Antimicrobial treatment in 2011

Pornpan Koomanachai, MD
Division of Infectious Diseases and Tropical Medicine
Department of Medicine
Faculty of Medicine Siriraj Hospital
Mahidol University
Optimal Antibiotics Administration

- Patient (Host) factors
- Basic principles of Pharmacokinetics & Pharmacodynamics
- Types of Antibiotics
- Drug selection
- Appropriate use; timing and duration
- Organism factors: drug-resistant
Patient (Host) factors
Patient (Host) factors

- advanced age
- chronic and/or severe disease
- polypharmacy
- immunodeficiency
- received prior surgical or medical interventions (i.e., blood products, oncologic, or rheumatologic medications)
Optimal Antibiotics Administration

**Patient (Host) factors**

- The prior use of antibiotic therapy \(\rightarrow\) increased risk of antibiotic-resistant pathogen infection
- More severe of the illness

- extended hospital stay
- frequently of intubation
- parenteral nutrition, or other medical devices (i.e., central venous or urinary catheters)

- Increase the risk of a hospital acquired infection (HAI) with a drug-resistant pathogen
Optimal Antibiotics Administration

- Basic principles of Pharmacokinetics & Pharmacodynamics
- Types of Antibiotics
- Drug selection
Common antibiotic pharmacokinetic and minimal inhibitory concentration (MIC) pharmacodynamic relationships

- Peak (peak/MIC)
- Pharmacodynamic index
Basic principles of Pharmacokinetics & Pharmacodynamics

Ceftazidime vs K. pneumoniae

Levofloxacin vs S. pneumoniae
Basic principles of Pharmacokinetics & Pharmacodynamics

Predictors of Bacterial Eradication: Pharmacokinetic/Pharmacodynamic Profiles

- **Peak/MIC**
  - Aminoglycosides

- **T > MIC**
  - Beta-lactams
  - Clindamycin
  - Erythromycin
  - Linezolid

- **24h-AUC/MIC**
  - Azithromycin
  - Quinolones
  - Vancomycin
Optimal Antibiotics Administration

- **Time-dependent antibiotics**
  - Optimal bacterial kill; maximum amount of time over the MIC
  - Extended or continuous infusions of beta-lactams
Optimal Antibiotics Administration

**Time-dependent**

- **%T>MIC < 50%**
  - More frequent infusion

- **%T>MIC > 50%**
  - Prolonged infusion

- **%T>MIC > 40%**
  - Continuous infusion

- **%T>MIC = 100%**
  - Continuous infusion

- **MIC**
  - 32
  - 8
  - 16
  - 24
Optimal Antibiotics Administration

- **Time-dependent antibiotics**

Several clinical studies:
- Extended infusion vs standard dosing beta-lactams in the acutely ill patient (include meropenem, piperacillin/tazobactam and doripenem)
- The outcome: varied from no difference in clinical cure in the infusion group to a clinically significant enhanced cure rate
Optimal Antibiotics Administration

- **Time-dependent antibiotics**
- **Glycopeptides: Vancomycin**
  - 100 courses of continuous infusion for the treatment of suspected MRSA infections
  - 78% of patients achieved plateau concentrations (>15 mg/L) on Day 1 with minimal risk of toxicity (<35 mg/L)
  - Increased to 85% on Day 2 sustained for the course
  - The lowest concentration; 9.3 mg/L (> MIC for most MRSA)

Guy’s and St Thomas’ NHS Foundation Trust (GSTT)
Concentration-dependent antibiotics

- A high initial concentration is required:
  - Maximum bacterial kill
  - Tissue penetration

- Aminoglycoside once daily dose
Optimal Antibiotics Administration

Loading dose (LD)

The LD = V × Cp
the volume of distribution (V)
the required plasma concentration (Cp)

*Hydrophilic agents: which disperse mainly in water
*Lipophilic agents: greater affinity for adipose tissue
Optimal Antibiotics Administration

**Hydrophilic agents**
- Smaller volume of distribution
- Likely to be renally eliminated unchanged
- Increased clearance in severe sepsis

