# Antimicrobial Overview

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# Objectives

1. Define the role and strategies used by hospital Antimicrobial Stewardship Programs (ASP)
2. Address how to interpret microbiology culture and sensitivity reports
3. Become familiarized with antibiograms and empiric antibiotic guidelines
4. Review the main antibiotic classes, spectrum of coverage and adverse drug events
5. Evaluate penicillin allergies & beta lactam cross reactivity
6. Briefly cover the evolution of gram-negative beta-lactamases
7. Establish short vs. long term treatment courses for specific disease states

# Definitions

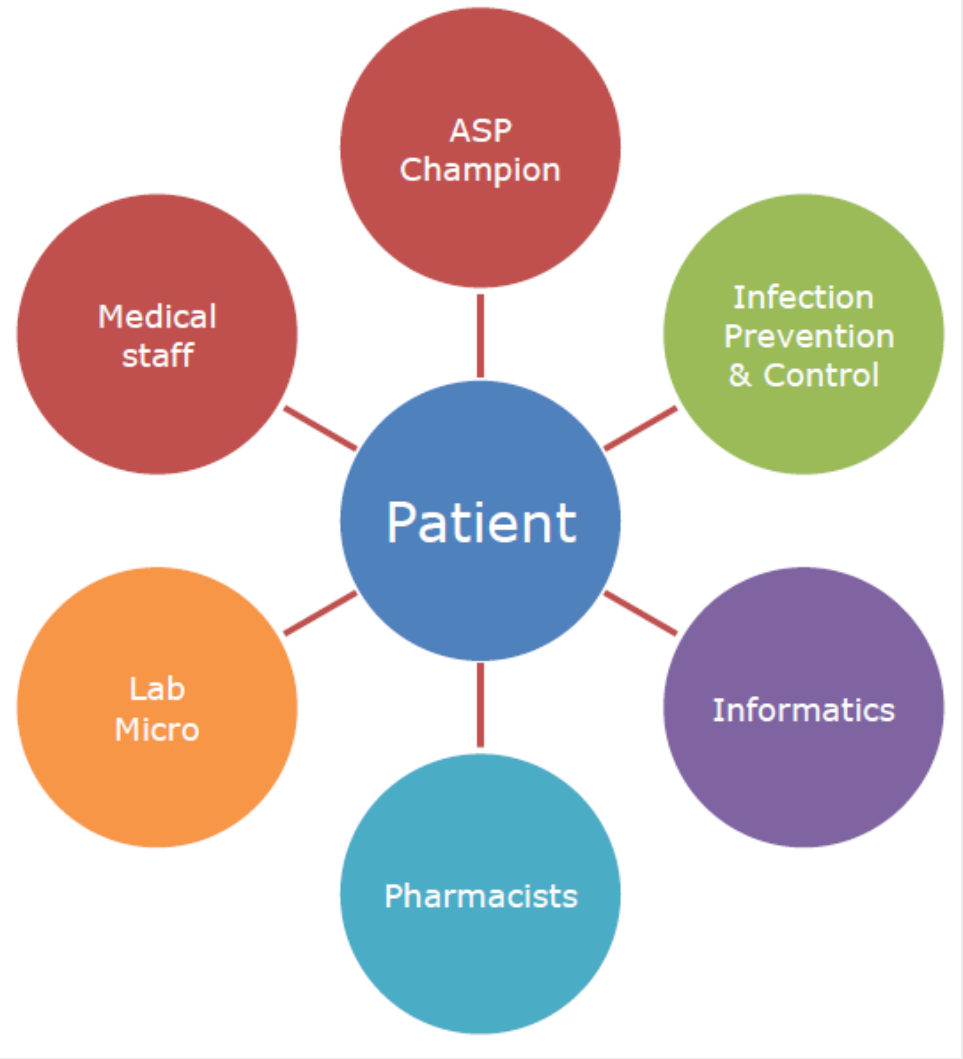
- **Stewardship**: the conducting, supervising, or managing of something; *especially*: the careful and responsible management of something entrusted to one's care

- **Antimicrobial Stewardship**: refers to coordinated interventions designed to improve and measure the appropriate selection, dosing, route and duration of antimicrobial therapy while optimizing clinical outcomes, and minimizing unintended consequences of antimicrobial use

