Fighting the Resistance

John Kappes, Pharm.D. BCCCP
Disclosures

• “I have had no financial relationship over the past 12 months with any commercial sponsor with a vested interest in this presentation”
Objectives

Pharmacist Objectives:
• Describe mechanisms of bacterial resistance
• Categorize various types of beta lactamase enzymes
• Identify emerging resistance organisms
• Evaluate two specific infectious disease conditions in South Dakota involving resistant organisms: CRE and MRSA

Pharmacy Technician Objectives:
• Define bacterial resistance
• Name the antibiotic classes negatively affected by beta lactamase enzymes
• Identify emerging resistance organisms
• Identify three primary infectious disease conditions in South Dakota involving resistant organisms
Abbreviations

• Abx – antibiotic
• AG - aminoglycoside
• AME - Aminoglycoside modifying enzymes
• ASP - Antimicrobial Stewardship Programs
• CSF – cerebral spinal fluid
• Cx - cultures
• CVC – central venous catheter
• ESBL - Extended spectrum β-lactamase
• FQ - fluoroquinolone
• Gen ceph – generation cephalosporins
• ID – infectious diseases
• KPC – *Klebsiella pneumoniae* carbapenemase
• MDR – multidrug resistance
• MOA – mechanism of action
• MV – mechanical ventilation
• PCN - penicillin
• Sulfa/trim – sulfamethoxazole/trimethoprim
• Vanco - vancomycin
• WHO – world health organization
The Futurists: Looking Toward A.D. 2000

• Quote:
  “Nearly all experts agree that bacterial and viral diseases will have been virtually wiped out by the year 2000.”
  -Time Magazine, 1966
Definitions

• Multi-drug resistance (MDR) – acquired resistance to at least one agent in ≥ 3 abx categories

• Extensively drug-resistant – acquired resistance in all but two or fewer abx categories

• Pandrug-resistant – acquired resistance to all agents
Resistance

- **WHO** – Antibiotic resistance is 1 of 3 most important public health threats of the 21st century

- **MDR organisms**
  - ≥23,000 die annually in the US
  - 300 million premature deaths by 2050

- **Economic burden:**
  - $6 – 30 thousand per patient
  - ≥$55 billion per year in US
  - $100 trillion in global economy by 2050

Cosgrove SE. Clin Infect Dis 2006;42:S82-9
Resistance

Deaths per annum for antimicrobial resistant infections and other causes by 2050 in millions. [1] and http://amr-review.org/

- Measles: 0.13
- Road accidents: 1.2
- Diarrhea: 1.4
- Diabetes: 3
- Cancer: 8.2
- Antimicrobial resistant infections: 10
Resistance

Death attributable to antimicrobial resistance every year by 2050 in different countries [1]
Resistance

- Poor abx penetration
  - Abx site concentration
    - CSF vs Urinary tract

- Size of bacterial inoculum

- Intrinsic resistance

- Acquired resistance
Definitions

• Intrinsic resistance – resistance is inherently present in the microorganism
  • Drug target is lacking
  • Prevent drug from reaching target

• Acquired resistance – change in the genetic composition of the microorganism, therefore a drug that once was effective is no longer active
Genetics

• Gene: molecules of DNA which are subunits of chromosomes that direct formation of proteins or enzymes

• Chromosomes: an array of genes responsible for determination of cellular characteristics

• Plasmid: circular extrachromosomal DNA molecules naturally present in bacteria that contain genetic information

• Transposon: genes that move from 1 DNA molecule to another

• Integrons: genetic elements that allow efficient capture and expression of exogenous gene
Genetics

Genetics
## Amino acids

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<tr>
<th>Essential</th>
<th>Nonessential</th>
<th>Conditional</th>
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<tbody>
<tr>
<td>Histidine</td>
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<tr>
<td>Isoleucine</td>
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<td>Leucine</td>
<td>Aspartic acid</td>
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<td>Lysine</td>
<td>Glutamic acid</td>
<td>Tyrosine</td>
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<td>Glycine</td>
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<td>Phenylalanine</td>
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<td>Ornithine</td>
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<td>Threonine</td>
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<td>Proline</td>
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<tr>
<td>Tryptophan</td>
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<td>Serine</td>
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<tr>
<td>Valine</td>
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</tr>
</tbody>
</table>

