Antimicrobial Resistance

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The speaker has no conflicts to disclose

Pharmacist Learning Objectives

- List 3 different types of resistance
- Describe 3 means by which antimicrobial resistance can be slowed
- Identify 2 antibiotics used for the treatment of Extended Spectrum Beta-lactamases, Carbapenem Resistant Enterobacteriaceae, Methicillin Resistant *Staphylococcus aureus*, Vancomycin Resistant *Enterococcus*, and resistant *pseudomonas*

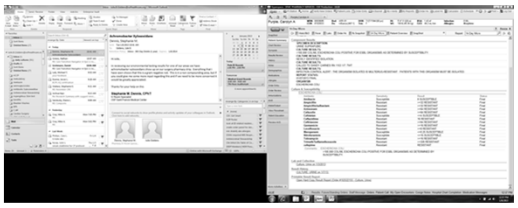
Pharmacy Technician Learning Objectives

- List 3 different types of resistance
- Describe 3 means by which antimicrobial resistance can be slowed
- Identify 2 antibiotics used for the treatment of resistant pseudomonas and methicillin resistant *Staphylococcus aureus*

Patient Case

- CP 68 yof
- Antibiotic Allergies: None
- PMH: Parapelegic; Neurogenic bladder; Suprapubic catheter; COPD
- SH: Lives at home with son
- Chief complaint: fever, nausea
- Positive Urine analysis
- Preliminary Diagnosis: UTI
- Antibiotics?

Day 3 Urinary Culture Results



Bad Bugs


Methacillin Resistant Staphyloccous (MRSA)

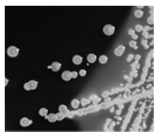

Vancomycin Resistant Enterococci (VRE)


Acinetobacter baumannii bacteria


Pseudomonas aeruginosa


Extended Spectrum β-lactamase E. Coli

Worse Bugs!!



Carbapenem-resistant Enterobacteriaceae (CRE)

The Economics of Hospital-Acquired Infections

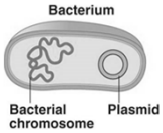
- Patients without infection:
  - Mortality = 2.0%
  - Length of stay = 4.7 days
  - Average Charge = $37,943
- Patients with hospital-acquired infection (HAI):
  - Mortality = 12.2%
  - Length of stay = 19.7 days
  - Average Charge = $191,872

Pennsylvania Health Care Cost Containment Council January 2009

8

Genes Encoding Resistance

- Chromosome
  - Does NOT exist as its own entity
  - Intrinsic resistance
  - Chromosomally mediated inducible enzymes
- Plasmid
  - Self replicating entity
  - Replicates independently of chromosomes
  - Acquired Resistance



Mechanisms Of Resistance

- Efflux Pumps
  - Decreased accumulation of the antibiotic
- Target Modifications
  - Changes in binding sites or cell wall receptors
- Porin Changes
  - Decreased outer membrane permeability
- Enzyme Inactivation
  - Beta-lactamases
  - Inactivates the beta-lactam ring

Mechanisms Of Resistance Breakdown

- By Antibiotic Classes
- By Organism
  - Gram Negative
    - Beta-Lactamases
  - Gram Positive
    - Beta-Lactamases
    - Penicillin Binding Proteins

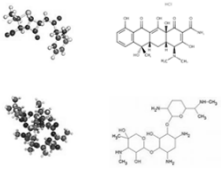


Table 1. Some representative antibiotics, their modes of action and mechanisms of resistance

Category	Some members	Mode of action	Major mechanisms of resistance
β-Lactams	Penicillins, Cephalosporins, Cefotaximes, Carbapenems	Inhibition of cell-wall synthesis	Cleavage by β-lactamases, ESBLs, CTX-mases, Carbapenemases, altered PBPs
Aminoglycosides	Streptomycin, Gentamycin, Tobramycin, Amikacin	Inhibition of protein synthesis	Enzymatic modification, efflux, ribosomal mutations, 16S rRNA methylation
Quinolones	Ciprofloxacin, Ofloxacin, Norfloxacin	Inhibition of DNA replication	Efflux, modification, target mutations
Glycopeptides	Vancomycin	Inhibition of cell-wall synthesis	Altered cell walls, efflux
Tetracyclines	Tetracycline	Inhibition of translation	Mainly efflux
Rifamycins	Rifampin (Rifampicin)	Inhibition of transcription	Altered β-subunit of RNA polymerase
Streptogramins	Virginiamycins, Quinupristin, Dalfopristin	Inhibition of cell-wall synthesis	Enzymatic cleavage, modification, efflux
Oxazolidinones	Linezolid	Inhibition of formation of 70S ribosomal complex	Mutations in 23S rRNA genes followed by gene conversion

Need Reference

Mechanisms Of Resistance Breakdown

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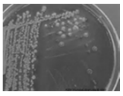