# The Role of Antimicrobial Stewardship Programs (ASPs)

- **Primary role**: improve the quality of patient care and patient safety
  1. Increase infection cure rates
  2. Reduce treatment failures
  3. Reduce adverse events associated with antimicrobial therapy
     I. Significantly reduce hospital rates of *Clostridioides difficile* infections (CDI)
  4. Decrease antibiotic resistance
- **Secondary role**: provide hospitals with opportunity for cost savings
- In 2017, CMS standards were established, hospitals are required to have ASPs
- SUCCESS of an ASP is dependent on defined leadership and a coordinated multidisciplinary approach

# Multidisciplinary Approach




Dellit TD, et al. Clin Infect Dis 2007;44:159-77
Drew RH, et al. Pharmacotherapy 2009;29:593-607

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# Hospital ASP Strategies

| | |
|---|---|
| Guidelines | Prior Authorization |
| Education | Prospective Audit with Feedback |
| Order Sets | Microbiology Cascading |
| EHR alerts for Pharmacist & Providers | |

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# Microbiology: Understanding the Pitfalls of a Culture and Sensitivity Report

## Which antibiotic(s) would you use to treat this infection?

Sputum culture: *Pseudomonas aeruginosa*

| | Sensitive |
|---|---|
| Ceftriaxone | R |
| Cefepime | S |
| Ciprofloxacin | S |
| Meropenem | S |
| Gentamicin | S |
| Tobramycin | S |
| Aztreonam | S |
| Piperacillin/tazobactam | S |

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| Tobramycin | S |
| Aztreonam | S |
| **Piperacillin/tazobactam** | **S** |

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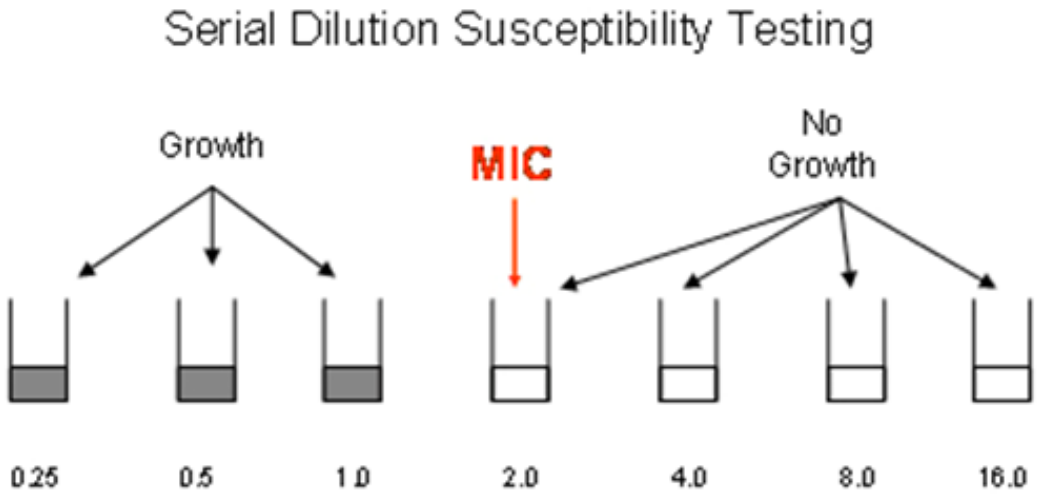
# MIC definition

- Minimum Inhibitory Concentration
- The **lowest** antimicrobial concentration that prevented **visible** growth of an organism after 24 hours of incubation



## What do the numbers mean and which antibiotic(s) would you use to treat this infection?

Trach Aspirate: *Pseudomonas aeruginosa*

| | Sensitive | MIC/ml |
|---|---|---|
| Ceftriaxone | R | >32 |
| Cefepime | S | 4 |
| Ciprofloxacin | S | ≤0.5 |
| Meropenem | S | ≤1 |
| Gentamicin | S | 2 |
| Tobramycin | S | ≤1 |
| Aztreonam | S | 8 |
| **Piperacillin/tazobactam** | **S** | **16** |

