Antimicrobial therapy in critical care

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Outline

1. Let’s talk about sepsis
2. PK/PD considerations
3. Selecting an antimicrobial
4. Take home messages
**RECOMMENDATIONS** Sepsis should be defined as life-threatening organ dysfunction caused by a dysregulated host response to infection. For clinical operationalization, organ dysfunction can be represented by an increase in the Sequential [Sepsis-related] Organ Failure Assessment (SOFA) score of 2 points or more, which is associated with an in-hospital mortality greater than 10%. Septic shock should be defined as a subset of sepsis in which particularly profound circulatory, cellular, and metabolic abnormalities are associated with a greater risk of mortality than with sepsis alone. Patients with septic shock can be clinically identified by a vasopressor requirement to maintain a mean arterial pressure of 65 mm Hg or greater and serum lactate level greater than 2 mmol/L (>18 mg/dL) in the absence of hypovolemia. This combination is associated with hospital mortality rates greater than 40%. In out-of-hospital, emergency department, or general hospital ward settings, adult patients with suspected infection can be rapidly identified as being more likely to have poor outcomes typical of sepsis if they have at least 2 of the following clinical criteria that together constitute a new bedside clinical score termed quickSOFA (qSOFA): respiratory rate of 22/min or greater, altered mentation, or systolic blood pressure of 100 mm Hg or less.

Special Communication | CARING FOR THE CRITICALLY ILL PATIENT

The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3)

Mervyn Singer, MD, FRCPE; Clifford S. Deutschman, MD, MS; Christopher Warren Seymour, MD, MSc; Manu Shankar-Hari, MSc, MD, FFICM; Eiji Imai, MD, PhD; Michael Bauer, MD; Rinaldo Bellomo, MD; Gordon R. Bernard, MD; Jean-Daniel Chiche, MD, PhD; Craig M. Coopermonth; Richard S. Hotchkiss, MD; Mitchell M. Levy, MD; John C. Marshall, MD; Gregg S. Martin, MD, MSc; Steven M. Opal, MD; Gordon B. Rubenstein, MD; MG; Tom van der Poll, MD, PhD; Jean-Louis Vincent, MD, PhD, Derek C. Angus, MD, MPH

*JAMA. 2016;315(8):801-810*
RECOMMENDATIONS Sepsis should be defined as life-threatening organ dysfunction caused by a dysregulated host response to infection.

...dysfunction can be represented by an increase in the Sequential [Sepsis-related] Organ Failure Assessment (SOFA) score of 2 points or more.

Septic shock should be defined as a subset of sepsis in which particularly profound circulatory, cellular, and metabolic abnormalities are associated with a greater risk of mortality than with sepsis alone. Patients with septic shock can be clinically identified by a vasopressor requirement to maintain a mean arterial pressure of 65 mm Hg or greater and serum lactate level greater than 2 mmol/L (>18 mg/dL) in the absence of hypovolemia.

have poor outcomes typical of sepsis if they have at least 2 of the following clinical criteria that together constitute a new bedside clinical score termed quickSOFA (qSOFA): respiratory rate of 22/min or greater, altered mentation, or systolic blood pressure of 100 mm Hg or less.
Sepsis – New guidelines

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JAMA. 2016;315(8):801-810
Previous Surviving sepsis campaign

SIRS (need>2)
- Temperature >38 or <36
- RR >20 or PaCO2 <32
- WC >12
- HR >90 BPM

SEPSIS
- SIRS + presumed infection

SEVERE SEPSIS
- Sepsis with organ dysfunction (SBP or MAP <90; INR >1.5 or PTT >60 sec; Bili >34; U/O <0.5/kg/hr; Cr >177 micromole/L; plt <100; SpO2< 90% on RA; lactate >2)

SEPTIC SHOCK
- Sepsis with refractory hypotension (SBP<90 or MAP <70) despite adequate fluid resuscitation

- SIRS is quite non-specific for infection
- 4 of 5 ICU patients without infection have ‘SIRS” criteria
- Fever and other SIRS criteria may be present in other conditions such as pancreatitis and buns
- Elderly patients, malnutrition and immunosuppression may prevent the patient mounting a SIRS response
- SIRS criteria don’t account for changes in WCC and fluctuations in vital signs over time
- Retrospective analysis by Kaukonnen et al (2015) suggested that SIRS criteria lacked specificity and sensitivity for diagnosis severe sepsis and septic shock
PK-PD
Physiology vs PK in critically ill

