ANTIMICROBIAL RESISTANCE
HOW CAN THE LAB HELP?

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LEARNING OBJECTIVES
- Describe difference between qualitative & quantitative antimicrobial susceptibility testing [AST] and the clinical value of each
- Discuss resistance mechanisms utilized by gram negative bacteria
- Recognize unusual/improbable AST result

ANTIBIOTIC SUSCEPTIBILITY TESTING
ROLE OF THE LAB
- IMPLEMENT CURRENT CLSI (CLINICAL LAB STANDARDS INSTITUTE) GUIDELINES
- TEST & REPORT DRUG SUSCEPTIBILITIES BASED ON PATHOGEN & SOURCE OF INFECTION
  - E.G. URINE, BLOODS
  - IN VIVO & IN VITRO CORRELATION
- DRUG RESISTANCE MECHANISMS OF ACTION
- ANNUAL ANTIBIOTIC GRAMS
  - UNIT SPECIFIC, e.g. MICU, SICU, PICU
  - CHOOSE APPROPRIATE EMPIRIC THERAPY BASED ON PREDICTABLE RESISTANCE PATTERNS
- LAB REPORTING SYSTEMS
  - SIR vs. MIC
- TESTING NEW ANTIMICROBIAL AGENTS
  - PROVIDE INTERPRETIVE CONSULTATION

WHAT AFFECTS CHOICE OF ANTIMICROBIAL AGENTS?
- ANTIMICROBIAL SUSCEPTIBILITY TEST RESULTS
- PHARMACODYNAMICS
  - AUC:MIC, RATIO
  - HALF LIFE OF DRUG
  - TIME ABOVE THE MIC
- CONCENTRATION DEPENDENT KILLING
  - Greater cidal activity with higher concen (e.g. aminoglycosides, B-lactams)

ANTIBIOTIC SUSCEPTIBILITY TESTS
- MIC VALUE
  - LOWEST CONCENTRATION OF ANTIMICROBIAL WHICH WILL INHIBIT GROWTH
  - MICROSCAN or VITEK SEMIAUTOMATED
  - E-STRIPS (DISK GRADIENT)
  - TIME TO RESULTS: 18 - 24 HRS
- SIR, NO MIC
  - QUALITATIVE INTERPRETATION
  - DISK DIFFUSION (KIRBY- BAUER)
  - TIME TO RESULTS: 18 - 24 HRS
  - NOT SUFFICIENT FOR STERILE FLUIDS
- QUESTIONS TO ASK......
  - S.aureus IS ERYTHRO RESISTANT
    - IS IT A PREDICTOR OF CLINDA RESISTANCE?
  - LAB REPORTS PENICILLIN RESISTANT GP A STREP
    - IS THIS BELIEVABLE?
  - LAB REPORTS YEAST FROM BLOOD CULTURE
    - WHAT EMPIRIC TREATMENT IS RECOMMENDED?

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SUSCEPTIBILITY TESTING

Assumptions

- BLOODSTREAM INFECTION
- HOMOGENEOUS BACTERIAL POPULATION
- SUCCESS = ERADICATION OF ORGANISM

SUSCEPTIBILITY TESTING

Reality

- SITE OF INFECTION:
  - INFLAMED LUNG W/ PURULENT SECRETIONS
  - ABSCESS
  - CSF
- HETEROGENEOUS BACTERIAL POPULATION
  - MULTIPLE SPECIES
  - MULTIPLE MORPHOTYPES
- BIOFILM

Implications of Multi-Resistant Organisms

- EPIDEMIOLOGY
- TREATMENT
- INFECTION CONTROL
- TRANSPLANT ELIGIBILITY

ANTIMICROBIAL SUSCEPTIBILITY TESTING METHODOLOGIES

- DISK DIFFUSION
  - Kirby-Bauer
- BROTH DILUTION
  - Microbroth
  - Microscan
  - Vitek
- E TEST

