Antibacterial prescription in the ICU – Physiologically sound dosing

Dr. Andrew Udy BHB MB ChB FCICM
Specialist Intensive Care Physician, Department of Intensive Care Medicine, Royal Brisbane & Womens Hospital
Senior Lecturer, Burns, Trauma, and Critical Care Research Center, University of Queensland
Sepsis – An ongoing problem

- Incidence of severe sepsis in adults treated in Australian & NZ ICUs is 0.77 (0.76–0.79) per 1000 of population
- 26.5% died in ICU
- 32.4% died within 28 days
- 37.5% died in hospital

Antibacterial Dosing
Bacterial Susceptibility

Figure 6. Minimum inhibitory concentration (MIC) distribution for 61 tigecycline-treated patients who had sufficient pharmacokinetic data for analysis and who were clinically and microbiologically evaluable, stratified by hospital-acquired bacterial pneumonia (HABP) and ventilator-associated bacterial pneumonia (VABP) status.

From: Ambrose PG. et al. Pharmacokinetic-Pharmacodynamic Considerations in the Design of Hospital-Acquired or Ventilator-Associated Bacterial Pneumonia Studies: Look before You Leap! Clinical Infectious Diseases (2010); 51:Supp 1, S103-10.
Mediators of Sepsis

Cardiovascular Manifestations

Microvascular Considerations

Clinical Interventions

**Initial resuscitation (first 6 hrs)**
- Begin resuscitation immediately in patients with hypotension or elevated serum lactate >4 mmol/L; do not delay pending ICU admission (1C)
- Resuscitation goals (1C)
  - CVP 8–12 mm Hg
  - Mean arterial pressure ≥ 65 mm Hg
  - Urine output ≥0.5 mL·kg⁻¹·hr⁻¹
  - Central venous (superior vena cava) oxygen saturation ≥70% or mixed venous ≥65%
- If venous oxygen saturation target is not achieved (2C)
  - Consider further fluid
  - Transfuse packed red blood cells if required to hematocrit of ≥30% and/or
  - Start dobutamine infusion, maximum 20 µg·kg⁻¹·min⁻¹

**Vasopressors**
- Maintain MAP ≥65 mm Hg (1C)
- Norepinephrine and dopamine centrally administered are the initial vasopressors of choice (1C)
- Epinephrine, phenylephrine, or vasopressin should not be administered as the initial vasopressor in septic shock (2C). Vasopressin 0.03 units/min may be subsequently added to norepinephrine with anticipation of an effect equivalent to norepinephrine alone
- Use epinephrine as the first alternative agent in septic shock when blood pressure is poorly responsive to norepinephrine or dopamine (2B).
- Do not use low-dose dopamine for renal protection (1A)
- In patients requiring vasopressors, insert an arterial catheter as soon as practical (1D)

**Inotropic therapy**
- Use dobutamine in patients with myocardial dysfunction as supported by elevated cardiac filling pressures and low cardiac output (1C)
- Do not increase cardiac index to predetermined supranormal levels (1B)

Getting it right – Saves lives

**Antibiotic therapy**
- Begin intravenous antibiotics as early as possible and always within the first hour of recognizing severe sepsis (1D) and septic shock (1B)
- Broad-spectrum: one or more agents active against likely bacterial/fungal pathogens and with good penetration into presumed source (1B)
- Reassess antimicrobial regimen daily to optimize efficacy, prevent resistance, avoid toxicity, and minimize costs (1C)
- Consider combination therapy in *Pseudomonas* infections (2D)
- Consider combination empiric therapy in neutropenic patients (2D)
- Combination therapy ≤3–5 days and de-escalation following susceptibilities (2D)
- Duration of therapy typically limited to 7–10 days; longer if response is slow or there are undrivable foci of infection or immunologic deficiencies (1D)
- Stop antimicrobial therapy if cause is found to be noninfectious (1D)

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From: Kumar A, et al. Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock* Crit Care Med (2006); 34:1589–1596
Sepsis in ICU

- Bacteria are less susceptible
- The host response is characterised by marked changes in organ function
  - Increased CO / capillary leak / microvascular dysfunction
- This is exacerbated by common clinical interventions – fluids / vasopressors
- Improved outcomes with the ‘right’ antibacterial agent
Basic Pharmacology

► Pharmacokinetics – Concentration - Time
► Pharmacodynamics – Effect - Concentration

- **Volume of distribution (Vd)** = Hypothetical volume of fluid that the total amount of administered drug distributes into, generating a concentration equal to that measured in plasma.
- **Clearance (CL)** = Volume of plasma effectively cleared of the drug per unit time. Total drug clearance is the combination of the clearances for each eliminating organ or tissue.
- **Plasma half-life (T1/2)** = Time required for the plasma concentration to fall by one half.
- **C_{max}** = The maximum concentration measured after one dose. Ideally at the effect site, although commonly measured in plasma.