[https://medlineplus.gov/ency/article/002222.htm](https://medlineplus.gov/ency/article/002222.htm)
Genetic Adaptation

• Gene mutation - is a permanent alteration in the DNA sequence that makes up a gene
  • Deletion
  • Duplication
  • Inversion
  • Translocation
Genetic Adaptation: Chromosomal Mutation

- **Deletion**
  - Original: ABCDEF
  - Result: ACDEF

- **Duplication**
  - Original: ABCDEF
  - Result: ABBCDEF

- **Inversion**
  - Original: ABCDEF
  - Result: AEDCBF

- **Translocation**
  - Original: ABCDEJF
  - Result: ABCJIKL
Transposon

http://scienceblogs.com.br/cronicamoscas/category/transposons/
Integrons
Genetic Adaptation

- Horizontal Gene Transfer (HGT) - acquisition of foreign DNA
  - Transformation
  - Transduction
  - Conjugation

Mechanisms of Resistance

- Modification of abx
  - Prevent abx from reaching target
  - Change target site
  - Global cell adaptive processes
Modification of Abx – chemical alteration

**Acetylation**

Polypeptide

\[ \text{N-terminal amino group} \]

\[ \text{N}^\alpha\text{-terminal acetytransferases (NATs)} \]

\[ \text{Ac-CoA} \rightarrow \text{CoA} \]

\[ \text{N-terminal acetylated Polypeptide} \]

**Adenylation**

**Phosphorylation**
Modification of Abx – chemical alteration

• Aminoglycoside modifying enzymes (AME)
  • Two nomenclature systems
    • Phosphoryltransferases (APH)
    • Nucleotidyltransferases (ANT)
    • Acetyltransferase (AAC)
  • May inhibit FQ

• Bacteria affected
  • S. aureus
  • E. faecalis
  • S. pneumoniae
Modification of Abx – chemical alteration
<table>
<thead>
<tr>
<th>AACs</th>
<th>Gene names</th>
<th>Genetic location</th>
<th>Accession number</th>
<th>Host</th>
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<td>Streptomyces albus</td>
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<td>AM283489, AM283490</td>
<td>P. aeruginosa, P. aeruginosa, E. cloacae, K. pneumoniae</td>
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<td>EF37562, EU085533</td>
<td>E. cloacae, K. pneumoniae</td>
</tr>
</tbody>
</table>
Modification of Abx – destruction of abx

Modification of Abx – destruction of abx

• β-lactamases
  • First described in early 1940s
  • >2,000 identified

• Classification schemes:
  • Common name
  • Ambler Class
  • Bush-Jacoby
Modification of Abx – destruction of abx

![Diagram of β-lactamase action on Penicillins and Cephalosporins](image)
β-lactam ring

Water

Open ring

β-lactamase
Modification of Abx – destruction of abx

- Common name
  - Penicillinase
  - Cephalosporinase
  - ESBL
  - Carbapenemase
Modification of Abx – destruction of abx

• Penicillinases
  • Commonly Ambler Class A or Bush-Jacoby Group 2
  • Treat with β-lactamases inhibitors
  • Examples: SHV-1, TEM-1

• Cephalosporinase
  • Ambler Class C or Bush-Jacoby Group 1
  • Most Enterobacteriaceae as chromosomal enzymes
  • Examples: AmpC

Bush K. Critical Care 2010;14:224
Modification of Abx – destruction of abx

• Extended spectrum \(\beta\)-lactamase (ESBL)
  • Hydrolyse
    • PCN
    • 3\textsuperscript{rd} gen ceph (hallmark characteristic)
    • Monobactams

