Infectious Disease: Drug Resistance Pattern in New Mexico

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Are these the world’s sexiest accents?

• 13. Argentine
• 12. Thai
• 11. Trinidadian
• 10. Brazilian Portuguese
• 9. U.S. Southern
• 8. Scottish
• 7. Irish
• 5. Queen’s English
• 4. Czech
• 3. Spanish
• 2. French
• 1. Italian

• 6. Nigerian - Dignified, with just a hint of willful naivety, the deep, rich "oh's" and "eh's" of Naija bend the English language without breaking it, arousing tremors in places other languages can't reach.

Penicillin became commercially available in 1941, when was the first case of penicillin resistant Staphylococcus species reported?

• A. 1941
• B. 1942
• C. 1947
• D. 1952
• E. 1957

Methicillin was introduced in 1961, when was the first case of methicillin resistant Staphylococcus aureus (MRSA) in the U.S. reported?

• A. 1962
• B. 1964
• C. 1968
• D. 1968
• E. 1970

Vancomycin became commercially available in 1954, when was the first case of vancomycin resistant Staphylococcus aureus (VRSA) reported?

• A. 1972
• B. 1982
• C. 1992
• D. 2002
• E. 2012
Reasons for Increasing Antibiotic Resistance

- Total antibiotic consumption growing worldwide.
- 2000 – 2010 about 30% increase
- USA consumes 10% of world output
- Increased use of antibiotics in livestock
- Inappropriate use

- We know everything about antibiotics except how much to give – Maxwell Finland.

Largest five consumers of antimicrobials in livestock in 2010

Estimates of antimicrobial consumption in cattle, chickens, and pigs in OECD countries

Antibiotics and Obesity

Antibiotics as Growth Stimulants for Dairy Cattle: A Review

C. A. Lexier
Timing of Low-Dose Penicillin Treatment and Risk of Obesity.

Principles of Anti-infective Therapy
- Identification of the infecting organism and source of infection
- Determination of antimicrobial susceptibility of infecting organism
- Host factors
  - Previous adverse reactions
  - Age
  - Genetic or metabolic abnormalities
  - Pregnancy
  - Renal and hepatic function
  - Site of infection

Antibacterial Drug Classes
- β-lactams
- Aminoglycosides
- Tetracyclines and chloramphenicol
- Macrolides, clindamycin and ketolides
- Glycopeptides
- Polymyxins
- Oxazolidinones
- Quinolones
- Metronidazole
- Sulfonamides and Trimethoprim
- Rifamycins

Which of the following antibiotic class has the most drug-drug interactions?
- A. Penicillins
- B. Fluoroquinolones
- C. Macrolides
- D. Aminoglycosides
- E. Rifampin

β-lactams

Contains a β-lactam ring in their molecular structures.
Nitrogen is attached to the beta carbon relative to the carbonyl ring and hence the name.
How bacteria acquire genes that control resistance mechanisms

- Transduction via bacteriophages (bacterial viruses) – species specific
- Transformation: scavenger and incorporate DNA from dead bacteria
- Conjugation: cytoplasmic bridges between species with transfer of plasmids
- Spontaneous mutations

What is a plasmid?

- Extra chromosomal circular DNA
- Can replicate independent of chromosomal DNA
- Exchanged between species by conjugation
- Can carry multiple antibacterial resistance determinants

What is a transposon?

- Mobile short stretch of DNA
- Can move between different point within a genome by a process termed transposition
- Not capable of self-replication

What is an integron?

