuous infusion (1 g over 360 min every 6 h), v. intermittent infusion (1 g over 30 min every 6 h). (Plus tobramycin; 14 days)
  - Continuous infusion greater clinical cure rate (36 of 42, 86.05%, vs 26 of 39, 65.39%, respectively, with OR 2.03 [95% CI 1.27 to 3.24]; p < 0.001).
**Doripenem in Extended Infusion**

- 531 VAP cases treated for 7-14 days
  - doripenem 500 mg q 8 hrs via a 4-hr intravenous infusion
  - imipenem 500 mg q 6 hrs or 1000 mg every 8 hrs via 30- or 60-min intravenous infusions respectively
- Clinically evaluable cure rates = 68.3% doripenem and 64.2% imipenem
- Pseudomonas aeruginosa clinical cure = 80.0% doripenem and 42.9% imipenem
- Microbiological cure was 65.0% doripenem and 37.5% imipenem


**Extended Infusion Meropenem**

Extended infusion meropenem in VAP due to MDR A. baumanii:
- 1g q1h over 1 hour versus 500mg q1h over 3 hours

<table>
<thead>
<tr>
<th></th>
<th>traditional group</th>
<th>infusion group</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 3 % Success</td>
<td>40% (6/15)</td>
<td>33.33% (5/15)</td>
<td>p=0.05</td>
</tr>
<tr>
<td>Day 5 % Success</td>
<td>86.67% (13/15)</td>
<td>93.33% (14/15)</td>
<td>p=0.05</td>
</tr>
<tr>
<td>Day 7 % Success</td>
<td>100% (15/15)</td>
<td>100% (15/15)</td>
<td>p=0.05</td>
</tr>
<tr>
<td>Relapse ratio</td>
<td>6.67% (1/15)</td>
<td>0</td>
<td>p=0.05</td>
</tr>
<tr>
<td>Days of treatment*</td>
<td>5.27±1.95</td>
<td>4.80±1.36</td>
<td>p=0.05</td>
</tr>
<tr>
<td>Meropenem Cost</td>
<td>7115.25±348.84</td>
<td>4685.33±248.26</td>
<td>p=0.01</td>
</tr>
</tbody>
</table>

*Days of treatment = Mean ± 1 Standard Deviation


**Meropenem Infusion in the Critically Ill**

- Critically ill patients with sepsis and without renal dysfunction.
- Continuous infusion > median trough concentrations
  - plasma (intermittent bolus 0 versus infusion 7 mg/L)
  - subcutaneous tissue (0 versus 4 mg/L).


**Meropenem Infusion in the Critically Ill**

Meropenem – best of both worlds

- Optimized two-step infusion therapy (OTIT = 0.25-1 g/0.5 h + 0.25-1 g/4 h t.i.d.) v. prolonged infusion therapy (PIT = 0.5-2 g/4 h t.i.d) and traditional infusion therapy (TIT = 0.5-2 g/0.5 h t.i.d) against Pseudomonas aeruginosa
- Bactericidal effect of OTIT ≥ PIT > TIT.
- TA probabilities of OTIT at MICs of 2-8 mg/L > TIT and 4- and 6-h-PIT


Cost and the paradigm

<table>
<thead>
<tr>
<th>Outcome</th>
<th>OR (95% CI) or ME</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality</td>
<td>3.6 (1.4-9.5)</td>
<td>0.008</td>
</tr>
<tr>
<td>Length of stay</td>
<td>1.56</td>
<td>0.001</td>
</tr>
<tr>
<td>Delay in appropriate therapy</td>
<td>25.1 (10.5-60.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cost of hospitalisation</td>
<td>1.57</td>
<td>0.003</td>
</tr>
</tbody>
</table>

CI: confidence interval; ME: multiplicative effect

$\chi^2=0.035$ for using meropenem


Cost and the paradigm

Economic impact of bacteraemia with ESBL-producing Enterobacteriaceae

- Cost of short-term meropenem treatment: 1 week: £601.65, 10 days: £859.50
- Mean increase in equivalent cost attributable to ESBL production is $9620 (£5288)


Conclusions

- Start broad-spectrum empiric therapy at first suspicion of severe infection: consider the likelihood of antibiotic-resistance and sensitivities within the unit
- De-escalate: as soon as culture results available
- Stop therapy as quickly as possible
- Use antibiotics to their best advantage
  - Using the right dose
  - Using the right route and mechanism of delivery
- Employ every means at your disposal to reduce sepsis