• Modest (or no) activity against
  • Cephemycins
  • Carbapenems

• Example: predominately CTX-M
Modification of Abx – destruction of abx

<table>
<thead>
<tr>
<th>Risk factors for ESBL</th>
<th>Risk factors for ESBL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Community onset</td>
<td>Hospital onset</td>
</tr>
<tr>
<td>Age &gt;70</td>
<td>Local prevalence, outbreak</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>Prolonged hospitalization</td>
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<tr>
<td>Charlson index &gt;3</td>
<td>Invasive procedures (&gt;MV)</td>
</tr>
<tr>
<td>Previous hospital admission</td>
<td>Previous colonization ESBL</td>
</tr>
<tr>
<td>Transfer from another healthcare facility</td>
<td>Previous use of cephalosporins</td>
</tr>
<tr>
<td>Use of a urinary catheter</td>
<td>Previous use of fluoroquinolones</td>
</tr>
<tr>
<td>Recurrent or obstructive UTIs</td>
<td>Previous use of carbapenems</td>
</tr>
<tr>
<td>Previous use of aminopenicillins</td>
<td></td>
</tr>
<tr>
<td>Previous use of cephalosporins</td>
<td></td>
</tr>
<tr>
<td>Previous use of fluoroquinolones</td>
<td></td>
</tr>
<tr>
<td>Recent travel from high-endemic area</td>
<td></td>
</tr>
</tbody>
</table>
Modification of Abx – destruction of abx

• Carbapenemases
  • Hydrolyze carbapenems

• Often resistant to other classes as well

• Salvage agents
  • Polymyxins
  • Tigecycline

• Mortality 32-44%
Modification of Abx – destruction of abx

• Carbapenemases

  • Examples
    • KPC – *Klebsiella pneumoniae* carbapenemases
    • VIM - Verona integron-encoded metallo β-lactamase
    • NDM - New Delhi metallo β-lactamase
    • OXA – oxacillinase carbapenemases

  • Global distribution with substantial regional variability
Modification of Abx – destruction of abx

Carbapenemases

Logan L, Weinstein R. J Inf Dis 2017;215(S1):S28-36
Modification of Abx – destruction of abx Carbapenemases

![Chart showing the number of countries with carbapenemase genes, by gene and prevalence types.](image)

Logan L, Weinstein R. J Inf Dis 2017;215(S1):S28-36
Modification of Abx – destruction of abx Carbapenemases

<table>
<thead>
<tr>
<th>Risk factors for CRE Hospital onset</th>
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<tbody>
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<td>Age &gt;70</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
</tr>
<tr>
<td>Charlson index &gt;3</td>
</tr>
<tr>
<td>Admission to ICU</td>
</tr>
<tr>
<td>Invasive procedures (CVC, endoscopy)</td>
</tr>
<tr>
<td>Previous use of cephalosporins</td>
</tr>
<tr>
<td>Previous use of fluoroquinolones</td>
</tr>
<tr>
<td>Previous use of carbapenems</td>
</tr>
</tbody>
</table>

**CRE:** Carbapenem-resistant Enterobacteriaceae, family of bacteria that are difficult to treat because of very high levels of resistance to antibiotics.

<table>
<thead>
<tr>
<th>Regions</th>
<th>Cases</th>
<th>Rate**</th>
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</thead>
<tbody>
<tr>
<td>Sioux Falls MSA</td>
<td>9</td>
<td>3.5</td>
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<tr>
<td>Rapid City MSA</td>
<td>4</td>
<td>2.9</td>
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<tr>
<td>Northeast</td>
<td>8</td>
<td>4.6</td>
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<tr>
<td>Southeast</td>
<td>4</td>
<td>3.5</td>
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<tr>
<td>Central</td>
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<td>2.1</td>
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<tr>
<td>West</td>
<td>2</td>
<td>2.1</td>
</tr>
<tr>
<td>South Dakota</td>
<td>29</td>
<td>3.4</td>
</tr>
</tbody>
</table>

**Rate:** cases per 100,000 population.
MSA: Metropolitan Statistical Area


Modification of Abx – destruction of abx

- Ambler Classification
  - C
  - A^\dagger
  - D
  - B

- Functional group
  - 1
  - 2
  - 2^\dagger
  - 3

- Inhibitory Profile
  - Clavulanic acid
  - EDTA

- ESBLs

- Carbapenemases

- Classical examples
  - ESBL: AmpC
  - Penicillinase: TEM-1, SHV-1
  - ESBLs: CTX-M, TEM-3
  - Carbapenemase: KPC