## What do the numbers mean and which antibiotic(s) would you use to treat this infection?

Trach Aspirate: *Pseudomonas aeruginosa*

| | Sensitive | MIC/ml | CLSI BP |
|---|---|---|---|
| Ceftriaxone | R | >32 | 8 |
| Cefepime | S | 4 | 8 |
| Ciprofloxacin | S | ≤0.5 | 0.5 |
| Meropenem | S | ≤1 | 4 |
| Gentamicin | S | 2 | 4 |
| Tobramycin | S | ≤1 | 4 |
| Aztreonam | S | 8 | 8 |
| **Piperacillin/tazobactam** | **S** | **16** | **16** |

# Burke A Cunha

*Medical Clinics of North America; Vol 84. No 6: Nov 2000. Pp 14071429*

"Susceptibility testing is an in vitro phenomenon and does not necessarily reflect or predict in vivo efficacy. Susceptibility testing is subject to great variability depending on pathogen tested, media used, conditions of incubation, and method of accessing bacterial growth"

Take Home Message: Do not just look for the "S"

# Interpreting a C/S Report

## WHAT IT TELLS YOU

- Identifies bacteria present: Does not identify infection vs colonization vs contamination

## WHAT IT DOES NOT TELL YOU

- Which antibiotic should be used to treat an infection
- That needs your interpretation of the C/S report

# Case 1

1. AT is a 49-year-old female (No hx of MDROs) with uncontrolled diabetes who is hospitalized with significant flank pain, chills, and a temperature of 101.3°F (38.5°C). She is very uncomfortable because of flank pain, and her vital signs are blood pressure 130/95 mm Hg, heart rate 85 beats/minute, and respiratory rate 23 breaths/minute. Her laboratory test results are remarkable only for a WBC of 11.3 x 10^3 cells/mm^3. She has no history of renal insufficiency. Which one of the following is best to recommend for this patient?

A. Piperacillin/tazobactam 4.5g x1, then 3.375g intravenously every 8 hours
B. Ceftriaxone 1 g intravenously every 24 hours
C. Trimethoprim/Sulfamethoxazole 1 DS q12h
D. Levofloxacin 750 mg intravenously every 24 hours

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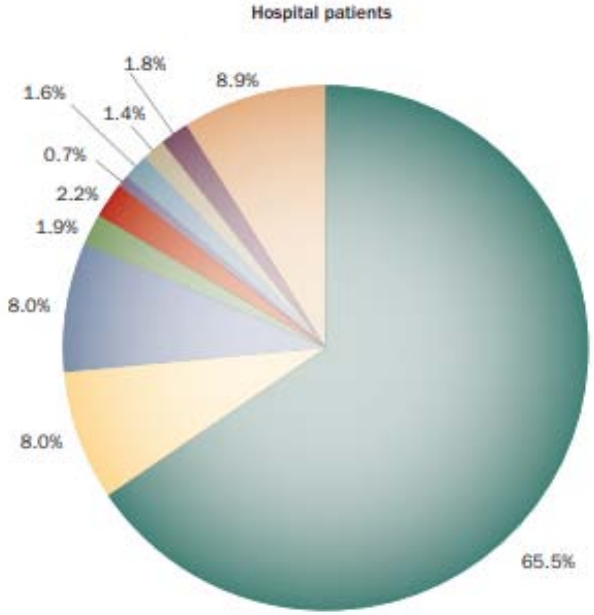
# Epidemiology of Urinary Tract Infections


Foxman, B. *Nat. Rev. Urol.* 7, 653-660 (2010)

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# Hospital Antibiogram


[Antibiograms]

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# Antibiograms

Banner Health

## Banner Empiric Antimicrobial Recommendations for Adult Patients

Banner Corporate Antimicrobial Stewardship Committee

When applicable, please order antimicrobial agents through Cerner Power Plans. Power Plans can be ordered from the "Orders" tab in Cerner. These order sets are not available to be ordered through the "Medication" tab in Cerner.

