Antibiotic Therapy
What Nurses Should Know

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Basic conditions for an optimal AB therapy

Three conditions:

1. 1st shot of empiric AB therapy as soon as possible but after sampling relevant cultures
2. Empiric therapy covers the causative pathogens
3. Adequate dosing
Basic conditions for optimal antibiotic therapy

1st antibiotic dose without delay

- Start empiric (“blind”) antibiotic therapy asap
- SSC-guidelines: <1 hr in septic shock/severe sepsis
Basic conditions for optimal antibiotic therapy

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  - CAVE: literature data report delays in start AB therapy often from the time of blood culture sampling

Basic conditions for optimal antibiotic therapy

1st antibiotic dose without delay

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Onset (subtle) symptoms of sepsis
Onset hypotension
Blood culture sampling
Start antibiotics

Basic conditions for optimal antibiotic therapy

**Appropriate empiric therapy**

- Empiric therapy should cover causative pathogens (target usual suspects)

- Microbiological results (generally) available after 48 hrs.
  - Appropriate therapy $\rightarrow$ de-escalation (?)
  - Inappropriate therapy $\rightarrow$ odds for survival compromised…
    $\rightarrow$ adjust therapy as soon as possible

Nursing point of interest

(!) Do not postpone start new AB in case of switch

- Culture & antibiogram: MDR bacteria
- Switch to adequate AB therapy
Nursing point of interest

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Nursing point of interest

(!) Do not postpone start new AB in case of switch

- Culture & antibiogram: MDR bacteria
- Switch to adequate AB therapy

Limit the time period of inappropriate therapy

Consider accumulated risk of toxicity!
Basic conditions for optimal antibiotic therapy

**Adequate dosing**

- Maximize of “Bacterial killing capacity”
- Minimize risk of resistance development (caused by underdosing)
- Minimize adverse effects (caused by overdosing)
Pharmacokinetics (PK)

PK ➔ relation between dose and concentrations in body

- Mostly used = plasma concentrations
- Assumption of a fixed balance between plasma- and tissue concentrations
- PK parameters = **clearance** en **volume of distribution (Vd)**
- Secondary PK parameters = $C_{max}$, $C_{min}$, AUC
Pharmacokinetics (PK)

- Concentration
- $C_{\text{max}}$
- AUC
- $C_{\text{min}}$

Time (hours)
Pharmacokinetics (PK)

- PK only describes concentration-time curve
- PK does not provide information on antibiotic activity (i.e. “bacterial killing”)
Pharmacodynamics (PD)

**PD** ➔ relation between AB concentration and effect on pathogen

- **(!) MIC**, minimal inhibitory concentration
- Three classes of antibiotics:
  - Time-dependent
  - Concentration-dependent
  - Concentration-dependent with time-effect
Pharmacodynamics (PD)

- Time-dependent antibiotics

**Objective:**
- Optimizing time period in which concentration $AB > MIC$
- $T>MIC$ (% of dosing interval):
  - $\sim50\%$ for penicillins
  - $\sim60-70\%$ for cephalo’s
  - $\sim40\%$ for carbapenems
- Optimal bacterial killing at $AB$ concentrations = $4-5 \times MIC$
Pharmacodynamics (PD)
- Time-dependent antibiotics

Examples:

- Carbapenems
- Cephalosporins
- Erythromycin
- Linezolid
- Clarithromycin
- Lincosamides
- Penicillines
Pharmacodynamics (PD)

- Concentration-dependent antibiotics

Objective:
- Antibiotic effect determined by $C_{\text{max}}$
- Optimal bacterial killing at AB concentrations = 8-10 x MIC
Pharmacodynamics (PD)

- Concentration-dependent antibiotics

Examples:

- Aminoglycosides
- Daptomycin
- Fluoroquinolones
- Ketolides
- Metronidazole
- Quinupristine/dalfopristin
Mechanisms leading to PK of an antibiotic agent

- Absorption
  - Non-critically ill patients
    - Stable processes
    - PK = predictable
    - Standard doses $\Rightarrow$ desired [AB]

- Distribution

- Metabolism

- Elimination

PK
Mechanisms leading to PK of an antibiotic agent

- Δ Absorption
- Δ Distribution
- Δ Metabolism
- Δ Elimination

Sepsis: pathophysiological alterations

Δ PK response on standard dosing
The effect of pathophysiology on pharmacokinetics in the critically ill patient — Concepts appraised by the example of antimicrobial agents

Critical illness

- Severe infection
- Trauma & burn injury
- Major surgery
- Post-surgical drainage

Organ failure
- Extra-corporeal circuits

SIRS
- Vasodilatation
- ↑cardiac output
- Capillary leak
- ↑renal blood flow

Fluids and vasoactive agents
- Fluid extravasation
- Hypoalbuminemia

- ↑cardiac output
- Fluid extravasation

Hepatic failure
- ↓protein binding
- ↓clearance lipophilic agents
- ↑antimicrobial concentrations hydrophilic agents

Acute kidney injury
- ↓clearance hydrophilic agents
- ↑antimicrobial concentrations lipophilic agents
- ↑antimicrobial concentrations hydrophilic agents

↑renal blood flow

Augmented renal clearance

↑clearance hydrophilic agents

↓antimicrobial concentrations hydrophilic agents
PK of antibiotics in severe sepsis...