- Other examples
  - ESBL: OXA-11
  - Carbapenemase: OXA-23, OXA-48

- Carbapenemase: IMP, VIM, NDM

- Serine β-lactamase
- Metallo β-lactamase

Munita J, Arias C. Mechanisms of Antibiotic Resistance
Microbiol Spectr 2016
Modification of Abx – destruction of abx

- Ambler Class A
  - Serine (amino acid) residue in the catalytic site

- Ambler Class B
  - aka metallo- \(\beta\)-lactamases - Metal ion (mostly Zinc) as cofactor for activity

- Ambler Class C
  - aka “AmpC” - also serine

- Ambler Class D
  - aka “OXA” – also serine
Modification of Abx – destruction of abx

• Ambler Classification

β-lactamases

Class A (serine)
Class B (metallo)
Class C (serine)
Class D (serine)

subclass B1
subclass B2
subclass B3

Hydrolyse β-lactam bond in structurally related antibiotics

No consistent relationship

No consistent relationship

Hall B, Barlow M. J Antimicrob Chemother 2005
Modification of Abx – destruction of abx

- Ambler Class A
  - Serine (amino acid) residue in the catalytic site
  - MOA: Serine form acyl-enzyme intermediate $\rightarrow$ activate water molecule $\rightarrow$ hydrolysis of $\beta$-lactam ring
  - Most are inhibited by clavulanic acid or tazobactam
  - Cephamycins (cefoxitin & cefotetan) retain activity

- Examples:
  - Penicillinases: TEM-1 and SHV-1
  - ESBLs: CTX-M
  - Carbapenemas: KPC
Modification of Abx – destruction of abx

• Ambler Class B
  • Hydrolyze most β-lactams
  • aka metallo- β-lactamases
    • Metal ion (mostly Zinc) as cofactor for activity
  • MOA: Water molecule bound to metal ion cluster in catalytic center → activate hydrolysis
    • No covalent intermediate → refractory to inhibition
  • NOT inhibited by clavulanic acid or tazobactam
  • Aztreonam is a poor substrate
  • Examples:
    • Carbapenemase: NDM, IMP, VIM
Modification of Abx – destruction of abx

- Ambler Class C
  - Hydrolyze all PCNs & cephalosporins
  - MOA: Serine form acyl-enzyme intermediate → activate water molecule → hydrolysis of β-lactam ring
    - “attack” from opposite direction of Ambler Class A
  - Not inhibited by clavulanic acid or tazobactam
- Carbapenems, cefepime, & aztreonam may retain activity
- Examples: AmpC

References:
Modification of Abx – destruction of abx

• AmpC
  • Inducible gene
    • AmpR repressor of AmpC gene transcription
    • AmpR is bound to peptidoglycan precursors
    • β-lactams alter cell wall homeostasis (ie peptidoglycan)
    • Therefore AmpR cannot repress AmpC

• Incidence of induction
  • 1991 study – up to 19%
  • 2008 study – 5%
    • Cefepime group – 0%
    • More frequent in Enterobacter spp.
Modification of Abx – destruction of abx

- Ambler Class D
  - Class A differentiation: hydrolyze oxacillin
  - MOA: unknown
    - Similar to Class A but no equivalent activation hydrolyzing water molecule
  - Poorly inhibited by clavulanic acid
  - Particularly prevalent in *A. baumanii*

- Examples:
  - ESBL: OXA-11
  - Carbapenemase: OXA-23, Oxa-48
Modification of Abx – destruction of abx

• Bush-Jacoby
  • Group 1 – cephalosporinases
  • Group 2 – serine $\beta$-lactamases
  • Group 3 – metallo-$\beta$-lactamases

• >890 unique $\beta$-lactamases in Bush-Jacoby
Modification of Abx – destruction of abx

β-lactamase Inhibitors

• First utilized mid-to-late 1980s

• Most have a β-lactam backbone

• MOA - form stable intermediates with β-lactamases, thereby allowing their companion β-lactam to effectively bind to the penicillin binding protein

• Derived from natural products

Wong D, van Duin D. Drugs 2017;77:615-628
Modification of Abx – destruction of abx β-lactamase Inhibitors

• Clavulanic acid
  • Produced by *Streptomyces clavuligerus* & β-lactamase Inhibitory protein (BLIP)
  • Inhibit Ambler A
  • Irreversible