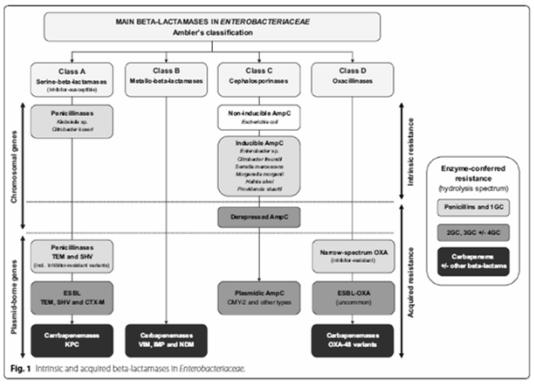

Fig. 1 Intrinsic and acquired beta-lactamases in *Enterobacteriaceae*.

Ruppe et al. *Ann Intensive Care*. (2015)5:21

Clinical Scenario (Maybe about SPACE organisms)

- 53 yof with fever, chills, and abdominal pain
- Admitted for cholangitis and gallstones
- Blood Cultures:
  - Citrobacter freundii
    - R Benzylpenicillin, R Cefazolin, R Cefoxitin, R Ceftriaxone, S Cefepime, S Meropenem
- True or False
  - This is most likely an extended spectrum beta-lactamase, plasmid mediated resistance that would require a patient to be placed in isolation

Mechanisms Of Resistance Breakdown

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  - Gram Positive
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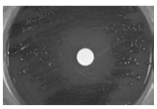

Staphylococci Mechanisms of Resistance

Table 1. Resistance Mechanisms in Clinically Important Gram-positive Pathogens

Pathogen and Resistance Strategy	Antibiotic	Gene(s) Involved	Comments
Staphylococci			
Drug inactivation	β-lactams (penicillins with or without cefazolin[a])	*blaZ*	Plasmid-encoded β-lactamase that hydrolyzes penicillins; isoxazolyl penicillins (eg, nafcillin), cephalosporins,[a] and carbapenems are stable
Target replacement	β-lactams	*mecA*	PBP2a has low affinity for β-lactams (except ceftaroline and ceftobiprole)
	Vancomycin (VRSA)	*vanA* Gene cluster	Acquired from enterococci; rare isolates described
Target modification	Linezolid	23S rRNA genes, L3/L4 ribosomal proteins *cfr*	Mutations in 23S rRNA genes are main mediators of resistance; *cfr* gene is the only transferable determinant of LNZ-R
	Ceftaroline	*pbp2a*	Mutations in *pbp2a* associated with high-level ceftaroline resistance (MIC >32 μg/mL)
Changes in cell surface adaptation	Vancomycin (VISA)	*vraRS, yycFG, graRS, rpoB*	Many genes involved in the resistance phenotype, most related to regulatory systems
	Daptomycin	*mprF, dlt, vraRS, yycFG, pgsA, cls*	Many genes involved in the resistant phenotype; main pathway seems to be repulsion of the antibiotic through an increase in the net positive charge of the cell envelope

Munita etal. *Clinical Infectious Diseases*. 2015:61(S2); S48-57.

Clinical Scenario

- 43 yom injured right index finger at work
- Finger red, swelling, painful, and patient is with fever
- Blood Cultures:
  - Staphylococcus Aureus
    - Beta-lactamase positive
- Which would be an appropriate statement?

A. This organism will most likely be resistant to Methicillin

B. This organism will most likely be resistant to Penicillin, but sensitive to Methicillin

C. This organism will most likely be resistant to Cefazolin

Enterococci Mechanisms of Resistance

Table 1. Resistance Mechanisms in Clinically Important Gram-positive Pathogens

Enterococci			
Drug inactivation	β-lactams (penicillins)	*blaZ*	Rare, found mostly in *E. faecalis*
Target replacement	Vancomycin	*van* Gene clusters	Several gene clusters described, most acquired on mobile elements; intrinsic low-level resistance seen in *E. gallinarium* and *E. casseliflavus* (*vanC* phenotype)
Target modification	β-lactams (penicillin and ampicillin)	*pbp5*[h]	PBP5-R differs from PBP5-S in only about 5% of amino acid sequence; certain amino acid substitutions have been directly implicated in ampicillin resistance (see text)
	Linezolid	23S rRNA genes, L3/L4 ribosomal proteins, *cfr*	Rare, mutations in 23S rRNA and L3/L4 are similar to those found in staphylococci, as is the *cfr* gene
Changes in cell surface adaptation	Daptomycin	*liaFSR*, *yycGF*, *gdpD*, *cls*	Most frequent mutations found in daptomycin-resistant clinical isolates; many genes involved; resistance pathways differ between *E. faecalis* and *E. faecium*
Streptococci			
Target modification	β-lactams (penicillin)	PBPs (*pbp2x*, *pbp2b* in pneumococci), *murM*, *cpoA*, *pdgA*	PBP changes are the most important determinant of β-lactam resistance; mosaic PBPs are often found in penicillin-resistant isolates
	Linezolid	23S rRNA genes, L3/L4 ribosomal proteins, *cfr*	Rare
Unknown	Daptomycin	Unknown	Rapid development of daptomycin resistance in certain species of streptococci

Munita etal. *Clinical Infectious Diseases*. 2015:61(S2); S48-57.