All dose recommendations are for adult patients over 40kg with normal renal and hepatic function. Doses provided may need to be adjusted based on each patient's estimated renal function, hepatic function, weight, clinical status, other co-morbid conditions and other factors. Consult pharmacy if questions regarding dose adjustments. While these recommendations are based on published data and Banner corporate formulary agents, use clinical judgement, local susceptibility patterns, and institutional formulary when prescribing antimicrobial agents.

| *Disease State* | *Recommended Therapy or Banner Cerner Power Plan* | *Comments and Alternative Therapy* |
|---|---|---|
| CAP | **See Cerner ED Sepsis Treatment or Sepsis Adult IP Power Plans [under Antimicrobials select Community Acquired Pneumonia (CAP) Antimicrobials]** | If patient from an endemic region for coccidioidomycosis, consider testing for this disease state |
| HAP/VAP | **See Cerner ED Sepsis Treatment or Sepsis Adult IP Power Plans [under Antimicrobials select Hospital/Ventilator Acquired Pneumonia (HAP/VAP) Antimicrobials]** | |
| Influenza | Oseltamivir 75 mg PO BID X 5 days | Therapy should be started within 48 hours of symptoms in most cases to shorten the duration of symptoms |
| COVID-19 | **See Cerner COVID-19 ICU, COVID-19 IP, or ED COVID-19 Power Plans (depending on patient location)** | |
| Acute Bronchitis | Antibiotics not recommended (even for purulent/green sputum) | Consider symptomatic treatment (acetaminophen, NSAIDS, ipratropium) |
| Sepsis or Septic Shock | **See Cerner ED Sepsis Treatment or Sepsis Adult IP Power Plans [under Antimicrobials select Unknown Source or Line Infection Antimicrobials]** | |
| Febrile Neutropenia | Cefepime 2 gm IV q8hr + Vancomycin (pharmacy to dose) if meets criteria | Criteria for vancomycin: Hemodynamic instability or other evidence of severe sepsis, pneumonia, clinically suspected catheter related infection, blood culture positive for gram positive cocci, skin or soft-tissue infection, colonization with MRSA, VRE, or penicillin resistant *Streptococcus pneumoniae*, severe mucositis, if fluoroquinolone prophylaxis given and on ceftazidime |
| Meningitis | **See Cerner ED Sepsis Treatment or Sepsis Adult IP Power Plans [under Antimicrobials select Meningitis Antimicrobials]** | |
| Uncomplicated Cystitis | Nitrofurantoin 100 mg BID X 5 days (Do not use in CrCl < 30 ml/min) | Alternatives: Cefuroxime 250 mg BID or cephalexin 500 mg QID X 5 days Sulfamethoxazole-trimethoprim is not recommended first-line without known susceptibilities given resistance issues. Fluoroquinolones are not first line given warnings and resistance issues. Please weigh risks versus benefits. |
| Complicated Cystitis | **See Cerner ED Sepsis Treatment or Sepsis Adult IP Power Plans [under Antimicrobials select Urosepsis Antimicrobials]** | Recommend reviewing previous culture results before selecting initial therapy |
| Pyelonephritis | Ceftriaxone 1 gm IV q24h | Use caution using fluoroquinolones first-line due to resistance issues. Nitrofurantoin and fosfomycin are not recommended for pyelonephritis. |
| Asymptomatic Bacteriuria | Antimicrobials usually not recommended | Only treat pregnant patients or prior to invasive urologic procedures. Treat same as complicated cystitis. |

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# Restricted Antimicrobial Agents

## Formulary

- Amikacin
- Aztreonam
- Ceftaroline
- Colistin
- Daptomycin
- Ertapenem
- Fidaxomicin
- Fosfomycin
- Isavuconazole
- Linezolid
- Meropenem
- Micafungin
- Moxifloxacin
- Polymyxin B
- Posaconazole
- Tigecycline
- Voriconazole

## Non-Formulary*

- Ceftazidime/avibactam
- Ceftolozane/tazobactam
- Eravacycline
- Cefiderocol
- Imipenem-Cilastin
- Imipenem-cilastin-relebactam
- Meropenem/vaborbactam

*Patient may receive first dose to avoid delays in care, for future doses ID consult is expected

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**B. Ceftriaxone 1 g intravenously every 24 hours**

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D. Levofloxacin 750 mg intravenously every 24 hours

