# Episode 56: Bugs and Drugs Part 1 with Rachel Kruer

On this episode: Dr. Jed Wolpaw and Rachel Kruer

In this episode, episode 56, I welcome Rachel Kruer to the show. Rachel is one of our amazing ICU pharmacists and we discuss common bacteria and the drugs we use to treat them. This is part 1 of a 2 part series that I'll be doing with Rachel on this topic.

## Table of Contents

Hyperlinks to section of notes.

## Pharmacodynamics vs. Pharmacokinetics

1:08 – 7:09

- **Pharmacodynamics** is what drug does to body
    - **Time dependent killing** → drugs require certain amount of time above minimum inhibitory concentration
    - **Concentration dependent killing** → peak dependent killing
        - Eg. aminoglycosides
    - Total exposure dependent → dependent on area under the curve (AUC) above MIC
        - Eg. Vancomycin
    - **Minimum inhibitory concentration (MIC)** → minimum concentration of drug that inhibits the growth of the bacteria
        - Specific to bug-drug combination
        - Most microbiology lab will indicate whether infection is susceptible, intermediate, or resistant
        - Break point = highest MIC at which antibiotic will be able to achieve good killing
        - Also have to consider tissue penetration
- **Pharmacokinetics** is what body does to drug
    - Eg. body clearance of drug, renal dosing

## Categorizing Bacteria

7:10 – 12:09

- Gram positive vs. gram negative AND aerobic vs. anaerobic
    - For gram positive bugs, further categorized by:
        - Cocci vs. bacilli
        - Chains vs. clusters
    - For gram negative aerobic bugs, further categorized by:
        - Lactose fermenting or non-lactose fermenting
            - For non-lactose fermenting bugs, further categorized by:
                - Oxidase positive vs. oxidase negative
    - If have very sick patient, want to be broad → what grows initially may not be everything that is going on
- Rapid genetic tests may provide results within 3 hours

## Beta-Lactams

12:10 – 19:39

- Good gram positive activity, do NOT cover MRSA
- **Penicillins** → type of beta-lactams
    - Broadest penicillin is *Piperacillin Tazobactam* (aka Tazocin) → only one in this class that covers Pseudomonas
- May contain beta-lactamase inhibitor which would extend coverage
    - One of resistance mechanisms of bacteria is to upregulate beta-lactamase enzyme → enzyme inactivates beta-lactams in antibiotics
    - Eg. *ampicillin sulbactam*

    - Extended beta lactamase bacteria (ESBLs) are not going to be susceptible to beta-lactam and beta-lactamase inhibitor combinations
- **Cephalosporins** → another type of beta-lactams
    - Good gram positive activity
    - Gram negative coverage improves from 1st to 4th generation
        - Enterococcus is resistant to cephalosporins
    - First generation cephalosporins
        - Eg. *Cefazolin*
        - Used for surgical prophylaxis because covers skin infections well
        - Some gram negative coverage: covers E. Coli, does not cover Pseudomonas
    - Second generation cephalosporins: less gram positive, but ↑ gram negative coverage
        - Eg. *Cefoxitin, Cefotetan*
    - Third generation cephalosporins
        - Eg. *Ceftriaxone, Ceftazidime*
        - Ceftriaxone used for non-catheter associated UTI, community acquired pyelonephritis, community acquired pneumonia
    - Fourth generation cephalosporins
        - Eg. *Cefepime*
        - Really good gram negative coverage, covers Pseudomonas
        - Compared to Tazocin, Cefepime doesn't cover anaerobes or enterococcus
        - Used for urosepsis during hospital stay, hospital acquired pneumonia
    - Fifth generation cephalosporins
        - Eg. *Ceftaroline*
        - Covers MRSA
        - Good gram negative coverage, but doesn't cover Pseudomonas
- Cephalosporin and beta-lactam combination
    - *Ceftolozane and tazobactam*
        - New drug → reserved for salvage therapy for multi-drug resistant pseudomonas
    - *Ceftazidime-avibactam*
        - May have role in some ESBL and carbapenase producers
        - Reserved as salvage therapy for multi-drug gram negative infections

