How to Interpret Automated Susceptibility Antibiograms and “Don’t fall in the ditch!”

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Case 1
- 72 nursing home male admitted to ICU with Foley associated urosepsis.
- IV Fluids, Piperclillin/Tazobactam, and Pressors were started after blood and urine cultures were submitted.
- Patient is now intubated and vent supported.
- On Day 2 bullous erythematous rash with foul smelling fluid is noted.

Case 1 Continues
- Blood, Urine and Bulla fluid grew E coli
- Automated Susceptibility
  - Ampicillin/ Sulb MIC = 16 ----I
  - Cefazolin MIC > 64 -----------R
  - Cefotetan MIC < 4  ----------- S
  - Ceftriaxone MIC >64----------R
  - Ceftazidime MIC = 16--------I
  - Aztreonam MIC = 8 -----------S
  - ESBL Pos +
  - Piperclillin/tazobactam =8 ------S
  - Imipenem MIC = 4-- --------S
What is ESBL?

Extended-spectrum β-lactamase (ESBL) is an enzyme that confers resistance to most β-lactam antibiotics (including piperacillin and all cephalosporins) except carbapenems.

- The gene that encodes this enzyme is carried on a plasmid that can be transferred promiscuously among most Gram negative bacteria, particularly Escherichia coli, Klebsiella pneumoniae and Enterobacter.
- ESBL may be partially inhibited in vitro by β-lactamase inhibitors and complex side chain of advanced generation cephalosporins resulting in false susceptibility to β-lactam/β-lactamase combination antibiotics, and advanced generation cephalosporins (e.g. Zosyn and Cefepime) on automated testing. If these antibiotics are used in vivo the gene will be induced, the ESBL will be produced and the patient will fail antibiotic therapy.

Don’t fall in the ESBL ditch!

- Automated testing machine MAY only label E coli and Klebsiella as ESBL
- Other ESBL + Enterobacteriaceae, particularly Enterbacter species will be missed by automated machines
- Resistance or intermediate susceptibility to Astreonam, Ceftazidime, or Ceftriaxone raise the red flag>>> Ask the lab to perform manual phenotypic testing for ESBL production.

Phenotypic Testing For ESBL Production

Presence of multiple resistance mechanisms may MASK ESBL at phenotypic testing
- ESBL + AmpC
- ESBL + Porin mutation
- ESBL may be present in other species of Enterobacteriaceae e.g. Enterobacter and Proteus making test problematic

Bad News, Phenotypic Testing May Still Miss ESBL !!!


http://www.aphl.org/courses/Pages/588-601-10.aspx

Antibiotics to Treat Infections Caused by ESBL + Organisms

- Carbapenems e.g. imipenem, ertapenem, meropenem, and doripenem
- Tigecycline (For non-septic, non-bacteremic patient WITHOUT ESBL + Organism UTI)
- Aminoglycosides e.g. Tobramycin and Amikacin

Antibiotic Resistance in Hospitals

Carbapenems Are Not The Answer and Should Not be the Work Horse of the Hospital Formulary!

- Carbapenem use is associated with increasing Gram negative bacterial resistance
- Carbapenems also increases VRE colonization and infection

Antimicrobial resistance is largely a consequence of selective pressures of Antimicrobial use


Consumption of Imipenem and not Pipercillin Correlated well with $\beta$-Lactam Resistance in Pseudomonas aeruginosa


Crabapenem Restriction to Control a Hospital Outbreak of Multiresistant Acinetobacter baumannii


Local Antimicrobial Resistance Data Trend Down of MDR Gram – ve bacteria with Carbapenem Restriction

Infection Control- James H Quillen VAMC

Enterobacteriaceae
Revised... Breakpoints (MIC µg/ml)

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CLSI Recently revised MIC breakpoints to better detect ESBL + Organisms.

http://www.aphl.org/courses/Pages/588-601-10.aspx
Case 2

- 75 y male with h/o CAD, lung ca s/p lobectomy, and gastrocolonic fistula s/p removal of migrated PEG tube. Admitted with ileus 10 days after placement of feeding jejunostomy.
- Receives 10 days course of imipenem
- Hospital course gets complicated with VRE PICC line associated bacteremia and Enterbacter pneumonia for which patient received daptomycin and another course of imipenem.
- New PICC is placed

Case 2 continues

- Patient develops new fever despite aggressive antibiotic therapy.
- Blood cultures are now growing MDR Enterobacter
- Imipenem is continued and second PICC line discontinued.
WHAT IS KPC?