- **Hyperdynamic**
  - Increased cardiac output
  - Increased clearance
  - Decreased plasma concentrations
- **Altered fluid balance**
  - Third spacing or altered protein binding, or both
  - Increased volume of distribution
  - Decreased plasma concentrations
- **No organ dysfunction**
  - Unchanged volume of distribution and clearance
  - Normal plasma concentrations
- **Renal or hepatic dysfunction, or both**
  - Increased volume of distribution and decreased clearance
  - Increased plasma concentrations
- **Organ support**
  - RRT, or ECMO, or both
  - Increased volume of distribution and possible increased clearance
  - Increased or decreased plasma concentrations

Adapted from Roberts, The Lancet Infection; June 2014 Vol 14
VOLUME OF DISTRIBUTION

The volume into which a drug appears to be distributed with a concentration equal to that of plasma

- **Hydrophilic drugs**
  - Vd consistent with TBW (0.2-0.7 L/kg)

- **Lipophilic drugs**
  - Large Vd (can be variable eg. morphine 3L/kg → amiodarone 70L/kg)
  - Lipophilic drugs have very good distribution throughout body tissue
  - Important for LOADING DOSES
  - Vd is increased with illness severity

\[ \text{Vd (L/kg)} = \frac{\text{Ab (mg/kg)}}{\text{Cp (mg/L)}} \]
Critically ill patients often have ↑ Vd

- Patient’s inability to maintain blood pressure leads to:
  - Fluid boluses to restore MAP
  - Crystalloid (eg. NaCl, glucose) often leads to peripheral oedema
  - Vasopressor therapy
  - Inotropic agents

Fluid loading tends to increase extra- and intra-cellular water thereby ‘diluting’ the drug and increasing Vd → ↓ drug concentrations; ↓ effect
Therefore, increased drug doses (incl loading doses) may be required
Distribution – hydrophilic vs lipophilic

Hydrophilic antibiotics
- Low Vd
- Predominant renal CL
- Low intracellular penetration
- $\uparrow$ Vd
- CL $\uparrow$ or $\downarrow$ dependent on renal function
- β-lactams
- Aminoglycosides
- Glycopeptides
- Linezolid
- Colistin

Lipophilic antibiotics
- High Vd
- Predominant hepatic CL
- Good intracellular penetration
- Vd largely unchanged
- CL $\uparrow$ or $\downarrow$ dependent on hepatic function
- Fluoroquinolones
- Macrolides
- Lincosamides
- Tigecycline

Roberts (Crit Care Med 2009 37(3): 840-51)
RENAL ELIMINATION

- Reduced renal clearance
  - Maintenance dose reduction

- Augmented renal clearance
  - Sepsis, trauma, surgery burns
  - Increased CrCl with normal Cr

- Highly variable and fluctuating function

- Cockroft-Gault not useful in critical illness—use urinary creatinine (6 hr is OK)

- RRT may be required

\[
T_{1/2} = 0.693 \times \frac{V_d}{Cl}
\]
Augmented Renal Clearance

- **CrCl >130mL/min (using urinary creatinine collection)**
- **Often early in ICU admission**

**Process**
- Infection and inflammation
- Fluid administration
- Vasopressors and inotropes

- **As GFR ↑ so does clearance of renally cleared drugs (e.g. hydrophilic drugs)**
  - Potential for underdosing
    - High Cl typically observed in patients with high renal perfusion
    - Eg. Burns, Trauma, Sepsis, young people
    - High ClCr in presence of normal Cr!
Acute Kidney Injury

Common

Associated with higher morbidity and mortality

Difficult to assess in critically ill patients
  ◦ Use urinary creatinine, plasma creatinine and urine output

AKI due to hypoperfusion may require dose increases during polyuric recovery phase even if biomarkers are unchanged

Clearance of beta lactams and glycopeptides are directly correlated to GFR

TDM very useful – again, if available

Dose adjustment in ARF are based on non critical patients so careful consideration needs to be made to dose adjustments

Renal replacement may be required (doses need to be adjusted)
Pharmacodynamics (PD) of antimicrobials