## Aztreonam

19:40 – 21:09

- Mono-lactam
- No cross reactivity for patients with penicillin allergy → used for patients with severe penicillin anaphylaxis
    - <10% cross reactivity for patients with penicillin allergy to cephalosporins
- No gram positive coverage
- Good gram negative coverage, covers Pseudomonas
- Never used as monotherapy → combined with vancomycin

## Carbapenems

21:20 – 24:19

- Broad spectrum agents
    - Good gram positive coverage, does not cover MRSA, variable enterococcus coverage
    - Excellent gram negative coverage including ESBLs, Pseudomonas (except ertapenem)
    - Excellent anaerobic coverage
- Eg. *Ertapenem* → good for non-hospital intra-abdominal infections because when it is a community acquired infection, less worried about Pseudomonas and enterococcus infections
- Eg. *Merapenam* → common step-up option from Tazocin
    - Covers gram positive infections including enterococci
    - Covers gram negative infections including Pseudomonas and ESBL
    - Covers anaerobic
- Eg. *Imipenem / Cilastatin* → similar to Merapenam coverage
    - Adverse effects: neurotoxicity especially in patients with renal dysfunction

## Case Examples

24:20 – 30:35

- Empiric antibiotic for patient without penicillin allergy:
    - *Tazocin*
- Empiric antibiotic for patient with remote rash with penicillin, but tolerated Cefazolin:
    - *Cefepime* + *Metronidazole* (for anaerobic coverage) ± *vancomycin* (for enterococci)
- Empiric antibiotic for patient with anaphylaxis to penicillin:
    - Avoid penicillin, cephalosporins, and Carbapenems
    - Use *aztreonam* + *Metronidazole* + *vancomycin*
        - Consider previous antibiotic exposure because of resistant organisms
- Previous allergies:
    - A good history is important! Good questions to ask:
        - What happened last time?
        - How long ago did it happen?
    - If remote allergic reaction, consider re-challenge with cephalosporin because allergic reaction may have been due to impurities in drug, etc.
    - Penicillin skin test usually takes ~1 hr

## Fluoroquinolones

30:36 – 33:14

- Inhibit DNA replication
- Concentration dependent killing drugs
- Often used in patients w/ severe penicillin allergies
- Considered “broad spectrum,” but high rates of resistance
- (52:51) Fluoroquinolones have:
    - Potential to prolong QT interval
    - Bone and tendon toxicity
    - Absorption minimal if given enterally with divalent cations because of chelation
- Eg. *Moxifloxacin* → good option for community acquired pneumonia
    - Covers strep, but no enterococci coverage
    - Good gram negative coverage, but not Pseudomonas

    - Covers atypical organisms (ie. Legionella, Mycoplasma, Chlamydia)
        - Called atypical organisms because symptoms different than those who present with more typical bacteria
- Eg. *Ciprofloxacin* → good option for enteral gram negative infection with penicillin allergy
    - Limited gram positive coverage
    - Good gram negative coverage including Pseudomonas
    - Covers atypical organisms
- Eg. *Levofloxacin* → broad spectrum agent, but potential for overutilization
    - Good gram positive coverage including strep
    - Good gram negative coverage including Pseudomonas
    - Covers atypical organisms

## Vancomycin

33:15 – 35:30

- Glycopeptide that inhibits cell wall synthesis; slowly bactericidal
- Killing dependent on total exposure → AUC/MIC
- Use therapeutic drug monitoring for efficacy and toxicity →measure trough concentrations
- Good gram positive coverage
    - Not ideal for MSSA, but good option for MRSA
    - Covers enterococcus, but there is resistance
- No gram negative coverage
- Used enterally for C. diff infections → not systemically absorbed

## Aminoglycosides

35:31 – 39:44

- Inhibitors of protein synthesis
- Concentration dependent killing
- Trough dependent toxicity → nephrotoxicity and ototoxicity
- Usually as synergistic therapy for selected gram positive and resistant gram negative infections → target different peaks depending on situation
- Use therapeutic drug monitoring to ensure achieved desired peak and monitor trough because of the associated toxicity
- Eg. *Gentamycin*
    - Used for gram positive synergy with cell wall active agent
    - Good gram negative coverage
- Eg. *Tobramycin*
    - Similar coverage to gentamycin
- Eg. *Amikacin*
    - Broader gram negative coverage
    - Tend to reserve for really resistant gram negative organisms
    - Drug levels tend to be 4x that used for gentamycin or tobramycin

