Antimicrobial Stewardship: Maximizing Antimicrobial Utilization

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USC School of Pharmacy
Disclosure

I do not have relevant financial relationships with commercial interests.
Objectives

• Describe the key targets of an antimicrobial stewardship program.

• Analyze the potential gaps new technology can fill in your current clinical practice.

• Describe the factors to consider for antibiotic selection for common infectious diseases
Bacteria can develop drug resistance rapidly

https://www.youtube.com/watch?v=plVk4NVIUh8&feature=youtu.be
The Challenge: Multiple Mechanisms of Resistance

1. Production of hydrolytic or modifying enzymes

2. Alteration of targets such that they are no longer susceptible to antibacterial action

3. Modification of target accessibility
   - Permeability barrier
   - Energy-dependent antibiotic efflux pumps

Xian-Zhi et al. Drugs 2004
## Drug class specific mechanisms of resistance

<table>
<thead>
<tr>
<th>Drug</th>
<th>Bacterial target</th>
<th>Mechanism of resistance</th>
</tr>
</thead>
<tbody>
<tr>
<td>β-lactams</td>
<td>Cell wall synthesis (PBPs)</td>
<td>β-lactamases, alteration of PBPs, permeability barrier, active efflux</td>
</tr>
<tr>
<td>Aminoglycosides</td>
<td>Protein synthesis</td>
<td>Aminoglycoside-modifying enzymes, alterations of ribosomes, permeability barrier, active efflux</td>
</tr>
<tr>
<td>Quinolones</td>
<td>DNA synthesis (DNA gyrase, topoisomerase IV)</td>
<td>Alteration of DNA gyrase and topoisomerase IV, active efflux</td>
</tr>
<tr>
<td>Polymyxins</td>
<td>Cell membranes</td>
<td>Alterations of LPS</td>
</tr>
</tbody>
</table>

Xian-Zhi et al. Drugs 2004
Which organisms are affected by overuse?

| Urgent Threat | C. difficile  
Carbapenem-resistant Enterobacteriaceae (CRE)  
Drug-resistant Neisseria gonorrhoeae |
|--------------|---------------------------------------------------|
| Serious Threat | Multidrug-resistant (MDR) Acinetobacter  
Drug-resistant Campylobacter  
Fluconazole-resistant Candida  
Extended Spectrum β-lactamase producing Enterobacteriaceae (ESBL)  
Vancomycin-resistant Enterococcus (VRE)  
MDR Pseudomonas aeruginosa  
Drug-resistant Non-typhoidal Salmonella  
Drug-resistant Shigella  
Methicillin-resistant Staphylococcus aureus (MRSA)  
Drug-resistant Strep pneumoniae  
Drug-resistant tuberculosis |

http://www.cdc.gov/drugresistance/threat-report-2013
Epidemiology of *Staph aureus* Bacteremia

West Coast Rates

The Problem with Gram negatives

- More inherently resistant than Gram-positive
  - Due to cooperation between OM barrier and expression of broad-specificity multidrug efflux pumps
  - Also possess drug-specific efflux pumps which mediate resistance to certain classes of antimicrobials

# CDC: Antibiotic Resistance Threats in the US

<table>
<thead>
<tr>
<th>Urgent Threat</th>
<th>C. difficile</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Carbapenem-resistant Enterobacteriaceae (CRE)</td>
</tr>
<tr>
<td></td>
<td>Drug-resistant Neisseria gonorrhoeae</td>
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<td>Multidrug-resistant (MDR) <em>Acinetobacter</em></td>
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</tr>
<tr>
<td></td>
<td>MDR <em>Pseudomonas aeruginosa</em></td>
</tr>
<tr>
<td></td>
<td>Drug-resistant Non-typhoidal <em>Salmonella</em></td>
</tr>
<tr>
<td></td>
<td>Drug-resistant <em>Shigella</em></td>
</tr>
<tr>
<td></td>
<td>Methicillin-resistant <em>Staphylococcus aureus</em> (MRSA)</td>
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<td></td>
<td>Drug-resistant <em>Strep pneumoniae</em></td>
</tr>
<tr>
<td></td>
<td>Drug-resistant tuberculosis</td>
</tr>
</tbody>
</table>