- Concentration-dependent ($C_{\text{max}}/\text{MIC}$)
- Concentration-dependent with time-dependence ($\text{AUC/MIC}$)
- Time-dependent ($f_{T>\text{MIC}}$)
PK/PD of antibiotic classes

Table 1. Pharmacodynamic properties that correlate with efficacy of selected antibiotics

<table>
<thead>
<tr>
<th>Antibiotics</th>
<th>β-lactams</th>
<th>Aminoglycosides</th>
<th>Fluoroquinolones</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Carbapenems</td>
<td>Metronidazole</td>
<td>Aminoglycosides</td>
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<tr>
<td></td>
<td>Linezolid</td>
<td>Fluoroquinolones</td>
<td>Azithromycin</td>
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<tr>
<td></td>
<td>Erythromycin</td>
<td>Telithromycin</td>
<td>Tetracyclines</td>
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<tr>
<td></td>
<td>Clarithromycin</td>
<td>Daptomycin</td>
<td>Glycopeptides</td>
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<tr>
<td></td>
<td>Lincosamides</td>
<td>Quinupristin/dalfopristin</td>
<td>Tigecycline</td>
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<td></td>
<td></td>
<td></td>
<td>Quinupristin/dalfopristin</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Linezolid</td>
</tr>
<tr>
<td>PD kill characteristics</td>
<td>Time-dependent</td>
<td>Concentration-dependent</td>
<td>Concentration-dependent with time-dependence</td>
</tr>
<tr>
<td>Optimal PD parameter</td>
<td>T &gt; MIC</td>
<td>$C_{max} \cdot MIC$</td>
<td>$AUC_{0-24} \cdot MIC$</td>
</tr>
</tbody>
</table>

Pharmacokinetic issues for antibiotics in the critically ill patient

Jason A. Roberts, B Pharm (Honors); Jeffrey Lipman, FJFICM, MD Crit Care Med 2009 Vol. 37, No. 3
Cmax/MIC

- Aim – high ‘peak’ concentration to ensure bacterial kill then large interval between doses to utilise post antibiotic effect (PAE)

Eg Aminoglycosides
- *In vitro* data suggests $C_{\text{max}}$ : MIC ratio of 10
- Human data of 7mg/kg gentamicin dosing achieves ratio
- High Cmin and AUC are associated with toxicity
- Increased Vd in critically ill patients
- Monitoring essential
AUC/MIC

- Aim high peak and use TDM if possible to keep trough above MIC

Eg Fluoroquinolones

- AUC:MIC ratios associated with successful clinical outcome of
  - 125 GN Bacteria
  - 30 GP Bacteria
Time/MIC

- Aim – maintain concentration above MIC for a prolonged period of time

  Eg beta lactams

- Increased frequency of dosing increases time above MIC
  - Extended infusions
  - Continuous infusion
What antimicrobial to choose???
Empirical therapy for sepsis in adults, source not apparent

For immunocompetent adults with community-acquired severe sepsis or septic shock when the source of infection is not apparent, use:

- gentamicin 4 to 7 mg/kg IV, for the first dose; see Appendix 2.2 for further dosing and principles of use [Note 1] [Note 2]

PLUS

- fluclaxacinil 2 g IV, 4-hourly.

For patients hypersensitive to penicillins (excluding immediate hypersensitivity, see Antimicrobial hypersensitivity), replace fluclaxacinil in the above regimen with caphazolin. Use:

- caphazolin 2 g IV, 6-hourly.

For patients with immediate hypersensitivity to penicillins (see Antimicrobial hypersensitivity), replace fluclaxacinil in the above regimen with vancomycin. Use:

- vancomycin 25 to 30 mg/kg IV, as a loading dose; see Appendix 2.3 for further dosing and principles of use.

If patients weight is > 20% more than IBW then use IBW.
Empirical – intra-abdominal source

Peritonitis due to perforated viscus is usually a polymicrobial infection with aerobic and anaerobic bowel flora. Surgery is usually required. For empirical therapy, use:

- **gentamicin IV**; see Appendix 2.2 for dosage and principles of use

  PLUS

- amox/ampicillin 2 g (child: 50 mg/kg up to 2 g) IV, 8-hourly

  PLUS

- metronidazole 500 mg (child: 12.5 mg/kg up to 500 mg) IV, 12-hourly.