DISK DIFFUSION

PROS
- EASY TO PERFORM
- FLEXIBILITY
- NO EQUIPMENT NEEDED

CONS
- NON QUANTITATIVE
- NON AUTOMATED
- INACCURATE FOR POORLY DIFFUSING DRUGS
- DATA LACKING FOR SLOW GROWING ORGANISMS
**BROTH DILUTION**
- **PROS**
  - Quantitative
  - Wide range of organisms
  - Commercially prepared panels
  - Automation
- **CONS**
  - Pre-determined format
  - Less reliable for certain organisms

**E-STRIP MIC TEST**
- Gradient agar diffusion preformed antimicrobial gradient
- Plastic coated strip
- MIC read at point of elliptical growth inhibition
- Can use on fastidious organisms
- Confirmation of unusual resistance
- Expensive

**E TEST**
- **PROS**
  - Simple to perform
  - Flexibility
- **CONS**
  - Expensive

**EXAMPLES OF FLAGGED RESULTS**
- *E. coli*: Imipenem Resistant
- *S. pneumoniae*: Vancomycin Resistant
- *Kleb pneumo*: Amikacin Resistant, Gent/Tobra Susceptible
- *S. aureus*: Penicillin Susceptible
- *E. cloacae*: Ampicillin Susceptible
- *A. baumanii*: Aztreonam Susceptible

**SUSCEPTIBILITY TESTING CURRENT CHALLENGES**
- Focus time, effort and finances on critical care patients
- Does every patient isolate need an MIC?
- How good are we at detecting resistance?
WHEN IS MIC TESTING NECESSARY?
- Life threatening infections
  - Endocarditis
  - Meningitis
  - Osteomyelitis
- Immunocompromised patients
- Critically ill patients

HOW TO USE MIC DATA
- For individual patient therapy
  - Selection of antibiotic
  - Dosage
    - Efficacy
    - Efficiency
    - Toxicity
  - Combination therapy
- Investigation of unusual AST results
- Detection of specific resistance mechanisms

USING MICs TO OPTIMIZE THERAPY
- More institutions are utilizing MIC data to manage critical patients
- Pharmacokinetics
  - Drug levels in blood, CSF, tissue, infection site vs the MIC
- Pharmacodynamics
  - Drug properties that affect bacterial eradication rate vs the MIC

PHARMACOKINETICS
- Antibiotic:
  - Route of administration
  - Dose
  - Metabolism
  - Elimination
- Drug levels in blood and infected tissues
- PK is what the body does to the drug

PHARMACODYNAMICS
- Antibiotic penetration
- Receptor binding affinity
- Resistance mechanism
- Host immunity
- Virulence
- PD is what the drug does in the body

PK/PD REQUIRE PRECISE MICs
- Aminoglycosides
  - C max
- Fluoroquinolones
  - AUC
- Beta lactams
  - Time over the MIC
NAME CALLING AST JARGON

- MRSA - Methicillin-Resistant *S. aureus*  
  > 44% at CUMC
- VISA- Vanco-intermediate *S. aureus*
- VRSA- Vanco-resistant *S. aureus*
- VRE- Vanco R *E. faecium*  
  > 81% in CUMC
- ESBLs in GNR  
  > 18% in CUMC

PREDICTABLE RESISTANCE

- Salmonella, Shigella  
  - Stool: Ampicillin, quinolone, T/S ONLY will be reported  
  - Extraintestinal: above + chloramphenicol, 3rd gen cephalosporin
- Enterobacter, Serratia  
  - Ampicillin & 1st & 2nd generation cephalosporins are NOT reported  
  - Routine resistance
- Stenotrophomonas  
  - Inherent resistance to nearly all antimicrobics  
  - ONLY T/S, Timentin & fluoroquinolone are reported
- Enterococcus  
  - Cephalosporins, aminoglycosides, clinda, T/S will NOT be reported

THE “USED TO BE” PREDICTABLE AST PATTERNS

<table>
<thead>
<tr>
<th>ORGANISMS</th>
<th>PREDICTABLE [Not so much...]</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>K. pneu</em></td>
<td>Susceptible to Imipenem</td>
</tr>
<tr>
<td><em>P. aeruginosa</em></td>
<td>Susceptible to Cipro</td>
</tr>
<tr>
<td><em>Salmonella</em></td>
<td>Susceptible to Cipro</td>
</tr>
<tr>
<td><em>S. aureus</em></td>
<td>Susceptible to Vanco</td>
</tr>
<tr>
<td><em>E. faecium</em></td>
<td>Susceptible to Linezolid</td>
</tr>
<tr>
<td><em>Any organism</em></td>
<td>Susceptible to at least one antibiotic</td>
</tr>
</tbody>
</table>