What can we do?

https://www.ted.com/talks/ramanan_laxminarayan_the_coming_crisis_in_antibiotics
Declining Antibiotic Pipeline
New FDA Approved Drugs

- Oritavancin
- Dalbavancin
- Ceftolozane/tazobactam
- Ceftazidime/avibactam
- Tedizolid
- Bezlotoxumab
- Isavuconazole

Approved Dates:
- Oritavancin: 2015 December
- Dalbavancin: 2014 May
- Ceftolozane/tazobactam: 2015 December
- Ceftazidime/avibactam: 2016 October
- Tedizolid: 2015 February
- Bezlotoxumab: 2016 October
- Isavuconazole: 2015 August
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</tr>
</tbody>
</table>

## Practical Application of Newly approved antibiotics

<table>
<thead>
<tr>
<th>Drug/Combination</th>
<th>FDA Approved Indications</th>
<th>Available dosage forms</th>
<th>What’s special about it?</th>
<th>Cost*</th>
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</thead>
<tbody>
<tr>
<td>Dalbavancin</td>
<td>SSTI, including MRSA</td>
<td>IV</td>
<td>Long acting (only one IV dose needed)</td>
<td>$5,364/course $3,480/course</td>
</tr>
<tr>
<td>Oritavancin</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tedizolid</td>
<td>SSTI, including MRSA</td>
<td>IV/PO</td>
<td>Once daily dosing, less toxicity compared to linezolid?</td>
<td>PO: $386/day</td>
</tr>
<tr>
<td>Ceftolozane/tazobactam</td>
<td>Complicated UTI/_intra-abdominal infection</td>
<td>IV</td>
<td>Activity against MDR gram negative organisms (CRE- Ceftaz/avi)</td>
<td>$300 $855</td>
</tr>
<tr>
<td>Ceftazidime/avibactam</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Isavuconazole</td>
<td>Invasive Aspergillosis, mucormycosis</td>
<td>IV/PO</td>
<td>Less drug interactions, toxicity</td>
<td>PO: $192/day IV: $327/day</td>
</tr>
<tr>
<td>Bezlotoxumab</td>
<td>Adjunct therapy for <em>C. difficile</em> infection</td>
<td>IV</td>
<td>Monoclonal antibody against toxin B</td>
<td>$4560</td>
</tr>
</tbody>
</table>

*AWP Pricing

*Vancomycin (IV): $150/course

*Meropenem: $50

*Colistin: $70
Primary Goal of ASP

Goal: optimize the utilization of antimicrobial agents in order to improve clinical outcome while minimizing unintended consequences:

- Selection of pathogenic organisms (*C. difficile*)
- Toxicities
- Emergence of resistant pathogens

Unintended Consequences: Collateral Damage

“Collateral Damage”: ecological adverse effects of antibiotic therapy; selection of drug-resistant organisms and the unwanted development of colonization or infection with MDR organisms

Patient Level

• Antibiotics cause severe disruption of gut microbiota
  • Decrease in taxonomic richness and diversity → metabolic activity and products
  • Within 4 weeks after withdrawal of abx, microbiota may return to overall composition similar to what it was pre-exposure
  • Decrease in “colonization resistance” → increase risk for colonization with *C difficile* spores

Institution Level

• Increasing rates of ESBL, CRE, MDR gram negative organisms on Antibiogram

GUT Trivia

How many species of bacteria live in your gut?

A. 100 
B. 1,000 
C. 10,000 
D. 100,000 
E. 1 million
What concentration of organisms can be found in the small intestine?