**Beta lactams**
- Aminoglycosides
- Glycopeptides

**Lipophilic agents**
- Larger volume of distribution
- Likely to be hepatically metabolized
- More likely to penetrate deep tissues

**Fluoroquinolones**
- Macrolides
- Rifampicin
- Linezolid
Optimal Antibiotics Administration

Appropriate use;
Timing and Duration

Timeliness and appropriateness of antibiotic

- Dosage
- route
- duration of administration
Optimal Antibiotics Administration

- Get effective antibiotic selection, right first time

- Base antimicrobial selection, empiric and targeted; local susceptibility patterns

- Use broad-spectrum “but least” antibiotics early

- Optimize the dose and route of administration

- Administer for the shortest possible duration

- Adjust/stop antibiotic to best target the pathogen(s) and remove pressure for resistance development: de-escalation
Optimal Antibiotics Administration

- **Initiation of antibiotic**
  - Within the first hour after diagnosis of severe sepsis and septic shock

- **Systematic Review and Meta-Analysis**
  The Efficacy of Appropriate Empiric Antibiotic Therapy for Sepsis
  - Inappropriate empirical antibiotic treatment is significantly associated with all causes mortality in prospective studies
Optimal Antibiotics Administration

How long should a course of antibiotic therapy last?

- **The Surviving Sepsis Campaign**
  - The duration of therapy should typically be 7–10 days
  - Longer courses may be appropriate if
    - slow clinical response
    - an undrainable focus of infection
    - immunological deficiencies
    - neutropenia
Optimal Antibiotics Administration

How long should a course of antibiotic therapy last?

- **Ventilator-associated pneumonia**
  - Clinical effectiveness was achieved with 8 or 15 d treatment
  - Significant reduction in the emergence of multiresistant pathogens in the shorter course
## Optimal Antibiotics Administration

<table>
<thead>
<tr>
<th>Infection</th>
<th>Minimum duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>VAP</td>
<td>8 days</td>
</tr>
<tr>
<td>Pneumococcal meningitis</td>
<td>7 days</td>
</tr>
<tr>
<td>Pneumococcal pneumonia</td>
<td>5 days</td>
</tr>
<tr>
<td>Empyema/lung abscess</td>
<td>4 - 6 wks</td>
</tr>
<tr>
<td>Endocarditis</td>
<td>4 wks</td>
</tr>
<tr>
<td>Osteomyelitis</td>
<td>4 wks</td>
</tr>
</tbody>
</table>
Organism factors:

- Drug-resistant Gram-Negative Pathogens
- Drug-resistant Gram-Positive Pathogens
MDR bacterial infection

Risk Factors for MDR Pathogens for Both Nosocomial and Community-Acquired Infections

- Antimicrobial therapy in preceding 90 days
- Current hospitalization of 5 days or more
- High frequency of antibiotic resistance in the community or in the specific hospital unit
- Presence of risk factors for health care-associated pneumonia
- Hospitalization for 2 days or more in the preceding 90 days

MDR bacterial infection

Risk Factors for MDR Pathogens for Both Nosocomial and Community-Acquired Infections

- Residence in a nursing home or extended care facility
- Home infusion therapy
- Chronic dialysis within 30 days
- Home wound care
- Family member with multidrug-resistant pathogen
- Immunosuppressive disease and/or therapy

Antibiotics
For
Drug-Resistant GN Infection
Antibiotics For Drug-Resistant GN Infection