- Overdosing and toxicity is possible in context of organ failure

- Plenty of other factors (sometimes in the same patient) might cause underdosing through $\uparrow Vd$ and $\uparrow$ clearance.

- Risk of underdosing (with hydrophilic antibiotics) is a greater threat than risk of overdosing

- Errors in the administration of ABs (might) $\uparrow$ risk of underdosing
Nursing point of interest

(!) **Avoid too slow infusion rate of conc.-dep. AB**

- **Use an infusion pump**

<table>
<thead>
<tr>
<th>Concentration</th>
<th>Time (hours)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>C&lt;sub&gt;max&lt;/sub&gt;/MIC</strong> (optimal if 8-10 x MIC)</td>
<td><strong>T&gt;MIC</strong></td>
</tr>
<tr>
<td>Too long infusion time</td>
<td>Insufficiently high <strong>C&lt;sub&gt;max&lt;/sub&gt;</strong></td>
</tr>
</tbody>
</table>

**MIC**
### Nursing point of interest

(!) Do not increase time interval of time-dep. AB

<table>
<thead>
<tr>
<th>Time</th>
<th>MIC</th>
<th>T&gt;MIC</th>
<th>Danger zone (T&lt;MIC)</th>
</tr>
</thead>
<tbody>
<tr>
<td>09:00</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>17:00</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>01:00</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Time (hours)**

**Concentration**

**MIC**

**Dotted Line**

**T>MIC**
Nursing point of interest

(!) Do not increase time interval of time-dep. AB

Danger zone (T<MIC) ↑↑
- bad bacterial killing
- resistance development

Concentration

T>MIC

09:00 17:00 20:00 01:00 04:00

Time (hours)
Nursing point of interest - Continuous infusion

(!) No time between loading dose and C.I.

-Concentration versus Time (hours)-

08:00 | 16:00 | 00:00

T>MIC

MIC
Nursing point of interest - *Continuous infusion*

(!) No time between loading dose and C.I.

Loading dose

Start continuous infusion immediately after the loading dose
Nursing point of interest - Continuous infusion

(!) No time between loading dose and C.I.

Start continuous infusion immediately after the loading dose

T>MIC = 100%
Nursing point of interest - Continuous infusion

(!) No time between loading dose and C.I.

Loading dose

Start Continuous infusion

T>MIC=100%

BUT...
insufficient bacterial killing:
[AB] < 4-5 x MIC

T>MIC = 100%

08:00 16:00 00:00

Time (hours)
Nursing point of interest - **Continuous infusion**

(!) No time between loading dose and C.I.

**Loading dose**

**Start Continuous infusion**

**T>MIC=0%**!
- No bacterial kill
- Ideal scenario for resistance-development

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**Concentration**

**Time (hours)**

<table>
<thead>
<tr>
<th>08:00</th>
<th>16:00</th>
<th>00:00</th>
</tr>
</thead>
</table>

MIC
Failure to initiate continuous infusion immediately after the loading dose...

- Inform physician
- Await a second intermittent dose to start C.I.
Nursing point of interest - **Continuous infusion**

(!) **CAVE:** stability of solution at room $T^\circ$

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Concentration</th>
<th>Diluent</th>
<th>Stable at room $T^\circ$ (25°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amoxicillin/clavulanate</td>
<td>10 mg/mL</td>
<td>Sterile water, normal saline</td>
<td>4 hrs.</td>
</tr>
<tr>
<td>Meropenem</td>
<td>100</td>
<td>Sterile water</td>
<td>8 – 12 hrs.</td>
</tr>
<tr>
<td>Meropenem</td>
<td>30</td>
<td>Normal saline</td>
<td>12 – 16 hrs.</td>
</tr>
</tbody>
</table>

Mouton JW, Vicks AA. Curr Opin Crit Care 2007
Conclusion – What nurses should know

• Recognize sepsis at an early stage

• Take relevant cultures

• Start 1st dose as soon as possible

• Inappropriate empiric therapy...? → Start targeted AB therapy as soon as possible

• Infuse conc.-dependent ABs with 30-60 min.

• Respect dosing schedule of time-dependent ABs

• Start continuous infusion immediately after bolus dose