A. It depends
B. $10^2$
C. $10^4$
D. $10^6$
E. $10^8$
F. $10^{10}$
In the colon?

A. $10^2$
B. $10^5$
C. $10^7$
D. $>10^{11}$
Healthy Adults have Colonization Resistance

• Mechanism where intestinal microflora protects itself against incursion by new, potentially harmful bugs
  • Protects healthy adults from *C difficile* colonization and disease
  • Protection lost by disease states (inflammatory bowel disease) or other disruption (antibiotics, chemotherapy)
Limiting Overexposure to Antibiotics

ASP Targets

For every patient
• Right drug, right time, right duration, right disease state
• De-escalation

Institution/Health System level
• Utilizing resistance concepts
• Minimizing collateral damage
• Maximizing PK of antibiotics
• Improving procedures to prevent adverse events

*Targets must be tailored to the institution’s needs*
Can resistance be reversed?

Interventional Campaign to Limit FQ Prescribing at a 525-bed community teaching hospital in Los Angeles County

• Why is *Pseudomonas aeruginosa (Psa)* such a problem?
  • Rates of mortality up to 60%
  • Economic burden: more ICU admission, longer LOS

• Managing Psa infections is clinically challenging due to its ability to easily acquire resistance
  • Fluoroquinolone (FQ) resistant *Psa* are often multi-drug resistant
  • MDR *Psa* infections associated with higher mortality rates

The Problem Identified...

- FQ susceptibility to Psa was 43%
  - Many were cross resistant with other abx classes
- FQ-R Psa infections → ↑ LOS by 5 days, 3x ↑ for mortality

1 year Campaign to Limit Levofloxacin Use

• “Consider beta lactams as first line therapy…”
• “misconception of FQ being more potent than beta lactams…”
• “negative consequences of FQ overuse…”

• Education and real-time feedback to prescribers provided over 1 year period
  • One year later, levofloxacin was removed from the formulary

Improved Outcomes

Post-intervention data: 30% decrease in empiric FQ use

• Improved clinical outcomes
  • Decreased in length of stay by 10d!
  • Decreased in mortality by 50%

• Improved resistance pattern
  • Increased FQ susceptibility (2016-76% susceptible)

Methods to Cut Unnecessary Exposure
Target: Cutting Unnecessary Exposure

- Up to 50% of antibiotic use in hospitals are unnecessary or inappropriate
- In order to improve appropriate antibiotic prescription
  - Accurate diagnosis
  - Timely identification and resistance pattern of infecting organism
  - Patient characteristics: comorbidities, age, etc.
- Delay of administration of effective antibiotic therapy have been shown to significantly impact morbidity and mortality (OR 1.88, 95% CI 1.29-2.72)
- We need a sensitive and specific tool to increase effectiveness of ASP

New Technology- “Rapid Diagnostics”

• Improved patient outcomes
  • Decrease hospital length of stay
  • Decrease ICU stay
  • Decreased mortality
  • Decrease unnecessary antibiotic exposure

• Improve identification of previous methods that had low sensitivity/specificity
  • C. difficile
  • TB

Rapid Diagnostics shortens the time to organism identification
Most common infectious diseases seen in outpatient and inpatient visits

- Most frequent principal illness-related reason for visit: cough
- 7th leading primary diagnosis groups for office visits in the US in 2013: acute upper respiratory infection, excluding pharyngitis
- Infectious and parasitic disease is the most frequent primary diagnosis of ED visits in 2013
  - Acute upper respiratory tract infections
  - Cellulitis and abscess
  - UTI
  - Otitis media