- Carbapenem
- Colistin
- Tigecycline
- Combination therapy
# Carbapenem

<table>
<thead>
<tr>
<th></th>
<th>Ertapenem</th>
<th>Imipenem</th>
<th>Meropenem</th>
<th>Doripenem</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>I/C</strong></td>
<td>Community settings intraabdominal or skin and soft tissue infection Out patient ATB Rx</td>
<td>Empirical Rx of serious infections in previously multiple ATBs use Polymicrobial infection Suspected MDR or ESBL producer, Amp C producer GNR MDR <em>P. aeruginosa</em> infection</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>C/I</strong></td>
<td>Relative contraindication to prior hypersensitivity type I to ß lactams</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Dose</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>loading dose</strong></td>
<td>1 g IV</td>
<td>1 g IV (&gt; 1 g, epileptogenic)</td>
<td>2 g IV</td>
<td>500 mg (1 g ?) IV</td>
</tr>
<tr>
<td><strong>maintenance dose</strong></td>
<td>1 g IV once daily</td>
<td>500 mg-1 g IV q 6 h (max 4 g/d)</td>
<td>1-2 g IV q 8 h (max 6 g/d)</td>
<td>500 mg IV q 8 h (1 g IV q 8 h ?)</td>
</tr>
<tr>
<td><strong>prolonged infusion</strong></td>
<td>NA</td>
<td>√ (3 h)</td>
<td>√ (3 h)</td>
<td>√ (3-4 h)</td>
</tr>
<tr>
<td><strong>Renal dose adjustment</strong></td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

# Carbapenem

<table>
<thead>
<tr>
<th></th>
<th>Ertapenem</th>
<th>Imipenem</th>
<th>Meropenem</th>
<th>Doripenem</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Common ADRs</strong></td>
<td>Phlebitis</td>
<td>Phlebitis</td>
<td>Phlebitis</td>
<td>Headache, insomnia</td>
</tr>
<tr>
<td></td>
<td>GI upset</td>
<td>GI upset</td>
<td>GI upset</td>
<td>GI upset</td>
</tr>
<tr>
<td></td>
<td>Rash</td>
<td>Rash</td>
<td>Rash</td>
<td>Elevated liver enz.</td>
</tr>
<tr>
<td></td>
<td>Pruritus</td>
<td>Pruritus</td>
<td>Pruritus</td>
<td>Phlebitis</td>
</tr>
<tr>
<td><strong>Epileptogenicity</strong></td>
<td>Less</td>
<td>0.5-2%</td>
<td>Less</td>
<td>Less</td>
</tr>
<tr>
<td></td>
<td>Risk factors: renal ds, pre-existing CNS ds or infection, Hx of seizure, high dose (≥ 4 g/d)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Special issues</strong></td>
<td>Lowest collateral damage to <em>P. aeruginosa, A. baumannii</em></td>
<td>Intraabdominal infection suspected enterococcal coninfection</td>
<td>US FDA approved for Rx of CNS infection</td>
<td>Similar structure to meropenem</td>
</tr>
<tr>
<td></td>
<td>Resist to imipenem ≠ Resist to meropenem, or doripenem</td>
<td>Resist to meropenem, or doripenem</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>US FDA approved for Rx of CNS infection</td>
<td>Similar structure to meropenem</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>In <em>vitro</em>: MIC90 for <em>P. aeruginosa</em> 2-4 times lower than meropenem, but limited clinical data</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Not substituted to older carbapenems</td>
</tr>
</tbody>
</table>

Optimal Antibiotics Administration

Carbapenems

- For ESBL and AmpC-producing organisms
- BUT! not for
  - Carbapenem-resistant *P. aeruginosa* and *Acinetobacter* sp.
  - Intrinsically carbapenem-resistant *Stenotrophomonas maltophilia* and *E. faecium*
Polymyxin: Colistin

- **Spectrums:**
  - Some GN *Enterobacteriaceaes*, *A. baumannii*, *P. aeruginosa*
  - No activity against GP, most anaerobes

- **Indication**
  Preserved for infection from MDR or pan-DR *A. baumannii*, *P. aeruginosa*, or enterobacteriaceaes

- **Contraindication:**
  polymyxin allergy

Mandell’s Principles and practice of infectious disease 7th 2010
**Colistin**

**Adverse effect**

- Nephrotoxicity (10% - 20%): Acute tubular necrosis
- Neurotoxicity (7%): Dizziness, weakness, facial paresthesia, vertigo, etc.
- Dose dependent & reversible

**Risk factors of nephrotoxicity**

- Previous renal insufficiency
- Duration of treatment
- Concomitant use of other nephrotoxic drugs