TOUGH BUGS ON THE BLOCK

- MRSA & VRE  
  > COST TO TREAT MRSA 3X MSSA
- ESBLs  
- Carbapenam- resistant GNR  
  > Klebsiella pneumoniae  
- Acinetobacter baumannii  
- Pseudomonas aeruginosa  
- Stenotrophomonas maltophilia
- Metallo- ß –Lactamases

AST NOT AS EASY AS IT SEEMS!

- > 1 method sometimes needed  
  - MRSA  
  - VRE  
  - ESBL
- Review results for unusual antibiogram patterns
- Update new interpretive guidelines
- Some microbes lack CLSI guidelines

ENDOCARDITIS CASE

- 61 yo male with persistent fevers  
- Suspected subacute bacterial endocarditis
- Two sets of blood cultures collected  
- Positive the next day for coagulase negative *Staphylococcus*
- AST panels are set up for isolates 1 & 2
ENDOCARDITIS CASE
MIC VALUES

- ISOLATE #1
  - OXACILLIN 0.5
    - Resist
  - PENICILLIN 1.0
    - Resist
  - VANCO 1.0
    - Susceptible
  - CLINDA
    - Susceptible
  - ERYTHRO < 0.25
    - Susceptible

- ISOLATE #2
  - OXACILLIN 1.0
    - Resist
  - PENICILLIN 0.5
    - Resist
  - VANCO 0.5
    - Susceptible
  - CLINDA <0.25
    - Susceptible
  - ERYTHRO < 0.25
    - Susceptible

ARE THESE THE SAME ISOLATE?
MICS WITHIN 1 2-FOLD DILUTION OF EACH OTHER ARE CONSIDERED THE SAME

ENDOCARDITIS CASE
POINTS TO PONDER

- ARE THE ISOLATES REALLY RESISTANT?
  - MICs ARE VERY LOW [0.5 AND 1.0]
  - S. AUREUS OXACILLIN RESISTANCE > 4
  - BREAKPOINTS FOR CNS & OXACILLIN WERE REVISED
  - MANY CNS STRAINS CONTAINED MECA BUT HAD OXACILLIN MICS BELOW THE 4 UG/ML BREAKPOINT
  - NOW THERE ARE TWO SETS OF OXACILLIN BREAKPOINTS

<table>
<thead>
<tr>
<th>SUB</th>
<th>RES</th>
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<tbody>
<tr>
<td>SA</td>
<td>≤ 2</td>
</tr>
<tr>
<td>CNS</td>
<td>≤ 0.25</td>
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ARE THESE THE SAME ISOLATE? MICS WITHIN 1 2-FOLD DILUTION OF EACH OTHER ARE CONSIDERED THE SAME

NEONATAL SEPSIS

- Female full-term neonate developed fever of 103 at 2 days of age
- Irritable & not feeding well
- Mom’s pre-natal screen at 36 wks gestation was positive for Grp B strep
  - MOM WAS PEN ALLERGIC SO RECEIVED IV CLINDAMYCIN DURING DELIVERY
  - PREGNANCY UNEVENTFUL OTHER THAN PROM @ 20H PRIOR TO DELIVERY
  - Blood cultures collected from neonate & prophylactic ceftriaxone was initiated
  - Signs of improvement w/in 6 hrs

SUS RES
SA < 2
CNS < 0.25

WHY WAS CLINDA NOT EFFECTIVE IN PREVENTING THIS INFECTION?