<table>
<thead>
<tr>
<th>Method</th>
<th>Types detected</th>
<th>Acceptable Specimens</th>
<th>Test Time</th>
<th>Sensitivity/specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rapid Flu Diagnostic tests (antigen)</td>
<td>A and B</td>
<td>NP, nasal, throat swab</td>
<td>&lt;15 min</td>
<td>50-70% / 90-95%</td>
</tr>
<tr>
<td>Rapid Molecular Assay (nucleic acid detection)</td>
<td>A and B</td>
<td>NP, nasal swab</td>
<td>&lt;20 min</td>
<td>97- 100% / 95-98%</td>
</tr>
<tr>
<td>Immunofluorescence staining</td>
<td>A and B</td>
<td>NP, bronchial wash, nasal or ET aspirate</td>
<td>1-4 hours</td>
<td></td>
</tr>
<tr>
<td>RT-PCR</td>
<td>A and B</td>
<td>NP, throat , swab, NP or bronchial wash, nasal or ET aspirate, sputum</td>
<td>1-8 hours, varies by assay</td>
<td></td>
</tr>
<tr>
<td>Rapid cell culture</td>
<td>A and B</td>
<td>NP, throat swab, NP or bronchial wash, nasal or ET aspirate, sputum</td>
<td>1-3 days</td>
<td></td>
</tr>
</tbody>
</table>

Group A Strep Pharyngitis

- Rapid Antigen Detection Test (RADT)- high specificity 95%, but sensitivity 70-90%
- Throat culture – gold standard 90-95% sensitive
- Neither test accurately differentiate acutely infected persons from asymptomatic streptococcal carriers with intercurrent viral pharyngitis
- In children and adolescents, negative RADT test → should perform throat culture for confirmation
- In adults, negative RADT test → not necessary to do throat culture
- Testing not recommended
  - If clinical symptoms strongly suggest viral etiology (cough, rhinorrhea, hoarseness, oral ulcers)
  - If <3 yo, as acute rheumatic fever is rare in this age group
- Testing or empiric treatment of asymptomatic household contacts not recommended

Is it MRSA or not?

Alere PBP2a Test

- Sensitivity 98.1%; Specificity 98.8%
- Results in 6 min after identification of *S. aureus*

Verigene Gram-Positive Blood Culture Test

- Sensitivity 92.6-100%; Specificity 95.4-100%
- Results in 2.5 hr after culture positivity
Prior to Availability of Susceptibilities
Sample Culture Report - Verigene

**BLOOD CULTURE**
- Specimen: Blood
- Special Requests: Left Hand
- Gram Stain: Anaerobic bottle: Gram positive cocci in clusters
  Called result(s) to, and read back by Arlene
  126071 4TH @ 0636 06/22/2015
  Aerobic bottle: Gram positive cocci in clusters
  Staphylococcus aureus DETECTED by Verigene nucleic acid test.
  (mecA) NOT detected by Verigene nucleic acid test.
  Verigene rapid molecular assay tests for the following organisms:
  Staphylococcus species, Staphylococcus aureus, Staphylococcus
  epidermidis, Staphylococcus lugdunensis, Enterococcus faecalis,
  Enterococcus faecium, Streptococcus species, Streptococcus pneumoniae,
  Streptococcus pyogenes, Streptococcusagalactiae, Streptococcus anginosus
  group and Listeria species.
  Emailed report to Pharmacy 1345 6/22/15
  Staphylococcus aureus
  2 of 2 sets positive.
  Unless otherwise specified, performed at:
  Genzyme Mass Lab 0636 Middle St 5th Fl.

**Vancomycin → Oxacillin or Cefazolin**
Staphylococcus aureus Isolated from Aerobic Blood Bottle

Oxacillin 

This isolate has been shown to be a beta-lactamase producing strain. Please note that beta-lactamase positive Staphylococci are resistant to penicillin, amino-, carboxy-, and ureidopenicillins.

Critical Value called to:
Location: 4A
Date & Time: 02/22/17 22:35 LT
Result: Gram positive cocci in clusters
Read Back? (Y/N): Y

Anaerobic Blood Bottle - No Growth at 5 Days

Vancomycin $\rightarrow$ Oxacillin or Cefazolin
Now you have the diagnosis and decide to treat...