If the results of susceptibility testing are not available by 72 hours and empirical IV therapy is still required, cease the gentamicin-containing regimen and use piperacillin-tazobactam or ticarcillin-clavulanate, as below.

If gentamicin is contraindicated or relevant precautions preclude its use (see Box 2.11), as a single preparation, use:

1. **piperacillin-tazobactam 4+0.5 g** (child: 100+12.5 mg/kg up to 4+0.5 g) IV, 8-hourly

OR

2. **ticarcillin-clavulanate 3+0.1 g** (child: 50+1.7 mg/kg up to 3+0.1 g) IV, 6-hourly.
Empirical – community lung (pneumonia) source

1. ceftriaxone 1 g IV, daily [Note 11]

OR

1. ceftazidime 1 g IV, 8-hourly [Note 12]

PLUS (with either of the above regimens)

azithromycin 500 mg IV, daily.

If GN more likely use piperacillin/tazobactam instead of ceftriaxone

The management of severe CAP in tropical regions of Australia is discussed below.

Benzylpenicillin plus gentamicin has been used in combination with azithromycin for severe CAP, and this regimen remains an effective alternative. For more information on the use of gentamicin, see Appendix 2.2.

For patients with immediate hypersensitivity to penicillins (see Antimicrobial hypersensitivity), use:

moxifloxacin 400 mg IV, daily.
Empirical – hospital lung (pneumonia) source

Treatment of hospital-acquired pneumonia (HAP) (Figure 2.3)

HAP (including VAP) [NB1] [NB2]

- Lower risk of MDR organisms
  - Low-risk ward (any duration)
  - OR
  - High-risk ward (e.g., ICU, high-dependency unit, areas with high rates of MDR organisms) for fewer than 5 days

  - Mild or moderate disease
    - Patients without additional risk factors for MDR organisms
      - Mild disease
        - amoxicillin + clavulanate oral or enteral
        - Moderate or severe disease [NB3]
        - ceftriaxone IV
        - OR
        - cefotaxime IV
        (see Mild to moderate disease or Severe disease for doses)
  - Severe disease
    - Patients with additional risk factor(s) for MDR organisms* or severe sepsis or septic shock (see Sepsis definitions)

- Higher risk of MDR organisms
  - High-risk ward (e.g., ICU, high-dependency unit, areas with high rates of MDR organisms) for 5 days or longer

  - All severities
    - Piperacillin + tazobactam IV
      - Always consider local epidemiology and the patient's recent antibiotic exposure and culture results
      - Add initial vancomycin for patients with severe sepsis and/or if there is an increased risk of MRSA
      - Add initial gentamicin for patients with severe sepsis if there is an increased risk of Pseudomonas or other MDR Gram-negative pathogens (see Higher risk of multibug-resistant organisms for doses)
Empirical – urinary source

**Dosage and Principles of Use**

- **Gentamicin IV**: See Appendix 2.2 for dosage and principles of use.
- **PLUS**
  - Amoxyl/ampicillin 2 g IV, 6-hourly.

For patients hypersensitive to penicillins (see *Antimicrobial hypersensitivity*), use gentamicin as a single drug for initial therapy. If gentamicin is contraindicated or relevant precautions preclude its use (see *Box 2.1*), as a single drug, use:

- **1 ceftriaxone 1 g IV, daily**
- OR
- **1 cefotaxime 1 g IV, 8-hourly.**

Critically ill patients (usually those requiring intensive care support) need higher doses of antimicrobials (see *Antibiotic choice and dosing*).

Ceftriaxone and cefotaxime are not effective against *Pseudomonas aeruginosa*, enterococci or organisms that produce extended-spectrum beta-lactamas (ESBL) enzymes.