Beta-hemolytic Streptococci*
Erythromycin/Clindamycin

<table>
<thead>
<tr>
<th>MECHANISM</th>
<th>DETERMINANT</th>
<th>ERY</th>
<th>CLIN</th>
</tr>
</thead>
<tbody>
<tr>
<td>EFFLUX</td>
<td>MEF</td>
<td>R</td>
<td>S</td>
</tr>
<tr>
<td>RIBOSOME MODIFICATION</td>
<td>ERM</td>
<td>R</td>
<td>5**</td>
</tr>
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* Groups A, B, C, G
**Requires induction to show resistance
BETA-HEMOLYTIC STREPTOCOCCUS RESISTANCE RATES (USA)*

- Beta-hemolytic Streptococcus spp.
  - AMPICILLIN/PENICILLIN/VANCO: 0%
  - Group A
    - ERYTHROMYCIN: UP TO 10%
    - CLINDAMYCIN: UP TO 7%
  - Group B
    - ERYTHROMYCIN: UP TO 25%
    - CLINDAMYCIN: UP TO 15%

*commonly quoted rates; select studies may have reported higher rates

When the pieces of the puzzle don’t quite fit....

- URINE CULTURE OBTAINED FROM LONG-TERM-CARE FACILITY PT
  - Patient hx significant for diabetes, peripheral vascular disease & chronic renal failure
- CULTURE RESULTS:
  - >100,000 CFU/ml Staphylococcus aureus
  - OXACILLIN 4 RESISTANT
  - CHLORAMPHENICOL 4 SUSCEPTIBLE
  - LINEZOLID 2 SUSCEPTIBLE
  - RIFAMPIN 1 SUSCEPTIBLE
  - TRIMETH/SULFA 2/38 SUSCEPTIBLE
  - VANCOMYCIN 4 SUSCEPTIBLE

Clindamycin Disk Diffusion Induction Of Resistance

- WHEN?
  - Erythromycin resistant/Clinda susceptible isolates
- WHY?
  - 2 mechanisms of macrolide resistance
    - Efflux [msrA]
    - Ribosome alteration [erm]
  - Inducible resistance requires ery-produced methylase

PUZZLE PIECES

- Patient was started on vancomycin
- Urine cultures remained positive for S. aureus
- WHAT’S GOING ON?
- Patient was started on vancomycin
- Urine cultures remained positive for S. aureus
- Further testing by lab
  - E test MIC = >256 RESISTANT!!
  - Isolate was positive for
  - meca OXACILLIN RESISTANCE
  - vanA VANCOMYCIN RESISTANCE MECHANISM FROM VRE
- WHAT HAPPENED??????
- Automated systems are unable to detect VRSA
- CDC recommends utilization of vancomycin screen agar plate

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**VISA**
- VISA—INTERMEDIATE TO VANCO
  - 1st ISOLATED IN 1996 IN JAPAN
  - 8 PTS TO DATE IN USA
  - MECHANISM OF RESISTANCE: THICKENED CELL WALL AND/OR AN EXTRACELLULAR MATRIX ??
  - PATIENTS HAD PRIOR EXPOSURE TO LONG TERM VANCOMYCIN THERAPY
- 2 VISA ISOLATES FOUND SUSCEPTIBLE TO OXACILLIN
  - ONE WAS MECA POS & ONE NEG
  - OXACILLIN RESISTANCE IS NOT NECESSARY FOR VISA PHENOTYPE
- NO CLONAL SPREAD OF SINGLE STRAIN

**VRSA JUNE 2002**
- 1st case in 40 yr old diabetic woman from Michigan
- VRSA from dialysis cath tip
- Recurrent foot ulcer infected with VRE & MRSA

**MICHIGAN VRSA CASE**
- THE USA VRSA ISOLATE
  - MRSA — METHICILLIN MIC >16 µg/mL
  - VANCOMYCIN MIC 1,024 µg/mL
  - SUSCEPTIBLE TO LINEZOLID, MINOCYCLINE, QUIN/DALFO, CHLORO and SXT
- CONJUGATIVE TRANSFER
  - VRSA ISOLATE HAD vanA RESISTANCE GENE & meCA
  - vanA TRANSPONSON JUMPED FROM VRE CONJUGAL PLASMID TO A RESIDENT PLASMID IN MRSA STRAIN TO BECOME VRSA