## Macrolides

39:45 – 40:32

- Inhibit protein synthesis
- Concentration dependent killing
- Eg. *Azithromycin*
    - Some strep coverage
    - Excellent atypical coverage → why it is used in ICU patients
    - Used in complicated COPD exacerbations, adjunct with ceftriaxone for community acquired pneumonia
    - May have immunomodulatory effects in Pseudomonas colonization

## Linezolid

40:33 – 43:04

- Bacteriostatic
- Inhibits protein synthesis
- Very good gram positive coverage including MRSA and vancomycin-resistant enterococcus
    - Non-inferior to vancomycin for MRSA pneumonia
- No gram negative coverage
- Toxicities:
    - Serotonin syndrome → linezolid was first discovered as MAOi
        - Case reports in literature when used with other serotonergic agents
    - Thrombocytopenia → no threshold of platelet count needed to start linezolid

## Daptomycin

43:05 – 44:04

- Bactericidal; concentration dependent
- Covers gram positive organisms including MRSA and resistant
    - Reserved as salvage therapy for MRSA bacteremia or VRE infection
- No gram negative coverage
- Cannot be used for respiratory infection as binds to surfactant
- Adverse effects:
    - Myopathies → requires CK monitoring at baseline and weekly afterwards

## Sulfonamide Antibiotics

44:05 – 45:48

- Eg. *Trimethoprim/sulfamethoxazole (TMP/SMX)*
    - Good staph coverage including MRSA, but not good for enterococci or strep
    - Fairly good gram negative coverage, but does not cover Pseudomonas
    - First line for Pneumocystis pneumonia or stenotrophomonas
    - Poor empiric choice for UTI
    - Toxicities:
        - Increases in serum creatinine
        - Hyperkalemia
        - Hypoglycemia
        - Bone marrow toxicity → related to total exposure

## Clindamycin

45:49 – 47:16

- Used for oral anaerobes and gram positive organisms
    - May be good agent for intraoral abscess or tooth infection
- Variable strep coverage and a lot of staphylococcal resistance developing
- No gram negative coverage
- High risk of C. diff infection
- **Tip!** For anaerobic infections: above the diaphragm use clindamycin, below the diaphragm use metronidazole

## Colistin

47:17 – 48:42

- It is a polymyxin → acts like cationic detergent → alters osmotic barrier of cells
- Concentration dependent bactericidal agent
- No gram positive or anaerobic coverage
- Gram negative coverage includes Klebsiella, Enterobacter, and Pseudomonas
    - Does not cover Proteus
- Used for Multidrug resistant gram negative organisms → not used empirically
- Nephrotoxic

## Glycylcycline

48:43 – 49:54

- Eg. *Tigecycline* → tetracycline derivative
    - Limited use for pneumonia or bacteremia because hard to achieve concentrations needed for good activity
    - Bacteriostatic
    - Reserved for multi-drug resistance gram negative organisms
    - Some gram positive coverage
    - Fairly good gram negative coverage, except for Pseudomonus, Proteus and Providencia

## Metronidazole (Flagyl)

49:55 – 51:10

- Excellent anaerobic coverage
- Do not need to add metronidazole for agents that have good anaerobic coverage (eg. Tazocin and Carbapenems)
- First line agent for mild to moderate C. diff
- Can't be co-administered with alcohol

## Vancomycin Resistant Enterococcus

51:11 – 52:50

- Vancomycin Resistant Enterococcus faecalis:
    - Often still susceptible to ampicillin, even if resistant to vancomycin
- Vancomycin Resistant Enterococcus faecium
    - Often also resistant to ampicillin → consider linezolid or daptomycin

## Surgical Prophylaxis

53:40 – 54:24

- Add metronidazole to cefazolin for intraabdominal procedures
    - Another option is to use second generation cephalosporin (eg. Cefoxitin, Cefotetan)