*Which antibiotic to choose?*
Antibiotic Selection

Factors to consider

• Pharmacokinetics/Pharmacodynamics
• Empiric therapy vs directed therapy
  • Know the local antibiogram
  • Does MIC matter?
• Known clinical efficacy of drug to treat bug
• Toxicity Risk
• Collateral Damage
• Drug Allergies
## Know the local antibiogram

**LAC-USC Medical Center**  
**Jan 2016-Dec 2016**  
**Reported as % susceptible**

<table>
<thead>
<tr>
<th></th>
<th># of isolates</th>
<th>Ampicillin</th>
<th>Clindamycin</th>
<th>Ceftriaxone</th>
<th>Cefotaxime</th>
<th>Daptomycin</th>
<th>Erythromycin</th>
<th>Gentamicin syner.</th>
<th>Levofloxacin</th>
<th>Linezolid</th>
<th>Oxacillin</th>
<th>Penicillin</th>
<th>TMP/SMX</th>
<th>Tetracycline</th>
<th>Vancomycin</th>
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</thead>
<tbody>
<tr>
<td>MRSA</td>
<td>656</td>
<td>-</td>
<td>71</td>
<td>-</td>
<td>-</td>
<td>79()</td>
<td>-</td>
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<td>100</td>
<td>-</td>
<td>-</td>
<td>89</td>
<td>93</td>
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<tr>
<td>MSSA</td>
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<td>74</td>
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<td>90</td>
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<td>22</td>
<td>98</td>
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<tr>
<td>Vancomycin susceptible E faecium</td>
<td>58</td>
<td>72</td>
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<td>21</td>
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<td>-</td>
<td>67</td>
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<td>Vancomycin susceptible E faecalis</td>
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<td>99</td>
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<td>-</td>
<td>-</td>
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<td>VRE faecium</td>
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<td>Streptococcus pneumoniae</td>
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<td>94()*</td>
<td>99()*</td>
<td>82</td>
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<td>69()</td>
<td>73</td>
<td>79</td>
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**Rate of MRSA 34%; VRE faecalis 1.2%; VRE faecium 49%**
<table>
<thead>
<tr>
<th></th>
<th># of isolates</th>
<th>Ampicillin</th>
<th>Amp/sulbact</th>
<th>Cefoxitin</th>
<th>Cefepime</th>
<th>Ceftriaxone</th>
<th>Meropenem</th>
<th>Gentamicin</th>
<th>Ciprofloxacin</th>
<th>TMP/SMX</th>
<th>Pip/tazo</th>
<th>Nitrofur.</th>
<th>Fosfomycin</th>
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<tbody>
<tr>
<td>Acinetobacter baumanii</td>
<td>49</td>
<td>-</td>
<td>96</td>
<td>-</td>
<td>90</td>
<td>12</td>
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<td>88</td>
<td>94</td>
<td>82</td>
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<tr>
<td>Enterobacter cloacae</td>
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<td>96</td>
<td>78</td>
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<td>Non-ESBL E coli</td>
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<td>97</td>
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<td>Proteus mirabilis</td>
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<td>Pseudomonas aeruginosa</td>
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<td>87</td>
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<td>96</td>
<td>100</td>
<td>50</td>
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</tbody>
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Rate of ESBL E coli 25%; ESBL Kleb pneumoniae 9%; CRE E coli 2 isolates; CRE Kleb pneumoniae 7 isolates