• Sulfones
  • Sulbactam
    • Inhibits Ambler A
    • Irreversible
  • Tazobactam
    • Inhibits Ambler C & D
    • Improved activity → modified reaction & higher affinity
    • Irreversible
Inert enamine ester
Modification of Abx — destruction of abx β-lactamase Inhibitors

• Novel inhibitors
  • Advantage: inhibit certain ESBLs & carbapenemases
  • Avibactam
    • Combination: Ceftazidime
    • Synthetic diazabicyclooctane non-β-lactam inhibitor
    • MOA — covalent acylation at β-lactamase serine residue
    • Inhibits Ambler class A, C, and some D
    • Reversible
  • Relebactam
  • Vaborbactam

Wong D, van Duin D. Drugs 2017;77:615-628
Modification of Abx – destruction of abx

- β-lactamase Inhibitor combinations
  - Vital factors
    - Amount of β-lactamase produced by the bacteria
    - Permeability of the inhibitor
    - Intrinsic susceptibility of the bacteria
    - Properties of the β-lactam agent
    - pH conditions

Livermore D. J Antimicro Chemo 1993;31(Suppl A):9-21
Mechanisms of Resistance

• Modification of abx

• Prevent abx from reaching target

• Change target site

• Global cell adaptive processes
Prevent abx from reaching target
Prevent abx from reaching target

• Decreased permeability
  • Alteration of porins
    • Shift in type of porins expressed
    • Change in level of porins expressed
    • Impairment of the porin function

• Efflux Pumps
  • Affects: fluoroquinolones, β-lactams, polymyxins, protein synthesis inhibitors
  • 5 major families of efflux pumps

Prevent abx from reaching target
Mechanisms of Resistance

• Modification of abx

• Prevent abx from reaching target

• Change target site

• Global cell adaptive processes
Change in Target Site

• Target protection
  • Dislodge abx from site

• Produce protein which competes for binding site

• Abx impacted:
  • Fluoroquinolones
    • Qnr (quinolone resistance) gene
    • Pentapeptide repeat protein
      • Binds to gyrase or topoisomerase IV
  • Tetracycline
Change in Target Site

• Modification of target site
  • Point mutations (ie alter amino acids)
  • Enzymatic alterations (ie addition of methyl groups)
    • AG – methylation of ribosome
  • Bypass the original target
Change in Target Site

SOUTH DAKOTA: 1 January – 30 June 2017: Provisional Data

MRSA
Invasive methicillin-resistant Staphylococcus aureus

<table>
<thead>
<tr>
<th>Regions</th>
<th>Cases</th>
<th>Rate†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sioux Falls MSA</td>
<td>17</td>
<td>6.6</td>
</tr>
<tr>
<td>Rapid City MSA</td>
<td>9</td>
<td>6.6</td>
</tr>
<tr>
<td>Northeast</td>
<td>4</td>
<td>2.3</td>
</tr>
<tr>
<td>Southeast</td>
<td>7</td>
<td>6.2</td>
</tr>
<tr>
<td>Central</td>
<td>10</td>
<td>10.7</td>
</tr>
<tr>
<td>West</td>
<td>14</td>
<td>15.0</td>
</tr>
<tr>
<td>South Dakota</td>
<td>61</td>
<td>7.0</td>
</tr>
</tbody>
</table>

†Rate: cases per 100,000 population.
MSA: Metropolitan Statistical Area.


Disease fact sheets: [http://doh.sd.gov/diseases/infectious/diseasefacts](http://doh.sd.gov/diseases/infectious/diseasefacts)
Change in Target Site

Fluoroquinolones bind to two nuclear enzymes, inhibiting DNA replication.
Change in Target Site

- DNA
- mRNA Transcription
- Mature mRNA
- Transport to cytoplasm for protein synthesis (translation)

- Nucleus
- Cell membrane

- mRNA

- Growing peptide chain
- Trp
- Lys
- Asp

- Outgoing empty tRNA
- ACG

- TRNA

- Incoming tRNA bound to Amino Acid
- TRNA
- AAG

- Ribosome

- MessengerRNA
  - UGG
  - AAA
  - GAG
  - AUG
  - UUU
  - UCU

- Peptide Synthesis
Change in Target Site

• Bactrim blocks bacterial enzymes which synthesis DNA, RNA, & proteins

• ↑ production of antimicrobial target → overwhelming Bactrim's ability to inhibit folate production

