Antibiotics in Critical Care

- What is essential?
- What do we suspect or think is important?
- How do we minimise the risk of adverse events?
What is Essential?

- Always begin intravenous antibiotics within the first hour after severe sepsis and septic shock are recognized.
- Use broad-spectrum agents with good penetration into the presumed site of infection.
- Reassess the antimicrobial regimen daily to optimize efficacy, prevent resistance, avoid toxicity and minimize costs.


- [www.survivingsepsis.org](http://www.survivingsepsis.org)
How well did we do?

Inclusion criteria
- Four month period (Sept 2009 to Jan 2010)
- Level 3 patients at St Thomas’ critical care (30 beds)
- Patients initiated on an antimicrobial

Exclusion
- First dose antimicrobial given before ICU admission
- Gentamicin 80mg IV used for catheter changes

Collation of data
- Carevue (ICIP) notes evaluated
- Time of prescription order and time of administration noted
- Drug prescriptions reviewed
Results

Number of patients = 175
Number of Rx evaluated = 413
After exclusion, number of patients = 164
After exclusion, number of Rx evaluated = 337
• Only 25% of antimicrobial prescriptions administered within 1 hour of prescription order.
The optimal starting dosage

Loading Dose = \( C_t \) (Plasma conc) \( \times \) \( V_d \)

\( V_d \) = volume of distribution

- Capillary leakage and fluid resuscitation > \( V_d \) decrease plasma concentration
- Significant for hydrophilic
- Loading is independent of renal function
Antibiotic Properties to be Considered

Site of infection

- Drug penetration is dependent on the PK properties of antibiotics
- Hydrophilic or lipophilic
- Treatment of deep seated infections
- Penetration of aminoglycosides into lung tissue


PMCID: PMC400530
Classification of antibiotic according to their solubility and pharmacokinetic/pharmacodynamic properties

Hydrophilic antibiotics

- Beta-lactams
  - Penicillins
  - Cephalosporins
  - Carbapenems
  - Monobactams
- Glycopeptides
- Aminoglycosides

- Limited volume of distribution
- Unable to passively diffuse through plasmatic membrane of eukariotic cells
- Inactive against intracellular pathogens
- Eliminated renally as unchanged drug

Lipophilic antibiotics

- Macrolides
- Fluoroquinolones
- Tetracyclines
- Chloramphenicol
- Rifampicin
- Linezolid

- Large volume of distribution
- Free diffuse through plasmatic membrane of eukariotic cells
- Active against intracellular pathogens
- Eliminated by hepatic metabolism
Changing Pathophysiology

SEPSIS

- Increased Cardiac Output
  - Increased CL
    - Low Plasma Concentrations

- Leaky Capillaries &/or altered protein binding
  - Increased Vd

- Normal Organ Function
  - Unchanged Vd
    - Normal Plasma Concentrations

- End Organ Dysfunction (e.g. renal or hepatic)
  - Decreased CL
    - High Plasma Concentrations
Does the dose interval matter?

Concentration dependent antibiotics

- High Cmax/MIC ratio (>10)
Pharmacodynamics of Time Dependent Antibiotics

[Graph showing antibiotic concentration over time for two different dosing regimens: 1g q8h over 30 min and 1g q8h over 3h. The graph illustrates the peak concentration at different time points and the clearance rate towards the MIC level.]
Time Dependent Antimicrobials

• “Achieve the target quickly and maintain it”
• Optimal Time > MIC?
• Increased probability of success with T>MIC at 90 to 100% of the dosing interval.
• ICU - Lower plasma conc and higher MIC
Optimising beta lactams

- Increase frequency, prolonged infusions, continuous infusions.

- Increase the frequency of administration.
  - Monte Carlo simulation study
  - Most relevant Gram-negative bacilli isolated from the ICU
  - Meropenem 500 mg every 6 hours may be equivalent to 1 g every 8 hours
Piperacillin-tazobactam for Pseudomonas aeruginosa infection: clinical implications of an extended-infusion dosing strategy Lodise et al CID 2007; 44: 357-363

Probability of achieving piperacillin concentration in excess of the MIC for 50% of the dosing interval
Piperacillin-tazobactam for Pseudomonas aeruginosa infection: clinical implications of an extended-infusion dosing strategy  Lodise et al

Method

- Retrospective cohort study

- 30-min infusion of 3.375 g every 4 -6 hrs vs 4hr of 3.375g infusion every 8 hours