Optimal Antibiotics Administration
**Optimal Antibiotics Administration**

**Colistin**

- Key therapeutic options for carbapenem-resistant organisms **P. aeruginosa, A. baumannii** and carbapenemase producing *Enterobacteriaceae*

- **BUT! not for**
  - Organisms inherently resistant to polymyxins include *Serratia* sp., *Proteus* sp., *Stenotrophomonas maltophilia*, *Burkholderia cepacia* and *Flavobacterium* sp.
Colistin: dose and administration

Suggested Dosing of Colistin based on PK/PD

- **Cr. Clearance > 50 ml/min**
  300 mg, then 150 mg q 12 h or 100 mg q 8 h
- **Cr. Clearance 41 – 50 ml/min**
  300 mg, then 150 mg q 12 h or 75 - 100 mg q 8 h
- **Cr. Clearance 31 – 40 ml/min**
  300 mg, then 75 - 100 mg q 12 h
- **Cr. Clearance 21 – 30 ml/min**
  300 mg, then 75 mg q 12 h or 150 mg q 24 h
- **Cr. Clearance 11 – 20 ml/min**
  300 mg, then 100 mg q 24 h

Thamlikitkul V., Koomanachai P, 2011, unpublished data
Tigecycline

- Derived from minocycline, similar to tetracycline
- Very broad spectrum with bacteriostatic activity
  - GP include MRSA, *E. faecalis*, *E. faecium*, and VRE
  - GN include ESBL producing *E. coli*, *Klebsiella* spp.,
    (*A. baumannii*, *Serratia* spp.) *S. maltophilia*
  - Anaerobes, atypical pathogens
  - No activity against *P. aeruginosa*, *Proteus* spp.

- **Contraindication:** hypersensitivity to tetracycline, pregnancy, severe hepatic impairment

- **FDA approved:** cSSSI, cIAI, CAP
Tigecycline

- **Loading dose:** 100 mg IV infusion 30-60 min

- **Maintenance dose:** 50 mg IV q 12 h

- **Hepatic dose adjustment**
  Severe liver impairment or C-P class C: 100 mg IV loading then maintenance dose 25 mg IV q 12 h

- **Common ADR:** GI disturbance

- **Not recommended:** UTI and Bacteremia

Acinetobacter baumannii
## Antibiotics against MDR *A. baumannii*

<table>
<thead>
<tr>
<th>Antibiotics</th>
<th>In vitro activities</th>
<th>Clinical efficacy</th>
<th>Limitation of usage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colistin</td>
<td>✓✓</td>
<td>✓✓</td>
<td>- Nephrotoxicity</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- Renal dysfunction: dose adjustment</td>
</tr>
<tr>
<td>Tigecycline</td>
<td>✓✓</td>
<td>✓</td>
<td>- Low serum concentration</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- Not enough clinical data</td>
</tr>
<tr>
<td>Sulbactam combination</td>
<td>✓✓</td>
<td>✓</td>
<td>- Increasing of resistant</td>
</tr>
<tr>
<td>Fosfomycin</td>
<td>✓</td>
<td>?</td>
<td>- Not enough clinical data</td>
</tr>
</tbody>
</table>
Antibiotics against MDR A. baumannii

Combination therapy

- Insufficient clinical data

- Polymyxins and carbapenems (even in the presence of carbapenem resistance)

- Polymixin and tigecycline

- Polymyxin; in vitro synergism together with or sulbactam/ampicillin, or rifampicin
Colistin in Combination Therapy

- Few comparative studies have analysed.
  - No clinical benefits for combination (colistin plus amikacin or β-lactams) therapy in critically ill patients with severe infections by *P. aeruginosa*

  *Clin Infect Dis 2003;37:e154-60*

- No superiority for the association of meropenem-colistin vs colistin alone

  *Clin Microbiol Infect 2006;12:1227-30*
Colistin in Combination Therapy

- The clinical response in the patients who received colistin alone was 84.8% and in those who received colistin with other antibiotics (aminoglycosides, or carbapenems) was 77.8%.