Mechanisms of Resistance

• Modification of abx

• Prevent abx from reaching target

• Change target site

• Global cell adaptive processes
Global cell adaptive processes


Thickened Peptidoglycan
Global cell adaptive processes

- hVISA

- Subpopulation with intermediate MIC (i.e. 8-16 mcg/ml)

- Reduced susceptibility not detected by disk diffusion

- Prevalence: 0 – 8.24%
  - Up to 30%

Rybak M. Presented at the 39th SCCM congress, Miami Beach, FL, January 9-13, 2010.
Global cell adaptive processes

Step 1: DAP complexes with Ca$^{++}$

Step 2: The positively-charged DAP-Ca$^{++}$ complex interacts with the negatively-charged CM.

Step 3: Interaction between DAP and PG Results in oligomerization of DAP molecules in the outer leaflet of the CM.

Step 4: DAP oligomers translocate to the inner leaflet of the CM producing pore-like structures that result in bacterial cell death
Biofilms

• Group of microorganisms

• Bacteria attach to a surface

• Extracellular polymeric matrix
  • Complex assembly of protein, polysaccharide & DNA

• Adaptive resistance vs genetic alteration

• Breading ground for mutations

• Examples: periodontitis, cystic fibrosis pna, indwelling catheters, heart valves, prostheses

Biofilms
Fluoroquinolone resistance

1. Mutations in genes encoding the target site
   • DNA gyrase & topoisomerase IV

2. Over-expression of efflux pumps

3. Alteration in porins

4. Target protection (Qnr)

## Mechanism of Abx Resistance

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Antibiotic Affected</th>
</tr>
</thead>
<tbody>
<tr>
<td>Altered PBP</td>
<td>β-lactam</td>
</tr>
<tr>
<td>Altered Target</td>
<td>Vanco, Macrolides, Linezolid, FQ, Sulfa/trim</td>
</tr>
<tr>
<td>Decrease uptake</td>
<td>AG, β-lactam, FQ</td>
</tr>
<tr>
<td>Efflux pump</td>
<td>Macrolides, FQ</td>
</tr>
<tr>
<td>Enzymatic degradation</td>
<td>β-lactam</td>
</tr>
<tr>
<td>Overproduction of target</td>
<td>Vanco</td>
</tr>
<tr>
<td>Enzymatic modification</td>
<td>AG</td>
</tr>
</tbody>
</table>

Alekshun M, Levy S. Cell 2007;128:1037-50
Antimicrobial Stewardship Programs

• ASP - Organized program to monitor, improve, and measure the responsible use of antibiotics

• Basic elements of ASP
  • Develop/implement facility-specific abx guidelines
  • Restrict certain types of abx
  • ID physician/pharmacist feedback to providers
  • Automatic stop orders
  • Automatic pharmacy interventions
  • Education
  • Cascade antibiotic sensitivity reporting

Antibiotic Discovery

• 1940+
  • Screening cx of soil-derived organisms

• 1990s
  • Genomics
  • High-tech chemical approaches
  • High-throughput screening
    • Cost ~$1 million per campaign

• 2015
  • iChip
Soil is cultured directly onto culture medium

Yields 1% bacterial recovery

The iChip is seeded with soil dilutions such that an average of one bacterial cell is placed in each microchamber; the iChip is then placed back into soil

Colonies are cultured and grown, with up to 40% bacterial recovery
Pathogen Identification

- Broth microdilution
- Disk Diffusion
- Etest strip

Pathogen Identification

- Rapid immunochromatographic assay
- Polymerase Chain Reaction (PCR)
- MALDI-TOF
- PNA FISH
Rapid Immunochromatographic Assay

https://www.slideshare.net/amerali6/immunochromatographic-assays
Polymerase Chain Reaction (PCR)
MALDI-TOF

https://www.researchgate.net/publication/261830922_MALDI-TOF_Mass_Spectrometry_a_Rapid_and_Reliable_Method_for_the_Identification_of_Bacterial_Species_in_Food-Microbiology_Laboratories
PNA-FISH

https://www.alphalabs.co.uk/pnafish
Procalcitonin

Guidelines for continuing or stopping of antibiotics

- Concentration <0.25 µg/L
  - Stopping of antibiotics strongly encouraged

- Decrease by ≥80% from peak concentration, or concentration ≥0.25 and <0.5 µg/L
  - Stopping of antibiotics encouraged