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# Antibiotic Class Review

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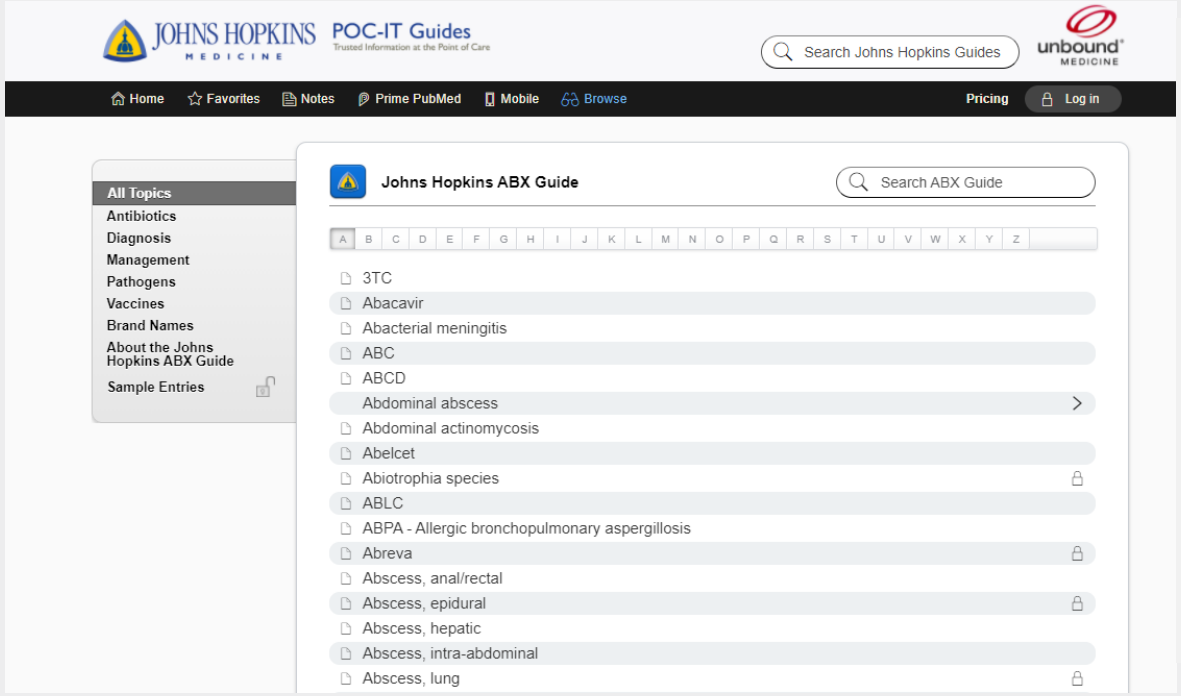
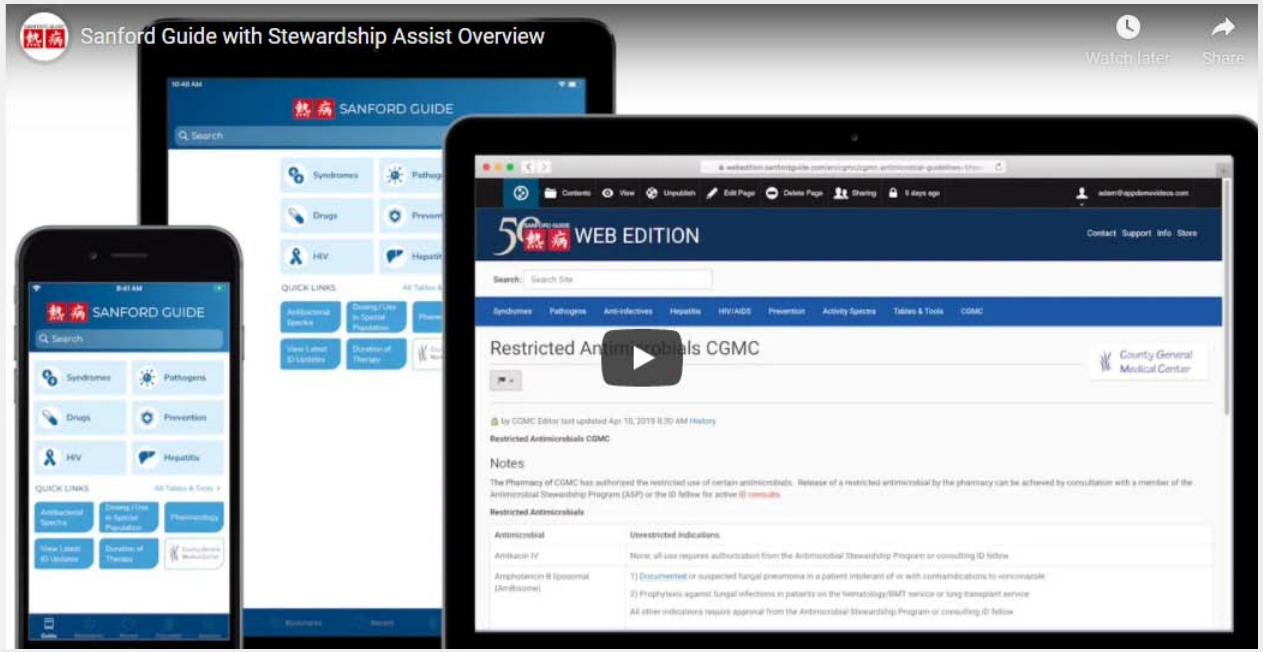
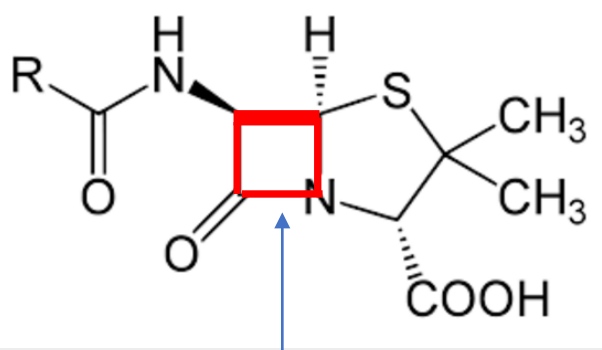
# Electronic Resources