  *Int J Infect Dis. 2007 Sep;11(5):402-6*

- Good response rate (100% of patients, 26/26) from colistin plus rifampicin (10mg/kg q12h) (No control group, limited number of patients).

  *J Infect 2006;53:274-8*
Aerosolized Colistin

- Adjunct to systemic treatment
- Current published data; too limited to allow determination
- Dosing 75-300 mg/d q 12-24h
- Adverse effect
  - Induce bronchospasm
  - Other minor symptoms: cough, sore throat, chest tightness

Crit Care 2005;9:R53-9
Antibiotics against MDR A. baumannii

- **Direct instillation of antimicrobial agents into the ventricles**
  - Occasionally necessary in patients
  - Infections that are difficult to eradicate
  - The patient is unable to undergo the surgical components of therapy
  - Must use with intravenous antimicrobial agents

<table>
<thead>
<tr>
<th>Antimicrobial Agent</th>
<th>Daily Intrathecal Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vancomycin</td>
<td>5-20 mg</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>1-8 mg</td>
</tr>
<tr>
<td>Tobramycin</td>
<td>5-20 mg</td>
</tr>
<tr>
<td>Amikacin</td>
<td>5-50 mg</td>
</tr>
<tr>
<td>Polymyxin B</td>
<td>5 mg</td>
</tr>
<tr>
<td>Colistin</td>
<td>10 mg</td>
</tr>
<tr>
<td>Teicoplanin</td>
<td>5-40 mg</td>
</tr>
<tr>
<td>Quinupristin/dalfopristin</td>
<td>2-5 mg</td>
</tr>
<tr>
<td>Amphotericin B</td>
<td>0.1-0.5 mg</td>
</tr>
</tbody>
</table>

Antibiotics against MDR *A. baumannii*

**Intrathecal colistin administration**

- Poorly CSF penetrate
  - CSF colistin concentration is 25% of serum levels, and remained > to the MIC

Eur J Clin Microbiol Infect Dis 2002;21:212

- Potentially safe, effective, and treatment option for MDR GNB infection

- Largest series, 51 cases of *A. baumannii* nosocomial meningitis
  - 100% (8/8) of patients treated with intravenous and IT colistin were survived (p = 0.04)

J Antimicrob Chemother 2008;61:908
Antibiotics against MDR A. baumannii

Intrathecal colistin administration

- **Dosing**

  Variable doses ranging from 1.6 to 20 mg/day (q12-48h)


- **Neurotoxicity**

  - Meningeal irritation; most frequent (20%)
  - 33% of patients had to be stop treatment
  - 33% of patients, doses had to be reduced
  - Neurological signs of meningismus with increased cell count in CSF

MDR bacterial infection

Extended-Spectrum \(\beta\)-Lactamases (ESBL)-producing bacteria
Extended-Spectrum $\beta$-Lactamases; ESBL-producing bacteria

- **Hydrolyze**
  - extended-spectrum cephalosporins with an oxyimino side chain
  - oxyimino-monobactam: aztreonam

- Resistance to these antibiotics and related oxyimino-beta lactams
ESBL-producing bacteria

Enterbacteriaceae spp.: ESBL testing?

**Epidemiology**
- Latin America: 44.0%
- Asia/Pacific Rim: 22.4%
- Europe: 13.3%
- North America: 7.5%

**Risk factors**
- Increasing length of hospital or intensive care unit (ICU) stay
- More severity of clinical status
- Insertion of various types of catheter or devices
- Invasive procedures or surgical interventions
- Oxyimino-beta-lactams or fluoroquinolones

_J Antimicrob Chemother 2007;60:1018_  
_J of Hosp Infec 2009: 73;345_
ESBL-producing bacteria

