OPTIMIZED ANTIBIOTIC THERAPY AND RESISTANCE DEVELOPMENT PREVENTION: PHARMACOLOGICAL AND CLINICAL STRATEGIES

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ANTIBIOTIC USE AND SELECTIVE PRESSURE

Cefazolin 10^6 MSSA 10^6 MRSA 10^6 VRE
Cefoxitin 10^6 MSSA 10^6 MRSA 10^6 VRE
Vancomycin 10^6 MRSA 10^6 MRSA 10^6 VRE

Pre-admission

Day 2 Day 7 Day 21

90% MRSA

WHY DO WE NEED CONTROL OF ANTIBIOTIC RESISTANCE?

THE 10 x '20 INITIATIVE: PURSUING A GLOBAL COMMITMENT TO DEVELOP 10 NEW ANTIBACTERIAL DRUGS BY 2020


THE ANTIBIOTICS MARKET

CURRENT STATUS OF ANTIBIOTIC RESEARCH & DEVELOPMENT

<table>
<thead>
<tr>
<th>Stage</th>
<th>Number of Molecules</th>
</tr>
</thead>
<tbody>
<tr>
<td>Discovery</td>
<td>54</td>
</tr>
<tr>
<td>Preclinical</td>
<td>10</td>
</tr>
<tr>
<td>Phase I</td>
<td>28</td>
</tr>
<tr>
<td>Phase II</td>
<td>9</td>
</tr>
<tr>
<td>Phase III</td>
<td>10</td>
</tr>
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<td>Approval</td>
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</tr>
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</table>

Adapted from Wenzel RP et al. Infect Control Hosp Epidemiol 2008; 29:1013–1018
**PK-PD RELATIONSHIPS**

**BETA-LACTAMS, GLYCOPHOSIDES, OXAZOLIDIONES**

- Time-dependent antibacterial activity

**PK-PD RELATIONSHIPS**

**AMINOGLYCOSIDES, FLUOROQUINOLONES**

- Concentration-dependent antibacterial activity

**HYDROPHILIC ANTIBIOTICS**

- MACROLIDES
- FLUOROQUINOLONES
- TETRACYCLINES
- CHLORAMPHENICOL
- RIFAMPICIN
- OXAZOLIDIONES

**LIPIDIC ANTIBIOTICS**

- BETA-LACTAMS
- PENICILLINS
- CARBAPENEMS
- CEPHALOSPORINS
- MACROLIDES
- FLUOROQUINOLONES
- TETRACYCLINES
- CHLORAMPHENICOL
- RIFAMPICIN
- OXAZOLIDIONES

**LIMITED VOLUME OF DISTRIBUTION**

- BETA-LACTAMS
- PENICILLINS
- CARBAPENEMS
- MACROLIDES
- FLUOROQUINOLONES
- TETRACYCLINES
- CHLORAMPHENICOL
- RIFAMPICIN
- OXAZOLIDIONES

**LARGE VOLUME OF DISTRIBUTION**

- AMINOGLYCOSIDES
- BETA-LACTAMS
- PENICILLINS
- CARBAPENEMS
- MACROLIDES
- FLUOROQUINOLONES
- TETRACYCLINES
- CHLORAMPHENICOL
- RIFAMPICIN
- OXAZOLIDIONES

**PLASMA AND LUNG CONCENTRATIONS OF CEFTAZIDIME ADMINISTERED AS CI TO CRITICALLY ILL PATIENTS WITH SEVERE NOSOCOMIAL PNEUMONIA**

ANTIMICROBIAL THERAPY IN THE CRITICALLY ILL PATIENT: A REVIEW OF THOSE PATHOPHYSIOLOGICAL CONDITIONS RESPONSIBLE FOR HUGE PK VARIABILITY

Pea F, Viale P. Crit Care 2006; 10: 113-129

CONCLUSIONS

• Appropriate dosing of plasma concentrations should be encouraged whenever possible, because these concentrations are difficult to predict in critically ill patients, even when their renal function is estimated using different formulae.