Clinical Scenario

- 84 yof has altered mental status at nursing home and fever
- Urine analysis is positive for leukocyte esterase and 100 WBCs
- Urine Culture:
  >100,000 Enterococcus (Sensitivities Pending)
- Physician Orders ampicillin/sulbactam (Unasyn®)
- True OR False:
  Enterococcus rarely produces beta-lactamses and ampicillin/sulbactam could be empirically changed to ampicillin alone

How can resistance be slowed?

Factors associated w/ decreasing antimicrobial resistance

- Decrease use of broad-spectrum agents for community-acquired infections
- Avoid exposure when possible
- Use different agents for repeat infections
- Shorten duration of therapy
- Limit use of invasive devices or catheters
- Appropriate infection control procedures & compliance

Clinical Scenario

- 54 yof admitted for CHF
- Routine Urine Culture: >100,000 E.coli
- No complaints of urinary symptoms, afebrile, CrCl > 50 ml/min
- Urine analysis: Trace Leukocyte esterase and 5 wbcs
- What should be the next steps?
  A. Start Ciprofloxacin (Cipro)
  B. Start Cephalexin (Keflex)
  C. Avoid treatment at this time

Principles of Antibiotic therapy:

- Right Medication
- Right Indication
- Right Dose
- Right Duration

Appropriate use of antibiotics suppresses growth of Multi Drug Resistant Organisms

Reassess Antibiotics at 48-72 Hours

- Take an Antibiotic Time Out
  - Are antibiotics still needed?
    - Has infection been ruled out?
    - Other causes for fever or leukocytosis?
  - Are 2 or 3 antibiotics still needed?
    - Narrow to 1 or 2 antibiotics
  - Can a projected stop date be determined?
    - Place stop date in progress notes
      - On ceftriaxone for UTI Day 4 of 7
    - Place stop date in computer system

Clinical Scenario

- 62 yom admitted 3 days ago for pneumonia
- Nursing Home Resident
- Allergies: NKA
- Started on Piperacillin/Tazobactam (Zosyn®) and Vancomycin
- Passed swallow evaluation today
- Cultures:
  - Sputum: Normal Flora
  - MRSA Nares: Negative
  - Blood: No growth

Clinical Scenario

- 62 yom admitted 3 days ago for pneumonia
- Nursing Home Resident
- Allergies: NKA
- Started on Piperacillin/Tazobactam (Zosyn®) and Vancomycin
- Passed swallow evaluation today
- Cultures:
  - Sputum: Normal Flora
  - MRSA Nares: Negative
  - Blood: No growth
- What should be the next steps?

A. Continue Zosyn®/Vancomycin for a total of 14 days
B. Discontinue Vancomycin and continue Zosyn® for a total of 7 days
C. Discontinue Vancomycin and change Zosyn® to Levofloxacin (Levaquin®) x 7 days

Duration of Antibiotic Therapy for Ventilator-Associated Pneumonia Caused by Non-Fermentative Gram-Negative Bacilli

- 452 Ventilator-Associated Pneumonias (VAP)
  - 154 Caused by Non-Fermenting Gram Negative Bacilli
- 27 patients treated for a mean of 6.4 days
- 127 patients treated for a mean of 17 days
- Recurrence Rates
  - Short Course: 22%
  - Longer Course: 34%

P=0.27

Hedrick TL etal. *Surgical Infections.* (2007):6(8);589-98

Resistance Potential

Not all antibiotics are equal

Least Resistance Potential
- **Pipperacillin/tazobactam (Zosyn®)**
- **Amoxicillin/Clavulanate (Augmentin®)**
- **Sulfamethoxazole/Trimthoprim (Bactrim®)**
- **Azithromycin (Zithromax®)**
- **Tobramycin**
- **Vancomycin**
- **Doxycycline**

More Resistance Potential
- **Levofloxacin (Levaquin®)**
- **Meropenem (Merrem®)**
- **Ceftriaxone (Rocephin®)**
- **Cefotetan (Cefotan®)**
- **Ceftazidime (Fortaz®)**
- **Clindamycin (Cleocin®)**