# Beta Lactam Antibiotics




- Includes your penicillins(PCNs), cephalosporins, carbapenems and monobactam
  - Natural: PCN VK/G
  - Antistaphylococcal PCNs: Nafcillin/oxacillin
  - Amino-PCNs: Amoxicillin/Ampicillin
  - Extended spectrum PCNs: Augmentin (amoxicillin/clavulanic acid), Unasyn(ampicillin/sulbactam), Piperacillin or Zosyn(piperacillin/tazobactam)
  - Cephalosporins: cefazolin, cefotetan, cefuroxime, cefotaxime/ceftriaxone, ceftazidime, cefepime, ceftaroline
  - Carbapenems: Imipenem/cilastain, Meropenem, Ertapenem, Doripenem
  - Monobactam: Aztreonam
- Narrow-broad spectrum coverage
- Time dependent killers, so we care how frequently/closely together we administer these agents
- MOA: work by inhibiting cell wall biosynthesis in the bacterial organism
  - Bactericidal
  - Alter the main site of action Penicillin binding proteins (PBPs)
- MOR: Bacteria often develop resistance to β-lactam antibiotics by synthesizing a beta lactamase, an enzyme that attacks the β-lactam ring

# **Beta lactam antibiotics**: Nafcillin, Ampicillin/Unasyn

- Narrow spectrum
- Preferred for Strep and Staph (MSSA) as the agents are “cidal”
  - Nafcillin DOC for MSSA
  - Yes-better than vancomycin for MSSA!!!
- Unasyn has extended coverage for gram negatives and (most)anaerobes
  - b/c of the sulbactam it is good for beta lactamase producing g-
  - No pseudomonas coverage
  - Covers *Bacteroides fragilis (~80%)*
- Both metabolized and cleared by the kidneys
- Unasyn generally well tolerated
- Nafcillin associated with hypokalemia, transaminitis, hyperbilirubinemia

# Zosyn®-piperacillin/tazobactam

- **Work horse**
- Should be consider first line for nosocomial infections
- Broad spectrum coverage:
  - excellent *Strep/Enterococcus*
  - good *Staph*(MSSA)
  - Good gram negative-including *Pseudomonas (75-80% per BUMCP antibiogram)*
  - Anaerobic-including Bacteroides (~96%)

- Go to agent for HAP/VAP, intra-abdominal processes, pneumonia, SSTI-including diabetic foot infections
- Generally well tolerated
- AE: phlebitis at infusion site, drug fever, leukopenia/thrombocytopenia, interstitial nephritis, rare cases of hepatitis
  - Concomitant use with vancomycin increases risk of AKI on days 3-5 of therapy
- Contains +++Na: 64 mg of Na per 1 gm of piperacillin, so 3.375g q8h =640 mg Na total if diluted in D5W