**URINE ISOLATES ONLY**

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<th>Ampicillin</th>
<th>Amp/sulbact</th>
<th>Cefoxitin</th>
<th>Cefepime</th>
<th>Ceftriaxone</th>
<th>Meropenem</th>
<th>Gentamicin</th>
<th>Ciprofloxacin</th>
<th>TMP/SMX</th>
<th>Pip/tazo</th>
<th>Nitrofur.</th>
<th>Fosfomycin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-ESBL E coli</td>
<td>2975</td>
<td>44</td>
<td>54</td>
<td>93</td>
<td>100</td>
<td>99</td>
<td>100</td>
<td>90</td>
<td>75</td>
<td>62</td>
<td>96</td>
<td>97</td>
<td>-</td>
</tr>
<tr>
<td>ESBL E coli</td>
<td>644</td>
<td>-</td>
<td>-</td>
<td>70</td>
<td>-</td>
<td>-</td>
<td>99</td>
<td>48</td>
<td>16</td>
<td>35</td>
<td>88</td>
<td>86</td>
<td>94</td>
</tr>
<tr>
<td>Non-ESBL Kleb pneumoniae</td>
<td>494</td>
<td>-</td>
<td>83</td>
<td>93</td>
<td>99</td>
<td>99</td>
<td>100</td>
<td>97</td>
<td>93</td>
<td>89</td>
<td>95</td>
<td>53</td>
<td>-</td>
</tr>
<tr>
<td>ESBL Kleb pneumoniae</td>
<td>81</td>
<td>-</td>
<td>-</td>
<td>88</td>
<td>-</td>
<td>-</td>
<td>98</td>
<td>40</td>
<td>41</td>
<td>20</td>
<td>78</td>
<td>30</td>
<td>-</td>
</tr>
<tr>
<td>Pseudomonas aeruginosa</td>
<td>229</td>
<td>-</td>
<td>-</td>
<td>94</td>
<td>95</td>
<td>90</td>
<td>81</td>
<td>-</td>
<td>90</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Rate of ESBL E coli 18%; ESBL Kleb pneumoniae 14%; CRE E coli 5 isolates; CRE Kleb pneumoniae 8 isolates
How does PK/PD factor into antibiotic selection?

- Antibiotic therapy sometimes fails to cure infections caused by apparently susceptible strains of bacteria

<table>
<thead>
<tr>
<th>Host-related factors</th>
<th>Infection site-related factors</th>
<th>Bacteria-related factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Altered pharmacokinetics</td>
<td>• Low pH</td>
<td>• High inoculum</td>
</tr>
<tr>
<td>• Inadequate delivery of antibiotic to infection site</td>
<td>• Low oxygen tension</td>
<td>• Stationary-phase growth</td>
</tr>
<tr>
<td>• Protein binding</td>
<td>• High conc of cations</td>
<td>• Undetected resistance mechanisms</td>
</tr>
<tr>
<td>• Immune deficiency</td>
<td></td>
<td>• High spontaneous mutation frequency</td>
</tr>
</tbody>
</table>

Dose optimization
Pharmacokinetics/Pharmacodynamics

Antimicrobial Pharmacokinetics

What to consider:

• Bioavailability of PO drugs

• Protein Binding of drugs: free unbound drug can have effect

• Route of drug elimination
  • Changing clinical condition such as organ damage or critical illness can affect rate of drug elimination

• Site of infection: Ability of antibiotic to reach the targeted tissue; ability to maintain adequate concentrations

## Pharmacokinetic considerations by infection site

<table>
<thead>
<tr>
<th>Infection Site</th>
<th>Pharmacokinetic Alteration</th>
<th>Potential Change to Dosing Regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood</td>
<td>Expanded Vd, enhanced CL</td>
<td>Provision of LD, increase frequency</td>
</tr>
<tr>
<td>Lung</td>
<td>Impaired permeability</td>
<td>Increase dose</td>
</tr>
<tr>
<td>Soft tissue</td>
<td>Contingent on body composition, comorbidities</td>
<td>Increase dose in obesity</td>
</tr>
<tr>
<td>Bone</td>
<td>Impaired permeability</td>
<td>Increase dose, duration of therapy</td>
</tr>
<tr>
<td>CNS</td>
<td>Impaired permeability</td>
<td>Maximal dose</td>
</tr>
</tbody>
</table>