IMIPENEM LEVELS ARE NOT PREDICTABLE IN THE CRITICALLY ILL PATIENT

Belzberg H et al. J Trauma 2004; 56: 111-117

CONCLUSIONS

• Inadequate dosing schedules may lead to suboptimal exposure at the infection site, increasing the risk for therapeutic failure or selection of resistant bacteria.

HYDROPHILIC ANTIBIOTICS

- BETA-LACTAMS
- MACROLIDES
- FLUOROQUINOLONES
- TETRACYCLINES
- OKAZOLIDONES
- PEPAMICINS
- AMINOGLYCOSIDES

LIMITED VOLUME OF DISTRIBUTION
- ELIMINATED WITHOUT CHRONIC INFLAMMATION
- ELIMINATED VIA RENAL METABOLISM

IMPAIRED UPTAKE OF HYDROPHILIC ANTIBIOTICS

• Therefore, TDM of plasma concentrations should be encouraged whenever possible, because these concentrations are difficult to predict in critically ill patients, even when their renal function is estimated using different formulae.
WHICH DRUG SCHEDULE FOR CONCENTRATION-DEPENDENT ANTIMICROBIALS IN THE CRITICALLY ILL PATIENTS?

SHORT COURSE HIGH-DOSAGE APPROACH

HIT HARD!! HIT FAST!!
P. Erlich, Lancet 1913

WHICH DRUG SCHEDULE FOR TIME-DEPENDENT ANTIMICROBIALS IN THE CRITICALLY ILL PATIENTS?

1. MULTIPLE DAILY DOSE
2. MULTIPLE DAILY DOSE + EXTENDED INFUSION
3. CONTINUOUS INFUSION

ACHIEVE THE TARGET QUICKLY AND MAINTAIN IT!!!
INSUFFICIENT BETA-LACTAM CONCENTRATIONS IN THE EARLY PHASE OF SEVERE SEPSIS AND SEPTIC SHOCK

Taccone FS et al. Crit Care 2010; 14:R136

Adequate concentrations of the four drugs, with regard to renal dysfunction:

- Thrombotic drug monitoring is necessary to optimize beta-lactam concentrations as renal or biological variables can predict beta-lactam concentrations in this population.

HIGH RATE OF COADMINISTRATION OF DI- OR TRI-VALENT CATION-CONTAINING COMPOUNDS WITH ORAL FQs: RISK FACTORS AND POTENTIAL IMPLICATIONS


COADMINISTRATION OF ORAL LEVOFLOXACIN WITH AGENTS THAT IMPAIR ITS ABSORPTION: POTENTIAL IMPACT ON EMERGENCE OF RESISTANCE


CASE-CONTROL STUDY N = 46 (32 LFX-R vs 14 LFX-S)

THE EFFECT OF MULTIFACTORIAL, MULTIDISCIPLINARY EDUCATIONAL INTERVENTIONS ON THE APPROPRIATE USE OF TEICOPANIN


THE EDUCATIONAL INTERVENTION:

1. Hospital-wide educational program to be repeated almost twice per each year concerning principles of good antimicrobial usage;
2. Semi-annual collegial discussion of microbiological reports on the incidence of different isolates and of their main resistance patterns;
3. Hospital-wide daily active consultation of the infectious disease specialists;
4. Optimization over time of antimicrobial exposure in each single patient by means of an “active TDM” carried out by the clinical pharmacologists.
THE EFFECT OF MULTIFACETED, MULTIDISCIPLINARY EDUCATIONAL INTERVENTIONS ON THE APPROPRIATE USE OF TEICOPHALIN


COMPARATIVE % OF OPTIMAL LOADING

TREND OF % OF OPTIMAL LOADING IN DIFFERENT HOSPITAL WARDS


The Antimicrobial Therapy Puzzle: Cool! Pharmacokinetic-Pharmacodynamic Relationships Be Helpful in Addressing the Issue of Appropriate Pneumonia Treatment in Critically Ill Patients

INVITED ARTICLES

CLINICAL PHARMACOLOGIST

CLINICAL MICROBIOLOGIST

CLINICAL MICROBIOLOGIST

CLINICAL PHARMACOLOGIST

Clinical Pharmacologist (AMI, EMIC, TMTPE, TMTPO)