Treatment of ESBL producing gram-negative bacterial infection

<table>
<thead>
<tr>
<th>Antibiotics</th>
<th>Micro activities</th>
<th>Clinical efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbapenem</td>
<td>√√</td>
<td>√√</td>
</tr>
<tr>
<td>Fluoroquinolone</td>
<td>×</td>
<td>×</td>
</tr>
<tr>
<td>Cephalosporin</td>
<td>×</td>
<td>?</td>
</tr>
<tr>
<td>BL/BI</td>
<td>／</td>
<td>／</td>
</tr>
<tr>
<td>Tigecycline</td>
<td>×</td>
<td>／</td>
</tr>
<tr>
<td>Aminoglycoside</td>
<td>／</td>
<td>／</td>
</tr>
<tr>
<td>Colistin</td>
<td>×</td>
<td>／</td>
</tr>
</tbody>
</table>

Cefepime was less effective than imipenem in the clinical studies

- Low serum concentration
- Not enough clinical data
- No clinical data to support
- No clinical data to support

Colistin

Pip/Tazo: One small retrospective study
Antibiotics
For
Drug-Resistant GP Infection
Antibiotics For Drug-Resistant GP Infection

- Vancomycin
- Fosfomycin
- Linezolid
- Daptomycin
- Tigecycline
# Anti-gram positive agents

<table>
<thead>
<tr>
<th>Activity</th>
<th>Vancomycin</th>
<th>Fosfomycin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bactericidal</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Spectrum</th>
<th></th>
<th></th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Indication</th>
<th></th>
<th></th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Precaution</th>
<th></th>
<th></th>
</tr>
</thead>
</table>

- *Vancomycin* activity: Bactericidal
- *Fosfomycin* activity: Bactericidal

- *Vancomycin* spectrum:
  - Gram+ve plus MRSA, PRSP
  - Enterococcus spp. (Increased MIC)

- *Fosfomycin* indication:
  - Community or nosocomial infection caused by GP esp. MRSA, MRCNS, PRSP

- *Fosfomycin* antibiotic-associated colitis (oral)

- *Vancomycin* indication:
  - Community or nosocomial infection caused by GP esp. MRSA, MRCNS, PRSP

- *Vancomycin* alternative to vancomycin

- *Fosfomycin* precaution:
  - Need drug monitoring
  - Patients with unstable renal function (either deteriorating or significantly improving)
  - Prolonged courses of therapy
  - Total trough serum vancomycin concentrations of 15–20 mg/L for bacteremia, endocarditis, osteomyelitis, meningitis, HAP

- *Fosfomycin* 1g has sodium salt 14.5 mEq

- *IV only* Anti-gram positive agents
## Anti-gram positive agents

<table>
<thead>
<tr>
<th></th>
<th>Vancomycin</th>
<th>Fosfomycin</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dose and Administration</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Common ADRs</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nephrotoxicity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Auditory toxicity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Interstitial nephritis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infusion-related reactions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild increased transaminase</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reversible</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Anti-gram positive agents

<table>
<thead>
<tr>
<th></th>
<th>Linezolid</th>
<th>Daptomycin</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Activity</strong></td>
<td>Bacteriostatic</td>
<td>Bactericidal</td>
</tr>
<tr>
<td><strong>Spectrum</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Indication</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Precaution</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Perry CM et al. Drugs 2001;61:525-51  
Sauermann R et al. Pharmacology 2008;81:79–91  
Mandell’s Principles and practice of infectious disease 7th 2010
### Anti-gram positive agents

<table>
<thead>
<tr>
<th>Dose and Administration</th>
<th>Linezolid</th>
<th>Daptomycin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral and IV formulations</td>
<td>Oral bioavailability 100%</td>
<td></td>
</tr>
<tr>
<td>Serious infection</td>
<td>600 mg IV or oral q 12 h</td>
<td></td>
</tr>
<tr>
<td>No renal and hepatic dose adjustment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IV formulation, diluted in 0.9% NaCl only</td>
<td></td>
<td></td>
</tr>
<tr>
<td>S. aureus infection - bacteremia w/ or w/o IE</td>
<td>6 mg/kg IV q 24 h</td>
<td></td>
</tr>
<tr>
<td>Skin/soft tissue infection</td>
<td>4 mg/kg IV q 24 h</td>
<td></td>
</tr>
<tr>
<td>Renal dose adjustment</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Common ADRs</th>
<th>Linezolid</th>
<th>Daptomycin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common ADRs</td>
<td>Diarrhea, headache</td>
<td></td>
</tr>
<tr>
<td>Important ADR:</td>
<td>-</td>
<td>reversible thrombocytopenia (esp. Rx duration ≥ 2 weeks)</td>
</tr>
<tr>
<td>Important ADR:</td>
<td></td>
<td>muscle toxicity, elevated CPK (interval F/U CPK recommended)</td>
</tr>
</tbody>
</table>