**CLSI Interpretive Criteria Vancomycin Staphylococcus spp.**

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<thead>
<tr>
<th>METHOD</th>
<th>VISA</th>
<th>VRSA</th>
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<tbody>
<tr>
<td>MIC (µg/ml)</td>
<td>≤4</td>
<td>8-16</td>
</tr>
<tr>
<td>Disk (30 µg) (mm)</td>
<td>≥15</td>
<td>-</td>
</tr>
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**VRSA (3 isolates encountered to date)**

<table>
<thead>
<tr>
<th>Isolate</th>
<th>Vanco MIC1 (µg/ml)</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>1,024</td>
</tr>
<tr>
<td>2</td>
<td>32 2</td>
</tr>
<tr>
<td>3</td>
<td>64 2</td>
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1 Reference broth microdilution MIC
2 Missed or inconsistent results (some ≤2 µg/ml) with automated methods

404 CDC RECOMMENDATION: ADD VANCOMYCIN AGAR SCREEN WITH AUTOMATED METHOD

**ICU SEPSIS**
- 64 yo male patient, cardiac ICU post-CABG
- Becomes febrile and hemodynamically unstable
- Blood cultures x 2 are collected
- Culture Results:
  - Klebsiella pneumoniae
    - Amikacin 8 S
    - Cefoxitin 4 S
    - Ceftazidime ≥32 R
    - Ceftriaxone 8 S
    - Imipenem 4 S
- Based on AST, patient treated w/ ceftriaxone
- Remains febrile
- Blood cultures collected
- Positive for K. pneumoniae
- What’s going on?
**KLEBSIELLA PNEUMONIAE**

**TYPICAL ESBL AST PATTERN**

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<td>8 S</td>
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<tr>
<td>Cefoxitin</td>
<td>4 S</td>
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<td>Cefazolin</td>
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</tr>
<tr>
<td>Ceftazidime</td>
<td>≥32 R</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>≤1 S</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>≥8 R</td>
</tr>
<tr>
<td>Imipenem</td>
<td>≤4 S</td>
</tr>
<tr>
<td>Piperacillin/Tazobactam</td>
<td>8/2 S</td>
</tr>
<tr>
<td>Aztreonam (monobactam)</td>
<td>≥32 R</td>
</tr>
<tr>
<td>Trimethoprim/Sulfamethoxazole</td>
<td>8/152 R</td>
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**IMPACT OF DRUG RESISTANT GNRs IN HOSPITALS**

- **NOTORIETY: OUTBREAKS & DRUG RESISTANCE**
  - Nosocomial NEMESIS
  - Drug resistance makes Gram-negatives more difficult to treat
  - Real-time molecular detection methods for GNR lag behind its Gram-positive relatives
  - Nosocomial infections are associated with poor patient outcomes
    - 5%–35% admitted to ICUs
    - Nosocomial pneumonia in the ICU is a leading cause of mortality

**BIRD’S EYE VIEW RESISTANT GNRs**

- **SUPER RESISTANT GNR PATHOGENS**
  - *ACINETOBACTER*
  - *KLEBSIELLA*
  - *PSEUDOMONAS*

- **ANTIMICROBIAL RESISTANCE ARSENAL**
- **AST CHALLENGES**
- **FUTURE PROSPECTS**

**DEFINING DRUG RESISTANCE**

- **MULTIDRUG-RESISTANCE (MDR)**
  - >1 of 5 drug classes

- **PANRESISTANCE**
  - Complete/nearly complete lack of treatment options
    - Due to multiple resistance mechanisms
    - Resistance to all antibiotics recommended for treatment
    - Colistin/polymyxin B

**WHAT DRIVES MDR INFECTIONS?**

- **ANTIBIOTIC SELECTIVE PRESSURE**
- **LONG TERM CARE FACILITIES & PRIOR HOSP**
  - Colonization pressure & transmission
- **RISE IN IMMUNOCOMPROMISED & ICU PATIENTS**
  - Require ventilation, catheters, etc