# Cephalosporins-general principals to apply

- 5 Generations of cephalosporins
- Early generations are best for Strep and Staph (MSSA), No Enterococcus
- Later generations (3-5th) have improved gram negative coverage, some with added Pseudomonas coverage
- Most cephalosporins are considered safe during pregnancy (category B)
- Some have IM routes of administration
  - Cefazolin
  - Ceftriaxone
- Most are primary metabolized and eliminated via kidneys
  - Except 1-ceftriaxone
- Overuse is associated with emergence of resistance primarily in g(-) & also selects for VRE
- Associated with *C. difficile* infections
- Cross reactivity w/ PCN allergies is lowest with higher generation cephs as they are structurally different enough from PCN
  - Safe to administer cefpodoxime, cefdinir, ceftriaxone/cefotaxime, ceftazidime and cefepime

# 1st Gen: Cefazolin (IV)

- Excellent gram-positive coverage
  - Consider first line, along with Nafcillin for *Strep* and *Staph aureus* (MSSA)
  - Pro: better side effect profile than Nafcillin
- **Preferred cephalosporin for *S. aureus* (MSSA)**
- Some gram-negative coverage for susceptible E. coli, Proteus
- Can dose escalate by weight for surgical prophylaxis
  - 80 kg use 1 gm
  - >80 kg use 2 gm
  - >120kg use 3gm
- AE: rare reports of eosinophilia, CNS disturbances (confusion, disorientation, hallucinations)

# Case 2

E.E. is a 45-year-old man who is started on empiric vancomycin for osteomyelitis of the radius after a traumatic injury. Five days later, E.E.'s culture grows MSSA. He has no history of renal insufficiency.

**Wound Culture - Accession: 000012020201003746**
**Result Status - Auth (Verified)**

Micro Reports | **Susceptibilities** | Specimen | Comments | Action List

| | A | B | C |
|---|---|---|---|
| 1 | Staphylococcus aureus | | |
| 2 | | MDIL | MINT |
| 3 | Ox/Nafcillin | <=0.25 | S |
| 4 | Erythromycin | >=8 | R |
| 5 | Clindamycin | >=4 | R |
| 6 | Trimethoprim/Sulfa | <=10 | S |

Which one of the following is best to recommend for E.E.?

A. Continue vancomycin 15mg/kg intravenously q12h for duration of therapy.
B. Change to ceftriaxone 2g q12h.
C. Change to cefazolin 2g intravenously every 8 hours for duration of therapy.
D. Change to nafcillin 2g intravenously every 8h for duration of therapy.

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# Penicillin Allergies & Beta Lactam Cross Reactivity

# Are Penicillin Allergies Benign?

- Penicillin
  - ~10% of the general population reports a PCN allergies
  - ~90% of these patients can tolerate PCNs

- Inaccurate Penicillin allergies labels are harmful!

↑ Vancomycin/FQs/Clindamycin (p<0.0001)

↑ C. difficile (23.4%), MRSA (14.1%), VRE (30.1%) prevalence

↑ Length of stay ( 0.59 more days) and cost $$$

*J Allergy Clin Immunol.* 2014 Mar;133(3):790-6.

# Adverse Drug Reactions

## Type: A

Predictable, dose dependent

Ex: Renal failure from aminoglycoside

## Type: B

Unpredictable, dose independent

### Drug allergy

Type I-IV

Ex: Type I IgE mediated PCN anaphylaxis

### Idiosyncratic

Distinct from known mechanisms.

May not be reproducible

Ex: Drug fever

### Pseudoallergic

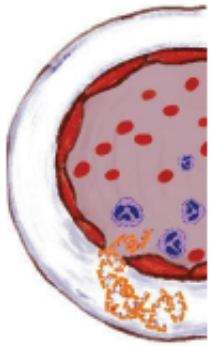
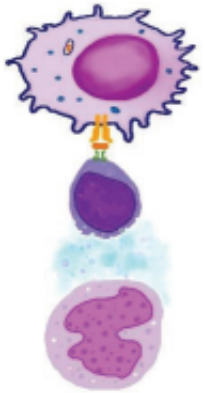
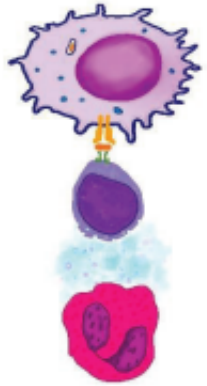
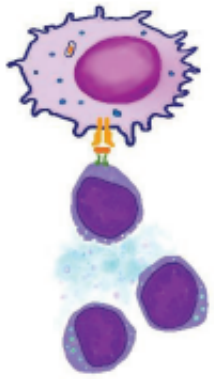
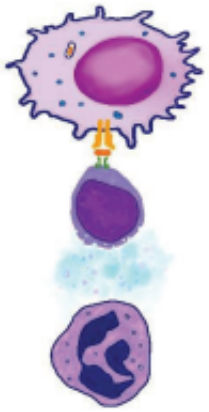
Mimic allergic syndrome w/o immune mechanism

