ID Pearl: How to Interpret Minimum Inhibitory Concentrations (MICs)

Intended Audience: Physicians, Nurses, and Allied Health Providers

Clinical Controversy:

Below is the urine culture from a 22 yo female with acute uncomplicated cystitis. Her renal function is normal and she has no allergies. Based on the culture and MIC results, which antibiotic is most appropriate?

Organism	Escherichia coli > 100,000 CFU/ml
. Ampicillin	Susceptible 4 Method: MIC
. Ampicillin/Sulbactam	Susceptible <=2 Method: MIC
. Pip/Tazobactam	Susceptible <=4 Method: MIC
. Cefazolin	Susceptible <=4 Method: MIC
	Interpretive criteria based on dosage regimen of 2 g every 8 hours.
. Ceftriaxone .	Susceptible <=1 Method: MIC
. Cefepime	Susceptible <=1 Method: MIC
	Interpretive criteria based on dosage regimen of 1 g every 8 hours or 2 g every 12 hours.
. Gentamicin	Susceptible <=1 Method: MIC
. Tobramycin	Susceptible <=1 Method: MIC
. Ciprofloxacin	Susceptible <=0.25 Method: MIC
. Trimeth /Sulfa	Susceptible <=20 Method: MIC
. Nitrofurantoin	Susceptible <=16 Method: MIC

Myth:

- Ciprofloxacin is the most appropriate antibiotic to treat this patient's *E. coli*, because its minimum inhibitory concentration (MIC) is lowest compared to all other antibiotics
- Nitrofurantoin and Trimeth/Sulfa should be avoided because their number is higher and they might develop resistance quickly

Fact: In this case, nitrofurantoin would be the most appropriate antibiotic since it has the least collateral damage (i.e., low risk of cross resistance to other antibiotics and doesn't cause colonization with multi-drug resistant pathogens) and concentrates heavily in the urine

- MICs for different antibiotics cannot be compared to one another (they are apples & oranges)
- When all options are susceptible, you should consider PO availability, allergies, renal function, and risk of adverse effects, including collateral damage and *C. difficile*, to find the best available choice

How are bacteria tested for susceptibility in our microbiology lab?

There are two basic methods of antimicrobial susceptibility testing available at SMH:

- Quantitative – Vitek (most common) or Etest method: Gives you interpretation (S, I, R) as well as the MIC result. Typically reported as a concentration (e.g., Susceptible ≤ 2)
- Qualitative – Disk diffusion (Kirby-Bauer): Only gives you interpretation; there is no ability to compare the result to the breakpoint and assess impact on dosing/selection. Typically reported as a zone size of inhibition (e.g., 33 mm)

What is MIC?

- The lowest concentration of an antibiotic that inhibits the growth of an isolated bacterium
- It must be compared against a standard value, called a breakpoint, to determine if a specific antibiotic can be used against a given isolate
- MIC results are especially useful in determining the best drug and dose for severe, deep seeded infection (e.g., bacteremia, meningitis, osteomyelitis)

What is a Breakpoints and where do they come from?

- A breakpoint is a chosen concentration (mg/L) of an antibiotic which defines whether a species of bacteria is susceptible or resistant to the antibiotic
    - If the MIC is less than or equal to the susceptibility breakpoint the bacteria is considered susceptible to that particular antibiotic
- Developed by the Clinical and Laboratory Standards Institute (CLSI) and the Food and Drug Administration (FDA)
- Breakpoints are specific to a given drug used against a certain bacterium
    - Since antibiotics have different breakpoints for the same bacterium, MICs for different antibiotics cannot be compared to each other
        - For example, the susceptibility breakpoint for ciprofloxacin against Pseudomonas is 1 mg/L whereas the susceptibility breakpoint for cefepime is 8 mg/mL
        - This is because antibiotics reach different levels in the body and are able to kill bacteria at different concentrations, so their breakpoints will naturally differ
- Breakpoints are established after the analysis of *in vitro* susceptibility, the drug's pharmacokinetic and pharmacodynamic properties, and clinical trial data

What do the different interpretations mean?

- Susceptible
    - The patient's isolate should respond to normal dosing regimens of the antibiotic in question
- Intermediate
    - The patient's isolate may respond to the antibiotic in question if greater than normal dosing regimens are used or if the drug concentrates at the site of infection (e.g., many drugs concentrate in the urine)
    - Other options that are fully susceptible should be considered first in most cases
- Resistant
    - The patient's isolate is unlikely to respond to the antibiotic. The drug concentrations required to overcome resistance would cause toxicity in humans

Clinical Pearls

- The lab does not test every antibiotic against every given isolate
    - In many cases, antibiotic susceptibility can be inferred based upon results for similar antibiotics
    - E.g., in the above culture, cephalexin would be an appropriate option, because isolates susceptible to cefazolin are considered to be susceptible to cephalexin too
- If an isolate is susceptible to an antibiotic, ensure that the antibiotic is appropriate for the site of infection
    - Nitrofurantoin should **not** be used for a bloodstream infection irrespective of susceptibilities
    - Daptomycin should **not** be used for pneumonia due to inactivation by pulmonary surfactant
- *E. coli* and *Klebsiella* spp. carrying extended spectrum beta-lactamases (ESBLs) may appear susceptible to piperacillin/tazobactam in laboratory testing, but treatment failure may occur if this combination is used to treat severe life threatening infections (bacteremia, pneumonia)
- When deciding on definitive therapy, always try to give the most narrow-spectrum and safest option that targets the patient's infection while avoiding excessive coverage and risk of future resistance
- For serious gram-negative infections, consider Infectious Diseases input to ensure optimal treatment and follow-up

For the most up-to-date version of the common bacteria breakpoints please visit the SMH Stewardship Website

References:

1. Jorgensen JH, Ferraro MJ. Antimicrobial susceptibility testing: a review of general principles and contemporary practices. *Clin Infect Dis.* 2009;49(11):1749-55.
2. Bennett J, Dolin R, Blaser M, et. al. *Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases.* 8th ed. Philadelphia, PA: Elsevier Saunders; 2015.
3. CLSI. *Performance Standards for Antimicrobial Susceptibility Testing; Twentieth Informational Supplement*. CLSI document M100-S26. Wayne, PA: Clinical and Laboratory Standards Institute; 2016

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