- Klebsiella pneumoniae carbapenemases (KPC 1-7) are class A β-lactamases that can hydrolyze penicillins, cephalosporins, monobactams, and carbapenems.
- KPC β-lactamases are partially inhibited by clavulanic acid, often encoded by genes that are plasmid mediated.
- KPC + bacteria often carry other genes encoding resistance for other antimicrobial agents including aminoglycosides, fluoroquinolones, and trimethoprim/sulfamethoxazole.

KPC β-lactamases

- Initially described with Klebsiella pneumoniae.
- Now known to occur with other species from Enterobacteriaceae, such as Escherichia coli, and Enterobacter.
- Also isolated from Pseudomonas aeruginosa.

Geographic distribution of KPC worldwide

Don’t fall in the KPC ditch!

- Most automated testing systems machine will NOT detect, flag or alert the clinician to KPC production and will falsely show KPC + isolates as susceptible to imipenem and meropenem.
- Resistance or intermediate susceptibility to Ertapenem with susceptibility to imipenem or meropenem in high MIC range (≥ 2mcg/ml) >>> Ask the lab to perform manual phenotypic testing for KPC production.
Phenotypic Testing for KPC Production: Modified Hodge Test

Local KPC + Enterobacter Cloacae isolate tested at ETSU Microbiology Lab, Courtesy picture by Dr. Donald Ferguson 2/2010

Case 3

- 42 y diabetic female presents with foot infection.
- Primary care physician prescribes oral ciprofloxacin for outpatient therapy.
- She develops fever, spreading leg cellulitis and gets admitted to hospital.
- IV clindamycin is added as she has history of anaphylaxis on PCN.
- She continues to have fevers.

Antibiotics to Treat Infections Caused by KPC + Organisms

- Tigecycline (For non-septic, non-bacteremic patient WITHOUT KPC + Organism UTI)
- Aminoglycosides e.g. Tobramycin and Amikacin if susceptible
- Colistin

Case 3 (Continued)

- Foot wound drainage and Blood cultures grew MRSA
- CEFAZOLIN >=32 R
- CIPROFLOXACIN =4 I
- CLINDAMYCIN <=0.5 S
- ERYTHROMYCIN >=8 R
- OXACILLIN >=8 R
- ICR + Positive
- TRIMETHOPRIM/S <=10 S
- VANCOMYCIN 2 S
- BETA LACTAMASE POS +
- LEVOFLOXACIN = 2 S

Automated Susceptibility mcg/ml
**What is ICR?**

- Inducible clindamycin resistance is conferred by *erm* genes that encode enzymes which may confer inducible or constitutive resistance to macrolide, lincosamide and streptogramin (MLSβ) antibiotics via methylation of the 23S rRNA, reducing binding by MLS agents to the ribosome.

  Fiebelkorn et al., Journal of Clinical Microbiology, Oct. 2003, p. 4740-4744

**Don’t fall in the ditch!**

- Look for ICR on automated susceptibility panel before using clindamycin. It may be +ve and the machine will still falsely show clindamycin as susceptible.
- If ICR is not declared, and Staphylococcus isolate is resistant to erythromycin ask for D-test if you still want to use clindamycin.
- Don’t use clindamycin alone to treat serious MRSA infections with suspected complicating bacteremia.

**D-test to detect ICR**

Fiebelkorn et al., Journal of Clinical Microbiology, Oct. 2003, p. 4740-4744

**Don’t fall in the ditch!**

- Do not use ciprofloxacin to treat MRSA infections.
- Ciprofloxacin has higher MICs for fluoroquinolone susceptible MRSA.
- Ciprofloxacin may not achieve mutant prevention concentration *in vivo* selecting for quinolone resistant MRSA.

In Summary

- The clinician rather than the automated susceptibility system should do the math!
- ESBL + KPC+ and ICR+ are out there and cause increasing morbidity and mortality especially when clinicians miss them.

Thank You