- Collects genes from transposons and forms chunks of DNA called cassettes
- Integrons allow transposons/cassettes to move from chromosome to plasmid DNA
- Then the plasmid DNA can spread via conjugation from one genus to another

Challenges Determining Resistance Mechanisms

- Bacterial have complex genetics including chromosomal and plasmid methods
- Phenotypic determination requires interpretation and can be subjective
- Molecular detection works well if the target of interest is known.
Major Mechanisms of Antibiotic Resistance

- Enzymatic inactivation – β-lactams
- Target site absent – intrinsic resistance
- Target site modification – MRSA PBP2 to PBP2a
- Excessive binding sites – hVISA and VISA
- Altered cell wall permeability - porin channel shrink up
- Drug efflux - tetracyclines

β-lactams Resistance

- β-lactams inhibit bacterial cell wall synthesis
- Peptidoglycan in cell wall protects bacterial against osmotic rupture
- β-lactams inactivate penicillin-binding proteins (PBPs)

Staphylococcal Resistance

- Penicillin became commercially available in 1941
- Staphylococcal resistance reported soon after
- Staphylococcal cassette chromosome (SCCmec) carries mecA gene that encodes an altered PBP2 – MRSA
- mecC is a novel gene that confers resistance, often cefoxitin resistant and oxacillin susceptible

Common Resistant Organisms in New Mexico

- Methicillin-resistant Staphylococcus aureus (MRSA)
- Escherichia coli (ESBL)
- Pseudomonas aeruginosa
- Vancomycin resistant Enterococcus faecium (VRE)
- Klebsiella pneumonia (ESBL and KPC)
- Acinetobater sp
- Stenotrophomonas maltophilia
- Clostridium difficile

β-lactams Resistance

- Destruction of antibiotic by β-lactamase
- Failure of of antibiotic to penetrate the outer membrane of gram-negative bacteria to reach PBP targets
- Efflux of drug across outer membrane of gram-negative bacteria
- Low-affinity binding of antibiotic to target PBPs
- NDM-1

Common Mechanisms of Resistance in Methicillin-Resistant Staphylococcus aureus.
**Vancomycin Resistance**

- HVISA: Heteroresistant VISA
  - Presence of subpopulations of VISA at a rate of 1 organism per $10^5$ to $10^6$ organisms
- VISA: Vancomycin intermediate S. aureus
  - MIC for vancomycin is 4-8µg/ml
- VRSA: Vancomycin resistant S. aureus
  - VRSA if the vancomycin MIC is ≥16µg/ml.

**Mechanisms of S. aureus resistance to vancomycin**

- Production of β-lactamase that hydrolyzes carbapenems
- Diminished permeability
- Efflux of drug across outer membrane of gram-negative bacteria
- Production of altered PBP target
- Intrinsic resistance – Proteus, Providencia, Morganella

**Carbapenem Resistant Organisms – CRE & KPC**

- Production of β-lactamase that hydrolyzes carbapenems
- Diminished permeability
- Efflux of drug across outer membrane of gram-negative bacteria
- Production of altered PBP target
- Intrinsic resistance – Proteus, Providencia, Morganella

**Treatment of Resistant Organisms**

- Consult local antibiogram
- Consult Infectious Disease
- Appropriate antibiotic therapy
- Antibiotic stewardship
MRSA and VRE Prevalence and Incidence Rates from 2012 to 2014

ESBL Rates from 2012 to 2014

MRSA, VRE and E.coli Resistant to ciprofloxacin from 2002 to 2013

Treatment of Resistant Bacteria – *Staphylococcus sp*

- TMP-SMX
- Doxycycline/Minocycline
- Clindamycin
- Linezolid
- Vancomycin
- Daptomycin
- Telavancin
- Tigecycline
- Quinupristin-Dalfopristin
- Oritavancin
- Dalbavancin
- Ceftaroline

Which of this drugs should not be used to treat MRSA that is resistance to erythromycin?