- Decrease by <80% from peak concentration, and concentration ≥0.5 µg/L
  - Continuing of antibiotics encouraged

- Increase of concentration compared with peak concentration and concentration ≥0.5 µg/L
  - Changing of antibiotics strongly encouraged

## Future Antibiotics

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Phase</th>
<th>Spectrum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ceftolazane-tazobactam</td>
<td>Approved 2014</td>
<td>ESBLs</td>
</tr>
<tr>
<td>Ceftazidime-avibactam</td>
<td>Approved 2015</td>
<td>KPCs &amp; OXA-48</td>
</tr>
<tr>
<td>Ceftaroline-avibactam</td>
<td>Phase 3</td>
<td>KPCs</td>
</tr>
<tr>
<td>Aztreonam-avibactam</td>
<td>Phase 2</td>
<td>NDMs</td>
</tr>
<tr>
<td>Meropenem-RPX7009</td>
<td>Phase 3</td>
<td>KPCs</td>
</tr>
<tr>
<td>Imipenem/cilastatin-relebactam</td>
<td>Phase 3</td>
<td>Ambler A &amp; C</td>
</tr>
<tr>
<td>Plazomicin</td>
<td>Phase 3</td>
<td>KPCs</td>
</tr>
<tr>
<td>Eravacycline</td>
<td>Phase 3</td>
<td>KPCs</td>
</tr>
<tr>
<td>New Cephalosporin</td>
<td>Phase 2</td>
<td>KPCs &amp; NDM-1</td>
</tr>
</tbody>
</table>

Future Agents

- Eligobiotics
- Anti-virulence factors
- Lysins
- Bacteriophages
- Immunostimulation
- Efflux pump inhibitor
- Lipopolysaccharide inhibitor
References

- South Dakota Department of Health
References

• Bush K. Bench-to-bedside review: the role of B-lactamases in antibiotic-resistant Gram-negative infections. Critical Care 2010;14:224
References

• Hall B, Barlow M. Revised Ambler classification of B-lactamases. J Antimicrob Chemother 2005
doi:10.1093/jac/dki130
• Livermore D. Determinants of the activity of B-lactamase inhibitor combinations. J Antimicro Chemo 1993;31(Suppl A):9-21
• Ramirez M, Tomasky M. Aminoglycoside modifying enzymes. Drug Resistance Updates 2010;13:151-171
• Wong D, van Duin D. Novel Beta-lactamase Inhibitors: Unlocking Their Potential in Therapy. Drugs 2017;77:615-628
Active Learning Question - Pharmacist

Which of the following is not an acquired resistance mechanism by bacteria to antibiotics?

a. Modification of antibiotic
b. Size of inoculum
c. Destruction of antibiotic
d. Change target site
Active Learning Question - Pharmacist

Which Ambler class of beta-lactamase enzymes has a metal ion as a cofactor for activity?

a. Ambler Class A
b. Ambler Class B
c. Ambler Class C
d. Ambler Class D
Active Learning Question - Pharmacist

Which of the following organisms can produce a carbapenemase?

a. *Klebsiella pneumoniae*

b. Group A *Streptococcus*

c. *Staphylococcus aureus*

d. *Bacteroides fragilis*
Active Learning Question - Technician

If an organism is sensitive to an antibiotic it will always be sensitive in the future?

a. True
b. False
Which of the following antibiotic class may be inactivated by beta lactamase enzymes?

a. Fluoroquinolones  
b. Cephalosporin  
c. Aminoglycoside  
d. Macrolides
Active Learning Question - Technician

Carbapenems are the only antibiotics which bacteria do NOT have a resistance mechanism against.

a. True
b. False
Active Learning Question – Pharmacist/Technician

South Dakota has no documented cases of carbapenem-resistant enterobacteriaceae (CRE)?

a. True
b. False