- **THE POWER OF THE MICROBE!!!**

**A.baumanni**

**Variety Pack of Resistance Factors**

- **Metallo-β-Lactamases**
  - OXA, IMP, VIM on Integrons, i.e., Genetic elements with
    - Gene cassettes with antibiotic resistance genes
    - Integration sites for the cassettes
    - Some are located within transposons
  - Carbapenemase-hydrolyzing Class D

- **AmpC**
- **Outer membrane protein (OMP)**
  - Porin loss: Less antibiotic entering periplasmic space

- **Efflux Pumps**
  - Natural role is to remove chemicals that could disorganize cytoplasmic membrane
  - Resistance: expels β-lactams & other antibiotics by pump out of porin channels to outer membrane
  - Aminoglycoside-modifying enzymes (Target modification)
β-LACTAMASES: CLASS A

**KPC**
- The most common Carbapenemase in the USA
- Enzyme may be hard to detect in vitro
- Plasmid-mediated
  - *K. pneumoniae*
  - *Enterobacter*
- CUMC *K. pneumoniae*
  - 13 strains KPC-2
  - 2 strains KPC-3

CARBAPENEMASE DETECTION

**AUTOMATED INSTRUMENTS**
- ACCURACY OF CARBAPENEM NONSUSCEPTIBLE RESULTS IS QUESTIONABLE
- IF CARBAPENEM INTERMEDIATE/RESISTANCE CONFIRM WITH OTHER TEST METHOD

**E-TEST CONFIRMATION**
- SUBSTRATES FOR ENZYME HYDROLYSIS
  - ERTAPENEM, IMPENEM, MEROPENEM
  - ERTAPENEM IS THE BEST IN VITRO INDICATOR FOR CARBAPENEM RESISTANCE

EXTENDED SPECTRUM β-LACTAMASES

- FIRST DESCRIBED IN 1983
- ESBLS ARE β-LACTAMASES THAT MEDIATE R TO
  - 3RD GEN CEPHALOSPORINS BUT THESE CAN APPEAR SUSCEPTIBLE WHEN TESTED IN LAB
  - MONOBACTAMS (E.G. AZTREONAM)
  - EXTENDED SPECTRUM PENICILLINS (E.G. PIPERACILLIN)
- STRUCTURAL GENES
  - PLASMID-MEDIATED
    - Altered configuration of TEM-1 & 2, SHV-1 near active sites to increase hydrolytic ability for cephalosporins
    - Susceptible to cefoxitin (cephamycin), β-lactamase inhibitors (but enzyme hyperproduction might overwhelm inhibitors)
    - Susceptible to carbapenems
    - CHROMOSOME-MEDIATED AMP C
      - AmpC in *Serratia, Pseudo, Proteus, Citro, Enterobacter*)
    - PLASMID-MEDIATED AMP C
      - Amp C in *K. oxytoca*
      - R1 in *K. oxytoca*
      - Resistant to cefoxitin (cephamycin) & β-lactamase inhibitors

ESBL LAB CONFIRMATION

- COMPARE SYNERGISTIC ACTIVITY OF CEFTAZIDIME & CEFOTAXIME WITH/ WITHOUT CA
  - E-strip shows MIC decrease of >3 doubling dilutions for either drug in presence of CA
  - SUSCEPTIBLE TO 3RD GEN CEPHALOSPORINS
  - RESISTANT TO AZTREONAM
  - LAB DETECTION: *K. pneumoniae, K. oxytoca, E.coli* & most recently *Proteus mirabilis*
  - ESBLs exist in many Enterobacteriaceae
  - Detection masked by other resistance factors
  - LAB REPORTS FOR ESBLs
    - Resistant to all β-lactams, penicillins, & β-lactam combination drugs (due to hyperproduction of enzyme that might overwhelm inhibitors)

ESBL PHENOTYPIC CONFIRMATORY TESTS

- To confirm screening results, compare the MIC values of:
  - Ceftazidime to ceftazidime+clavulanate
  - Cefotaxime to cefotaxime+clavulanate
  - ESBL = >3 DOUBLING DILUTION DECREASE FOR EITHER DRUG IN THE PRESENCE OF CLAVULANATE
MORE KLEBSIELLA RESISTANCE