Treatment of Bad Bugs

Clinical Scenario

- 75 yom hemodialysis patient
- Admitted for dialysis graft infection
- Blood Cultures:
  - MRSA with Vancomycin MIC 2
- What should be the next steps?
  - Vancomycin
  - Daptomycin
  - Ceftaroline

Treatment of MRSA with elevated MICs

- Patients with previous vancomycin therapy are at risk
- Cross-resistance to daptomycin
  - Higher doses are needed: 8 to 10 mg/kg
  - Monitor CPK
- Ceftaroline
  - Maintains activity for vancomycin and daptomycin intermediate/resistant strains[1]
  - Dose should be increased to q8[2]
  - Can be used with Daptomycin for enhanced activity[3]

[1]Saravolatz etal. Antimicrobial Agents and Chemotherapy. 2010;54(7):3027-30.
[2]Canut elal. *International Journal of Antimicrobial Agents.* 2015;45(4):399-405.
[3]Barber etal. *Journal of Antimicrobial and Chemotherapy.* 2015;70:505-509.

Clinical Scenario (VRE case)

- 45 yof quadriplegic due to a motor vehicle accident 1 year ago
- Presents with fever, increased wbc, and positive urine analysis
- Urine and Blood Cultures:
  - Enterococcus Faecium
    - Positive Vancomycin Resistance Screen
    - Other sensitivities pending
- Which is the most appropriate empiric therapy:
  A. Ampicillin IV
  B. Linezolid
  C. Daptomycin

Comparison of Effectiveness and Safety of Linezolid and Daptomycin in Vancomycin Resistant Enterococcal Bloodstream Infection: A National Cohort Study of Veterans Affairs Patients

- Retrospective Audit
  - VRE Blood Stream Infections from 2004-2013
  - Mortality, microbiologic failure, recurrence
  - N= 644
    - 319 Linezolid
    - 325 Daptomycin
  - Linezolid Arm
    - higher risk of treatment failure (P=0.001)
    - higher 30-day mortality (P=0.14)
    - Higher microbiologic failure rates (P=0.11)

Britt etal. *Clinical Infectious Diseases*. 2015;61(6):871-8.

Multi-Drug Resistant Pseudomonas

- Ceftazidime/avibactam (Avycaz®)
  - Avibactam
    - increased inhibition of class A and C β-lactamases
    - including ESBL, AmpC, and Klebsiella pneumoniae carbapenemase (KPC) enzymes[1]
  - Pseudomonas MIC breakpoints ≤ 8/4 mcg/ml
- Ceftolozane/tazobactam (Zerbaxa®)[2]
  - Ceftolozane inhibits Penicillin Binding Proteins of Pseudomonas aeruginosa
  - Pseudomonas MIC breakpoints ≤ 4/4 mcg/ml

[1]Zasowski etal. *Pharmacotherapy.* 2015;35(8):755-79.
[2]Zerbaxa Package Insert. http://www.merck.com/product/usa/pi_circulars/z/zerbaxa/zerbaxa_pi.pdf

Clinical Scenario

Case

- 32 yof sacral decub with osteomyelitis
- Paraplegic since 2013
- Resides in a nursing home
- **Now what??????**

Blood Culture

Susceptibility

	Klebsiella pneumoniae SFMC VITEK II	
Ampicillin	>=32 mcg/ml	Resistant
Ampicillin/sulbactam	>=32 mcg/ml	Resistant
Cefazolin	>=64 mcg/ml	Resistant
Cefepime	8 mcg/ml	Resistant
Cefoxitin	32 mcg/ml	Resistant
Ceftriaxone	32 mcg/ml	Resistant
Gentamicin	>=16 mcg/ml	Resistant
Levofloxacin	>=8 mcg/ml	Resistant
Meropenem	>=16 mcg/ml	Resistant
Piperacillin/Tazobactam	>=128 mcg/ml	Resistant
Tobramycin	>=16 mcg/ml	Resistant
Trimeth/Sulfamethoxazole	>=320 mcg/ml	Resistant

Carbapenem Resistant Enterobacteriaceae Treatment

- Studies support using multiple agents
- Which combinations to use are still debatable
  - Colistin + Meropenem +/- Rifampin
  - Colistin + Tigacycline 100 mg IV q12
  - Meropenem + Tigacycline 100 mg IV q12
  - Double Carbapenem therapy
- Tangden etal. Showed the best bactericidal effects with rifampin/meropenem/colistin
- Synergy effectiveness depends on the variant of beta-lactamase being produced

Tangden etal. *Antimicrobial Agents and Chemotherapy*. 2014;58(3):1757-62.

Post Test Questions

- What is the most common mechanism of resistances for gram negative bacteria
  - A. Beta-lactamases
  - B. Efflux Pumps
  - C. Porin Changes
- In a retrospective trial use of daptomycin for the treatment of vancomycin resistant enterococcus blood stream infections showed a decrease in mortality
  - A. True
  - B. False