Urinary tract sepsis caused by multidrug-resistant Gram-negative organisms (eg, ESBL-producing organisms) is an emerging problem, particularly in people who have recently travelled (within several weeks) to areas with a high prevalence of multidrug-resistant Gram-negative organisms (eg, South and East Asia). If infection with these organisms is strongly suspected, patients should receive empirical therapy with meropenem (500 to 1000 mg IV, 8-hourly).
Empirical – complicated skin source (diabetic skin)

1. Piperacillin + tazobactam 4+0.5 g IV, 8-hourly

OR

2. Ticarcillin + clavulanate 3+0.1 g IV, 6-hourly.

For patients hypersensitive to penicillins (see Antimicrobial hypersensitivity), use initially:

1. Ciprofloxacin 400 mg IV, 12-hourly

OR

1. Ciprofloxacin 750 mg orally, 12-hourly

PLUS (with either of the above regimens)

Cilindamycin 900 mg IV, 8-hourly (slow infusion required) [Note 4].

Vancomycin (see Appendix 2, 3) may be required for severe limb or life-threatening infection in addition to the above regimen, based on local epidemiology.

For a simple cellulitis use flucloxacillin
Empirical – necrotising skin

For empirical therapy, if diagnosis is uncertain, until the results of tissue and blood cultures are available, use:

meropenem 1 g (child: 25 mg/kg up to 1 g) IV, 8-hourly

PLUS

vancomycin IV; see Appendix 2.3 for dosage and principles of use

PLUS

clindamycin 600 mg (child: 15 mg/kg up to 600 mg) IV, 8-hourly [Note 7].

Despite limited clinical evidence, clindamycin (or lincomycin) is recommended to reduce bacterial toxin production. The addition of benzylpenicillin is unnecessary. Consider the use of IV immunoglobulin if S. pyogenes necrotising fasciitis is suspected (see below)—seek expert advice.

 Modify therapy based on the results of Gram stain and cultures and susceptibility testing of a surgical deep tissue specimen (see relevant section below). The duration of IV treatment depends on the patient’s response and the ongoing need for surgery, but is usually a minimum of 5 days.
Empirical - Brain

Dexamethasone 10 mg (child: 0.15 mg/kg up to 10 mg) IV, starting before or with the first dose of antibiotic, then 6-hourly for 4 days [Note 3]

PLUS EITHER
1. Ceftriaxone 4 g (child: 100 mg/kg up to 4 g) IV, daily

OR
1. Ceftriaxone 2 g (child: 50 mg/kg up to 2 g) IV, 12-hourly

OR
1. Cefotaxime 2 g (child: 50 mg/kg up to 2 g) IV, 6-hourly.

Add in aciclovir for viral cover

Antibiotics should not be delayed if corticosteroids are not available. If the patient received a dose of benzylpenicillin or ceftriaxone before hospitalisation, do not give corticosteroids because data show that the benefit is lost if given after the first dose of antibiotic.

Listeria monocytogenes is intrinsically resistant to cephalosporins. In immunocompromised patients, adults older than 50 years, patients with a history of hazardous alcohol consumption, or patients who are pregnant or debilitated, to cover Listeria, add the above regimen:

Benzylpenicillin 2.4 g (child: 60 mg/kg up to 2.4 g) IV, 4-hourly.

Add vancomycin if Gram-positive diploccoci are seen on Gram stain, if pneumococcal antigen assay of CSF is positive, or if the patient has known or suspected otitis media or sinusitis, or has been recently treated with a beta lactam. This is to ensure that Streptococcus pneumoniae isolates that have reduced susceptibility or resistance to penicillin and/or cephalosporins have adequate empirical therapy. Also consider vancomycin if Gram-positive coccii resembling staphyloccoci are seen on Gram stain, or if CSF tests are not possible because lumber...
Antimicrobial doses in **critical illness**

- **Cefotaxime**—use an increased dose (ie cefotaxime 2 g [child: 50 mg/kg up to 2 g] IV, 6- or 8-hourly depending on the likely source of infection).
- **Ceftriaxone**—use a 12-hourly dosing regimen (ie ceftriaxone 1 g [child: 25 mg/kg up to 1 g] IV, 12-hourly).
- **Cephalazolin**—use a 6-hourly dosing regimen for adults (ie cephalazolin 2 g IV, 6-hourly).
- **Flucloxacillin**—use a 4-hourly dosing regimen (ie flucloxacillin 2 g [child: 50 mg/kg up to 2 g] IV, 4-hourly).
- **Gentamicin**—see [Critically ill adults with severe sepsis](#).
- **Piperacillin+tazobactam**—consider giving the 6-hourly dose of piperacillin+tazobactam as an extended infusion over 3 to 4 hours (this increases the percentage time above minimum inhibitory concentration [MIC] and may achieve better outcomes).
- **Vancomycin**—give a 25 to 30 mg/kg vancomycin loading dose to adults (see [Principles of vancomycin use](#)). Although pharmacokinetic modelling data suggest a vancomycin loading dose of 30 to 35 mg/kg may be appropriate in critically ill patients in the intensive care unit (who often have augmented renal clearance), clinical data support a dose of 25 mg/kg.
7mg/kg for critically unwell patients (ie sepsis with an increased Vd)