Pharmacodynamic Considerations

• Antibiotic PD is the impact of the antibiotic on a targeted pathogen
• Complex relationship and affiliated with:
  • Susceptibility of pathogen to a given antibiotic - MIC
• Delivering an effective dose is more complex than simply giving dose found to be effective in clinical trials

Boils down to 3 PD targets

# Pharmacodynamics

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Concentration dependent killing</th>
<th>Time dependent killing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluoroquinolones</td>
<td></td>
<td>β-lactam antibiotics</td>
</tr>
<tr>
<td>Aminoglycosides</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metronidazole</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Goal of Regimen</th>
<th>Peak drug concentration</th>
<th>Maximize exposure time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Post antibiotic effect</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Parameters Correlating with Clinical Efficacy</th>
<th>C&lt;sub&gt;peak&lt;/sub&gt;/MIC, AUC/MIC</th>
<th>Time &gt; MIC</th>
</tr>
</thead>
</table>
Clinical applications of PD

• Knowledge of PDs of \( \beta \)-lactams can affect:
  • Susceptibility and resistance breakpoints
  • Select from multiple drugs which one are best for certain organisms
    • \( S.\ pneumoniae \): (PO) amoxicillin>cefuroxime>cefpodoxime
    • \( H.\ influenzae \): (PO) cefpodoxime>cefixime

• In critically ill patients, an extended infusion time for \( \beta \)-lactams can be used to increase the time the drug concentration is above the MIC

• Extended infusion used for \( \beta \)-lactams: carbapenems, zosyn, ceftazidime, cefepime
  • Decreased mortality rates in critically ill patients
  • Increased clinical cure rates

PK/PD considerations to minimize emergence of resistance

- Relation of PK/PD is complex and driven by MIC
  - MIC affected by inherent and acquired resistance and mutation frequency
  - Mechanical factors (biofilm, inoculum effects, stationary growth phase) can affect PD attainment
- Goal: achieve optimal drug exposure
- Optimal PD targets for resistance prevention are 2-4x higher than PD targets for clinical success
- High drug concentration needed:
  - For chromosomal resistance, suboptimum treatment might allow outgrowth of resistance pathogens with more costly and less efficient resistance mutations, which could lead to fully resistant organisms.
  - Acquisition of plasmid-borne resistance is facilitated by suboptimum treatment because low antimicrobial conc often have only bacteriostatic effects.
# Interpretation of MIC values on a C&S report

## Blood Culture Report

<table>
<thead>
<tr>
<th>+ <em>Staph aureus</em></th>
<th>Interpretation</th>
<th>MIC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clindamycin</td>
<td>≤0.5</td>
<td>S (D-Test Positive)</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>≥8</td>
<td>R</td>
</tr>
<tr>
<td>Oxacillin</td>
<td>≤4</td>
<td>S</td>
</tr>
<tr>
<td>Penicillin</td>
<td>≥0.5</td>
<td>R</td>
</tr>
<tr>
<td>Rifampin</td>
<td>≤0.5</td>
<td>S</td>
</tr>
<tr>
<td>Tetracycline</td>
<td>≤1</td>
<td>S</td>
</tr>
<tr>
<td>SMX/TMP</td>
<td>≤10</td>
<td>S</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>1</td>
<td>S</td>
</tr>
</tbody>
</table>
Urine Culture - *E. coli*

<table>
<thead>
<tr>
<th>Urine Culture Report</th>
</tr>
</thead>
<tbody>
<tr>
<td>+ <em>E. Coli</em></td>
</tr>
<tr>
<td><strong>Interpretation</strong></td>
</tr>
<tr>
<td>Ampicillin</td>
</tr>
<tr>
<td>Ampicillin/sulbactam</td>
</tr>
<tr>
<td>Cefazolin</td>
</tr>
<tr>
<td>Ceftriaxone</td>
</tr>
<tr>
<td>Gentamicin</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
</tr>
<tr>
<td>Nitrofurantoin</td>
</tr>
<tr>
<td>Trimethoprim/Sulfamethoxazole</td>
</tr>
</tbody>
</table>
Taking all these factors into consideration...