Results

- 102 extended infusions vs 92 intermittent infusions

- No differences in baseline clinical characteristics

- 14-day mortality rate

- Extended 8.8% vs Intermittent 15.2% but  P= 0.17

- Patients with APACHE II ≥ 17

- Extended 12.2% (n=41) vs. Intermittent et 31.6%(n=38);  P=0.04
Meropenem by continuous versus intermittent infusion in ventilator-associated pneumonia due to gram-negative bacilli - Lorente et al Ann Pharmacother 2006; 40: 219-223

• Method
  
  – Retrospective cohort study
  
  – Meropenem 1g 6 hourly over either 30mins or 6hours

• Results
  
  – No difference in baseline characteristics
  
  – Outcome = clinical cure rate
  
  – Continuous 90%(n=42) vs Intermittent 60% (n=47) P < 0.001
  
  – MIC> 0.50 mg/L (80% vs 29%)
  
  – MIC 0.25 to 0.49 mg/L (100% vs 79%)
Piperacillin-tazobactam /ceftazidime by continuous versus intermittent infusion in ventilator-associated pneumonia due to gram-negative bacilli - Lorente et al

- Ceftazidime  4g /day cont infusion or 2 g BD over 30min versus Pip/taz  4.5g 6 hourly over either 30mins or 6hours

- Ceftazidime results
  - Continuous 90%(n=56) vs Intermittent 52% (n=62) P < 0.001
  - MIC < 2mg/L  (92.190% vs 62%)
  - MIC = 4 mg/L  (90% vs 38%)

- Pip/Taz results
  - Continuous 89 % (n=37) vs Intermittent 56% (n=46) P < 0.001
  - MIC < 4 mg/L  (90% vs 76%)
  - MIC = 8 mg/L  (90% vs 40%)
  - MIC = 16 mg/L (87% vs 17%)

- Positive clinical outcomes was greater among patients with infection due to less susceptible bacteria.
Limitations Lorente et al studies
Clinical cure was decided by a panel of physicians.

- No randomization
- The allocation to treatment group was decided by the treating physician.
- All patients also received 14 days of tobramycin.
- Not clear if all the patients in that time period were included in the trial.
- None of studies showed a significant decrease in overall mortality.
Other considerations

- Meta analysis of the RCTs beta-lactam infusion vs bolus.
  - No difference in clinical cure or reduced mortality.
  - RCTs only recruited patients with low APACHE II scores
  - Higher doses of antibiotic in the bolus groups
- Doripenem licensed as prolonged 4hr infusion for treatment of VAP caused by less susceptible organisms.
Which dose then and for which patient

- Extended interval essential for aminoglycosides
- Vancomycin should probably be given by continuous infusion
- There is probably benefit in administering beta lactams by short or continuous infusions if possible
- Barza and colleagues Single or multiple daily doses of aminoglycosides: a meta analysis BMJ 1996; 312: 338-345
- Roberts and colleagues Pharmacokinetic issues for antibiotics in the critically ill patient Crit Care Med 2009; 37: 840-851
Antibiotic Clearance in Renal Support

- Antibiotic removal by renal support
- Many publications
- Essential informations is the molecular weight of the compound and whether it is protein bound
- Filter or dialysis cut off is usually above 20,000 daltons
- Higher the protein binding then less clearance of free drug
- Renally cleared drugs, generally cleared by renal support

Other considerations

- Low albumin states in sepsis and severe sepsis may increase clearance of free drug
- Higher flux haemofiltration may accelerate clearance
- Paucity of evidence relating to higher flux CVVH
- Consideration has to be given to each individual patient
- Flucloxacillin dosing in S Aureus endocarditis
- Flucloxacillin dosage in same patient who develops seizures
Keep it safe

• Reduce unnecessary exposure to allergens

• Up to 30% of patients may not have clear documentation of allergy. Hatton et al. Allergy documentation in intensive care. Crit Care 2010

• CNS toxicity reduced by slower administration (extended infusion)

• Aminoglycosides - nephrotoxicity, minimised by extended administration

• Oto and Vestibular toxicity - genetic screening?

• Avoid extravasation of vancomycin
Conclusions

- Early administration essential, especially in sepsis or septic shock.
- Optimise the use of current antibiotics, consider each individual patient, needs changes daily in ICU
- Evidence is mounting for prolonged/ continuous infusions of beta-lactam antibiotics.
- But no RCT
- Protect patient from unnecessary harm