Antimicrobial PK-PD

Antimicrobial PK-PD

Antimicrobial PK-PD

Drug Resistance

Altered Pharmacokinetics

Volume of Distribution

Hypoalbuminaemia

From: Finfer et al. Effect of baseline serum albumin concentration on outcome of resuscitation with albumin or saline in patients in intensive care units: analysis of data from the saline versus albumin fluid evaluation (SAFE) study. BMJ (2006); 333(7577): 1044
Altered Protein Binding

Assessing Renal Clearance

Augmented Clearances

Augmented Clearances

From: Ambrose PG. et al. Pharmacokinetic-Pharmacodynamic Considerations in the Design of Hospital-Acquired or Ventilator-Associated Bacterial Pneumonia Studies: Look before You Leap! Clinical Infectious Diseases (2010); 51:Supp 1, S103-10.
# Augmented Clearances

**Table 3. Creatinine Clearance Measures**

<table>
<thead>
<tr>
<th>Description</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CrCl on active treatment (maximum), mL/min/1.73 m²</td>
<td>179 (159–198)</td>
</tr>
<tr>
<td>Serum creatinine while on active treatment at peak CrCl, μmol/L</td>
<td>57 (50–64)</td>
</tr>
<tr>
<td>CrCl on active treatment (minimum), mL/min/1.73 m²</td>
<td>113 (95–130)</td>
</tr>
<tr>
<td>Serum creatinine while on active treatment at trough CrCl, μmol/L</td>
<td>73 (63–83)</td>
</tr>
<tr>
<td>CrCl in ICU off active treatment (n = 16), mL/min/1.73 m²</td>
<td>150 (134–167)*</td>
</tr>
<tr>
<td>Serum creatinine in ICU off active treatment, μmol/L</td>
<td>68 (62–73)</td>
</tr>
<tr>
<td>CrCl after discharge (n = 14), mL/min/1.73 m²</td>
<td>111 (91–131)†</td>
</tr>
<tr>
<td>Serum creatinine after discharge, μmol/L</td>
<td>65 (58–72)</td>
</tr>
<tr>
<td>Time from admission to commence active treatment, d</td>
<td>2.3 (1.7–2.8)</td>
</tr>
<tr>
<td>Duration of active treatment, d</td>
<td>7.6 (5.6–9.5)</td>
</tr>
<tr>
<td>Time to maximum CrCl on active treatment, d</td>
<td>4.7 (3.0–6.4)</td>
</tr>
<tr>
<td>Difference (maximum – minimum) CrCl on active treatment, mL/min/1.73 m²</td>
<td>66 (43–89)</td>
</tr>
<tr>
<td>Augmented renal clearance (at least 1 measurement), %</td>
<td>85</td>
</tr>
</tbody>
</table>

ARC and Antimicrobial PK

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Augmented Renal Clearance (ARC)

Patients ‘At Risk’:

- Young patients (age < 60 years)
- Multi-trauma
- Traumatic Brain Injury
- Burns Injury
- Post-operative Patients
- Sepsis (with normal renal function)
- Hematological Malignancy (Febrile Neutropenia)
- Hypoalbuminemia

**Tissue Penetration**

- Effect site -> tissues
- Can be impaired with ‘shock’
- Most PK-PD studies employ plasma concentrations as a surrogate
- More recently -> microdialysis (cutaneous), CSF, ELF (lung), ascitic fluid, urine
- Improved dosing to achieve ‘target concentrations’ at the site of infection
Table 3. Factors affecting elimination of antibacterials in patients receiving continuous renal replacement therapy CRRT

<table>
<thead>
<tr>
<th>Factors</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pharmacokinetic factors</td>
<td></td>
</tr>
<tr>
<td>Residual renal elimination</td>
<td>May be increased in acute renal failure but may be decreased by concomitant hepatic failure</td>
</tr>
<tr>
<td>Nonrenal elimination</td>
<td></td>
</tr>
<tr>
<td>Volume of distribution</td>
<td>Increase in volume of distribution results in need for larger loading dose and reduces efficacy of removal by CRRT</td>
</tr>
<tr>
<td>Protein binding</td>
<td>Only the unbound fraction is removed by CRRT</td>
</tr>
<tr>
<td>CRRT factors</td>
<td></td>
</tr>
<tr>
<td>Mode of CRRT</td>
<td>In clinical practice effluent volume is the most important CRRT variable in determining drug elimination. Effluent volume is dependent on both effluent flow and duration of CRRT</td>
</tr>
<tr>
<td>Dose of CRRT delivered</td>
<td></td>
</tr>
<tr>
<td>Blood flow rate</td>
<td>Within usual clinical limits varying blood flow has little effect on elimination</td>
</tr>
<tr>
<td>Filter material</td>
<td>Sieving coefficient may vary between different filter materials for some antibacterials</td>
</tr>
<tr>
<td>Surface area</td>
<td>This has no direct effect on elimination</td>
</tr>
</tbody>
</table>

Prescribing in the ICU

Prescribing in the ICU

► Team approach (ICU, Pharmacy, ID)
► Regular review of dosing of antibacterials – role of alternative dosing strategies
► Assessment of organ (dys)function
  ▪ Creatinine clearance
► Therapeutic Drug Monitoring
  ▪ Aminoglycosides
  ▪ Glycopeptides
  ▪ β-lactams
Prescribing in the ICU

Common Incorrectly Prescribed Antibiotics

► **CEFTRIAXONE** 1g q12h or q8h
► **GENTAMICIN** 7mg/kg EID
► **MEROPENEM** 1g q8h
► **CIPROFLOXACIN** 400mg q8h
► **VANCOMYCIN** 25-30mg/kg (TBW) LD, 35mg/kg/day MD
Aminoglycosides - EID

- Bailey et al, *CID* 1997;24:786-95
Extended / Continuous Infusion

- 500 mg IV administered over 1 h
- 500 mg IV administered over 4 h

T > MIC

Concentration (µg/mL)

Time (hr)
Continuous Infusions

Summary

► Sepsis is common, and continues to manifest a high mortality rate
► Significant homeostatic alterations -> CO, organ blood flow, capillary dysfunction
► Grossly altered antibacterial PK - therapeutic failure or selection of resistant strains
► Rational dosing must consider such changes
► Future -> extended / continuous infusion
Thank-you