What do you choose?
<table>
<thead>
<tr>
<th>Infectious Diagnosis</th>
<th>Empiric first line recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cystitis</td>
<td>nitrofurantoin (Macrobid®)* 100mg PO bid x 5 days (avoid if CrCl &lt; 30 ml/min) or cephalixin* 500mg PO bid x 3-5 days</td>
</tr>
<tr>
<td>Acute bacterial sinusitis</td>
<td>98% are viral</td>
</tr>
<tr>
<td>Community-acquired pneumonia</td>
<td>amoxicillin/clavulanate* 875/125mg PO bid x5 days</td>
</tr>
<tr>
<td>Cellulitis (No pus)</td>
<td>cephalixin* 500mg PO qid x 5 days</td>
</tr>
<tr>
<td>Purulent skin and soft tissue infection</td>
<td>Drainage first then trimethoprim/sulfamethoxazole* 800/160mg 1-2 tabs PO bid if MRSA is suspected cephalixin 500mg PO QID</td>
</tr>
<tr>
<td>Diabetic foot infection</td>
<td>amoxicillin/clavulanate* 875/125mg PO bid x7-14 days +/ trimethoprim/sulfamethoxazole* 1 DS tab PO bid</td>
</tr>
</tbody>
</table>
What to do if patient reports Penicillin Allergy?

- Patients labeled as penicillin allergic more likely to be treated with non-first line therapies, ↑ medical costs, ↑ LOS, ↑ complications like VRE or C difficile infections
- True penicillin (PCN) allergy is rare: 1-5 per 10,000 cases of PCN therapy
- 80% - 90% of pts who report a PCN allergy are NOT truly allergic to the drug, when assessed by skin testing
- In patients found to have PCN allergy, frequency of positive result on skin testing decreases by 10% per year of avoidance.
  - → 100% of patients are expected to test negative for penicillin allergy by 10 years after their reaction
- Common Types of PCN Reactions:
  - Immediate (Type I IgE mediated): < 1 hr after PCN administration
  - Sub-acute: 7-10 days after start of PCN treatment or 1-2 days after repeat therapy

Cross-Reactivity with other $\beta$-lactam Antibiotics

- **Cephalosporins**
  - Frequency of allergic reactions w/in 24hrs of ceph admin for
    - pts w/Hx of PCN allergy and + skin test = 5.6%
      - If no alternative drug, Ceph desensitization may be required
    - pts w/Hx of PCN allergy and (-) skin test = 1.7%
      - Cephalosporin may be used

- **Carbapenems**
  - Low (1% to 10%)
  - pts w/ +skin test or hx of type I allergy to PCN
    - Graded challenge if a carbapenem is needed

- **Aztreonam**
  - Least cross-reactive with PCN

Penicillin Skin Testing

• Skin testing Procedure
  • Average time – 40 min; Cost ~ $17
  • Reagents:
    • Major determinant (benzyl penicilloyl, commercially available as PrePen)
    • Minor determinant - freshly diluted aqueous PCN G
  • Two steps: Prick test $\rightarrow$ Intradermal test
  • Result:
    • False negatives? $\rightarrow$ 3%
    • Positive – avoid penicillins and aminopenicillins
    • Negative – can give penicillin
Summary of Key Points

• ASPs are important for all healthcare settings
  • Primary goal: Improve patient outcomes

• ASPs have core members to implement protocols, however appropriate antimicrobial use is everyone’s responsibility
  • Know the institution’s antibiogram and empiric guideline recommendations
  • Re-evaluate patient reported penicillin allergy
  • Use optimal dosing for antibiotics using PK/PD concepts

• ASP targets will be customized to the institution and patient population
  • Protocols are evaluated and updated regularly