5mg/kg in general patient population (non-septic) will suffice

Surgical prophylaxis is a whole different ballgame.

Current thoughts on vestibular toxicity is that it is unrelated to plasma concentration (ie will happen even with subtherapeutic dosing) and may persist after cessation of treatment

We administer gentamicin in 50mL over 30 mins (regardless of dose)
Renal failure dosing – Use TG

<table>
<thead>
<tr>
<th>Piperacillin + Tazobactam</th>
<th>Dosage Adjustment Based on GFR [NB1] [NB2]</th>
</tr>
</thead>
<tbody>
<tr>
<td>More than 40 mL/min</td>
<td>Normal</td>
</tr>
<tr>
<td>20 to 40 mL/min</td>
<td>4+0.5 g 8-hourly</td>
</tr>
<tr>
<td>Less than 20 mL/min</td>
<td>4+0.5 g 12-hourly</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Doses for Dialysis [NB1] [NB2]</th>
</tr>
</thead>
<tbody>
<tr>
<td>HAEMO</td>
</tr>
<tr>
<td>CAPD</td>
</tr>
<tr>
<td>CRRT</td>
</tr>
</tbody>
</table>
Probably only need to know a few for first doses in sepsis

Ceftriaxone
- covers head (add acyclovir), chest (add azithromycin), urine and abdo (add metro)
- Use 2g as first dose then 1g BD

Piperacillin/tazobactam
- Covers chest (including HAP), abdo, diabetic skin, almost everything
- Use 4.5g load then extended or continuous infusion (QID dosing)

Meropenem
- covers everything! Only use if you’re really worried about a MRO
- Give 2g load then 4g/day (extended or continuous infusion)

Gentamicin
- all gram negatives
- 7mg/kg first dose in sepsis (don’t give more than 3 doses without TDM)

Vancomycin
- all gram positives
- 30-35mg/kg loading dose then 25mg/kg/day in sepsis (as BD or continuous infusion)
- Use TDM
<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Administration</th>
<th>Storage/Additional Info</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flucloxacillin</td>
<td>2g load then total daily dose in 250mL over 24 hours</td>
<td>Only stable at &lt;30 degrees. If leaving the hospital where temp possibly &gt;30 needs solution buffered</td>
</tr>
<tr>
<td>Benzylpenicillin</td>
<td>2.4g load then the total daily dose in 250mL over 24 hours</td>
<td>Needs a buffered solution (with citrate). Made up in pharmacy dept</td>
</tr>
<tr>
<td>Piperacillin/tazobactam</td>
<td>4.5g load then 18g/ 250mL over 24 hours</td>
<td>Stable for &gt;24 hours</td>
</tr>
<tr>
<td>meropenem</td>
<td>1-2g/ 50mL over 8-12 hours</td>
<td>Stable for 12 hours</td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>2g in 50mL over 30 mins</td>
<td>No need for prolonged infusion</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>In 50mL over 30 mins</td>
<td>Prolonged infusion not recommended</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>30-35mg/kg load then total daily dose over 24 hours</td>
<td>Max concentration is 10mg/mL (2.5g in 250mL)</td>
</tr>
</tbody>
</table>
Take home messages

The FIRST dose of antibiotic is **THE MOST IMPORTANT**
- Broad enough to cover likely pathogens
- Big enough to achieve appropriate PK-PD targets
- Volume of distribution is important
- Clearance is NOT important

The subsequent doses of antibiotics needs a bit more thought
- Narrow enough to not cause antimicrobial resistance
- Specific cover to optimise kill
- Individualised dosing based on patient parameters
  - Clearance and Volume of distribution changes
Thanks

If you have any questions or comments please don’t hesitate to contact me:

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