Perry CM et al. Drugs 2001;61:525-51
Sauermann R et al. Pharmacology 2008;81:79–91
Mandell’s Principles and practice of infectious disease 7th 2010
MDR bacterial infection

*Enterococcus* spp.
Enterococcal infection

**Risk factors**
- cystoscopy
- cesarean section
- prostatectomy
- transrectal prostatic biopsy
- transjugular intrahepatic portosystemic shunt (TIPS)
- extracorporeal shock wave lithotripsy
- colonoscopy
- fiberoptic sigmoidoscopy
- liver biopsy

**The infection usually originates from**
- The genitourinary or gastrointestinal tract
- Procedures associated with the development of enterococcal endocarditis
- Malignant and inflammatory lesions of the gut and biliary tract may also be the source of endocarditis

*Clin Microbiol Rev 1990; 3:46-65
Medicine (Baltimore) 2007; 86:363-377
Mandell, et al. Principles and Practice of Infectious Diseases, 7th Ed(2010)*
Risk factors for VRE colonization and infection

- Prolonged hospital stays
- Exposure to intensive care units
- Post-transplantation
- Hematologic malignancies
- Exposure to antibiotics
  - Vancomycin
  - The extended-spectrum cephalosporins**
  - Antibiotics with potent activity against anaerobic bacteria
## Antibiotics against *Enterococcus* spp.

<table>
<thead>
<tr>
<th>Antibiotics</th>
<th><em>E. faecalis</em></th>
<th><em>E. faecium</em></th>
<th>VRE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Penicillin</td>
<td>+</td>
<td>+/-</td>
<td>-</td>
</tr>
<tr>
<td>Ampicillin</td>
<td>+</td>
<td>+</td>
<td>+/- (if suscept.)</td>
</tr>
<tr>
<td>Pip/Tazo</td>
<td>+</td>
<td>+/-</td>
<td>-</td>
</tr>
<tr>
<td>Imipenem</td>
<td>+</td>
<td>+/-</td>
<td>-</td>
</tr>
<tr>
<td>Meropenem</td>
<td>+/-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

*Microbiology (2009), 155, 1749-1757*
*Emerg Med Clin N Am 2008; 26:813-834*
*Mandell, et al. Principles and Practice of Infectious Diseases, 7th Ed(2010)*
## Antibiotics against *Enterococcus* spp.

<table>
<thead>
<tr>
<th>Antibiotics</th>
<th><em>E. faecalis</em></th>
<th><em>E. faecium</em></th>
<th>VRE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aminoglycoside</td>
<td>+</td>
<td>+ (gentamicin)</td>
<td>+ (if susceptible)</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Linezolid</td>
<td>+</td>
<td>+</td>
<td>+ (bacteriostatic)</td>
</tr>
<tr>
<td>Daptomycin</td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Tigecycline</td>
<td>+</td>
<td>+</td>
<td>+/- (limited clinical data)</td>
</tr>
</tbody>
</table>

*Microbiology (2009), 155, 1749-1757*
*Emerg Med Clin N Am 2008; 26:813-834*
*Mandell, et al. Principles and Practice of Infectious Diseases, 7th Ed (2010)*
Factors influencing antimicrobial use......

- **Consideration of drugs**
  - Dose and route of administration result in **adequate** drug level **at the site** in sufficient **period**
  - Have bactericidal activity against the pathogenic organism

- **Consideration of organisms**
  - MDR
  - Clinical data evidence

- **Consideration of host and site of infection**
  - **Local factors** at the site
  - **Host** defenses/host factors
  - Adjunctive therapies: remove foreign body, drainage, immunomodulation, etc
Thank You!