- A. TMP-SMX
- B. Doxycycline
- C. Clindamycin
- D. Linezolid
- E. Vancomycin
D-test for Macrolide-Inducible Resistance to Clindamycin

Treatment of Resistant Bacteria – Enterococcus sp
- Ampicillin
- Vancomycin
- Linezolid
- Daptomycin
- Quinupristin-Dalfopristin
- Combination treatment
  - Penicillin G + gentamicin
  - Ampicillin + ceftriaxone
  - Ampicillin + gentamicin
  - Daptomycin + Ampicillin or ceftaroline

What is the drug of choice for treatment of pansensitive Enterococcus faecalis?
- A. Ampicillin
- B. Vancomycin
- C. Linezolid
- D. Gentamicin
- E. Streptomycin

Treatment of MDR Gram-negative bacteria
- Carbapenems
- Colistin
- Polymyxin
- Tigecycline
- Sulbactam
- Doxycycline/Minocycline
- Ceftazidime/Aztreonam
- Ceftolozane/tazobactam

Treatment of Resistant Bacteria – ESBL
- Carbapenems
- Cephalosporin-β-lactamase agents
  - Ceftazidime-avibactam
  - Ceftolozane-tazobactam
- Aminoglycosides

Treatment of Resistant Bacteria – ESBL

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Treatment of Resistant Bacteria – MDR Pseudomonas

- Carbapenems
- Cephalosporin-β-lactamase agents
  - Cefazidime-avibactam
  - Ceftolozane-tazobactam
- Polymyxins
- Aminoglycosides

Carbapenems

- Imipenem, meropenem and doripenem (but not Ertapenem) are active against *P. aeruginosa* and *Acinetobacter*
- Used for ESBL producers and all are susceptible to *Acinetobacter* carbapenemases
- *Acinetobacter* activity of Doripenem > Imipenem > Meropenem, but differences are small
- Doripenem may be more effective for *P. aeruginosa* than other carbapenems.
- Use in combination therapy for MDR bacteria.

Polymyxins

- Active against most Gram-negative pathogens
  - >90% of *Acinetobacter, P. aeruginosa, E.coli, Klebsiella* and *Citrobacter*
  - >80% of *Enterobacter* are susceptible
- Resistance increasing, particularly in *P.aeruginosa, Acinetobacter*, and KPC producers
- Susceptibility issues/Formulation issues.
- Clinical indications
  - Bacteremia
  - VAP
  - Meningitis
  - Now mainstay treatment for MDR

Tigecycline

- Broad spectrum
  - Aerobes and anaerobes
  - Lacks activity for *P. aeruginosa*
- Activity against MDR isolates
- Clinical indications
  - VAP
  - Clinical resolution reported
  - Non-bacteremia
  - Low serum concentrations

Sulbactam

- Place in therapy
  - VAP
  - Aerosolized administration is experimental
- Bacteremia
- Meningitis
  - Limited data, non conclusive
- Not available in the US

What is the preferred dose of Piperacillin/tazobactam for treatment of *Pseudomonas aeruginosa* infections?

- A. 3.375 g IV q6h
- B. 3.375 g IV over 4 hours three times daily
- C. 4.5 g IV over 4 hours three times daily
- D. Continuous infusion of 13.5 g over 24 hours
- E. Continuous infusion of 16 g over 24 hours

Larry Danziiger, PharmD, FIDSA
Doxycycline/Minocycline

- Clinical indications
  - Minocycline has essentially the same spectrum of activity against microorganisms as doxycycline
  - *Stenotrophomonas maltophilia*
  - MDR *Acinetobacter baumannii*
- Clinical indications
  - VAP?
  - Bacteremia?

Combination Therapy

- Targets multiple mechanisms of action thereby preventing resistance
- Synergy among antibiotics resulting in broad spectrum
- To reduce severity or incidence of adverse effects
- No combination exhibits synergy consistently
- Combination therapy remains controversial

Potential Combinations

- Polymyxin B + carbapenems
- Polymyxin B + rifampin
- Polymyxin B + carbapenems + rifampin
- Polymyxin B + Doxycycline
- Polymyxin B + ceftriaxone
- Carbapenems + rifampin
- Tigecycline + aminoglycosides

Treatment of Resistant Bacteria – *Clostridium difficile*

- Metronidazole
- Oral vancomycin
- Fidaxomicin
- FMT

Questions?