- At least three mechanisms described that result in imipenem resistance among strains of *K. pneumoniae* among isolates recovered from patients in New York City
  - *ampC* hyperproduction with concomitant loss of outer membrane porins
  - KPC-2
  - KPC-3

AMP C β-Lactamases

- Class C β-Lactamase
- Plasmid-mediated or Chromosomal
- Hydrolyzes 2nd & 3rd generation cephalosporins
- Not inhibited by β-lactamase inhibitors

Test Amp C (plasmid-mediated)
- Disk impregnated with EDTA
- Place on lawn of cefoxitin-susceptible *E. coli*
- Disk inoculated with clinical strain, almost touching EDTA disk
- Incubate overnight
- Amp C Positive = cefoxitin resistance

AMP C TEST (EDTA)

PLASMID-MEDIATED Metallo-β-Lactamases

- Resistance to all β-lactams except Aztreonam
- Zinc containing β-lactamases
  - Inhibited by EDTA
- Not inhibited by CA, tazobactam or sulbactam
- IMPS 1-8: *K. pneumoniae, P. aeruginosa, A. baumannii*
  - Imipenem Resistant
- VIMs 1-4: *P. aeruginosa*
  - Imipenem Resistant

TREATMENT OF RESISTANT GNRs

- Bad bugs, No drugs!!
  - Limited new antimicrobials on the horizon
  - Optimize control measures & antimicrobial restriction policies
- Monotherapy
  - *A. baumannii*
  - Carbapenems, polymyxins
  - Stenotrophomonas
  - Bactrim
  - Timentin, Levoquin
- Combination Therapy? Still controversial
  - *Many in vitro and in vivo studies are associated with improved outcomes*

TO THE RESCUE?

- NEW ANTIBIOTICS
  - LINEZOLID
  - SYNERCID
  - DAPTOMYCIN
  - ERTAPENEM
  - TIGECYCLINE

- BACK FOR A 2ND CHANCE!
  - COLISTIN
  - POLYMYXIN B
NEW DRUG

TIGECYCLINE (TYGACIL)
- Active against *A. baumannii*, *K. pneumoniae*, *S. maltophilia*
- Not affected by any β-lactamases, including ESBLs
- Do NOT test *P. aeruginosa*
- Indicated for intra-abdominal infections
- No CLSI breakpoints currently exist

NEW APPLICATIONS OF OLD DRUG

Colistin (polymyxin E) or Polymyxin B
- IV: *P. aeruginosa* or *A. baumannii*
- Inhalation treatment for ventilator-associated pneumonia
- Nephrotoxicity 8-36%
- Neurotoxicity rare

SYNERGY TESTING
A NEW PLAN OF ATTACK!

- CHOOSE TWO ANTIBIOTICS WITH DIFFERENT MECHANISMS OF ACTION
- COMBINE THEM TO SEE WHETHER THEY ARE MORE EFFECTIVE IN COMBINATION THAN EITHER IS INDIVIDUALLY
- CLINICAL OUTCOME DATA NEEDED TO SUPPORT SYNERGY TESTING FOR:
  - CYSTIC FIBROSIS ISOLATES (*Pseudomonas*)
  - PANRESISTANT GRAM-NEGATIVES
  - Polymyxin + Rifampin, Imipenem or Azithro
  - Rifampin + Sulbactam, Imipenem or Azithro
- DETERMINE FIC (FRACTIONARY INHIBITORY CONCENTRATION)

CONTROLLING RESISTANCE

STRATEGIES
- ANTIBIOTIC AGENTS RESTRICTED TO ID CONSULTATION
- COMPUTERIZED GUIDE TO DRUG SELECTION
- SELECTIVE SUSCEPTIBILITY REPORTING
- EDUCATION
- ACTIVE FORMULARY COMMITTEE

CONTROVERSIAL
- COMBINATION THERAPY
  - THEORETICALLY ATTRACTIVE
  - USEFUL FOR TB
  - EFFICACY NOT ADEQUATELY TESTED
  - CAN IT REDUCE OVERALL RESISTANCE?
- INCREASED COSTS
- ANTIBIOTIC ROTATION OR CYCLING