Eg. Vancomycin ~~Redman syndrome~~ Infusion Reaction

### Intolerance

Ex: N/V, GI upset

# Gell & Coombs Hypersensitivity Classification

| | Type I (allergic) | Type II (cytotoxic) | Type III (immune complex) | Type IV (Delayed) | | | |
|---|---|---|---|---|---|---|---|
| **Mediator** | IgE | IgG or IgM | IgG or IgM | IVa | IVb | IVc | IVd |
| **Effector mechanism** | Mast cell mediated | Complement, antigen-antibody interaction | Complement, phagocytes | Monocyte directed | IgE production, eosinophil mediated | CD4+, CD8+ T cells | Neutrophils |
| |  |  |  |  |  |  |  |
| **Onset of symptoms** | Immediate, minutes to hours | Often <72 hours but can be up to 15 days | 1–3 weeks | Variable (days to weeks) | | | |
| **Clinical manifestation** | Hives, itching, wheezing, hypotension, anaphylaxis, angioedema | Autoimmune hemolytic anemia, thrombocytopenia | Serum sickness, fever, rash, lymphadenopathy, joint pain | Eczematous rash | DRESS, allergic rhinitis, maculopapular rash | Contact dermatitis, morbilliform rash | SJS, AGEP |
| **Antibiotic examples** | Penicillins<br>Cephalosporins | Penicillins<br>Cephalosporins<br>Sulfonamides<br>Dapsone<br>Rifamycins | Penicillins<br>Cephalosporins<br>Sulfonamides | Penicillins<br>Sulfonamides<br>Fluoroquinolones<br>Rifamycins<br>Vancomycin | | | |

Shenoy ES, JAMA 2019; 321:188-99.
Ann Allergy Asthma Immunol 2010;105:259-73

# Direct Oral Amoxicillin Challenge

**Figure. PEN-FAST Penicillin Allergy Clinical Decision Rule**

| | | |
|---|---|---|
| PEN | *Penicillin allergy reported by patient* | ☐ *If yes, proceed with assessment* |
| F | *Five years or less since reaction*[a] | ☐ **2 points** |
| A | *Anaphylaxis or angioedema* | |
| OR | | ☐ **2 points** |
| S | *Severe cutaneous adverse reaction*[b] | |
| T | *Treatment required for reaction*[a] | ☐ **1 point** |
| | | ☐ **Total points** |

**Interpretation**

| Points | |
|---|---|
| 0 | **Very low risk** of positive penicillin allergy test <1% (<1 in 100 patients reporting penicillin allergy) |
| 1-2 | **Low risk** of positive penicillin allergy test 5% (1 in 20 patients) |
| 3 | **Moderate risk** of positive penicillin allergy test 20% (1 in 5 patients) |
| 4-5 | **High risk** of positive penicillin allergy test 50% (1 in 2 patients) |

The PEN-FAST clinical decision rule for patients reporting a penicillin allergy uses 3 clinical criteria of time from penicillin allergy episode, phenotype, and treatment required. A total score is calculated using PEN-FAST score in the upper panel, and interpretation for risk strategy is provided in the lower panel.

[a] Includes unknown.

[b] Forms of severe delayed reactions include potential Stevens-Johnson syndrome, toxic epidermal necrolysis, drug reaction with eosinophilia and systemic symptoms, and acute generalized exanthematous pustulosis. Patients with a severe delayed rash with mucosal involvement should be considered to have a severe cutaneous adverse reaction. Acute interstitial nephritis, drug induced liver injury, serum sickness and isolated drug fever were excluded phenotypes from the derivation and validation cohorts.

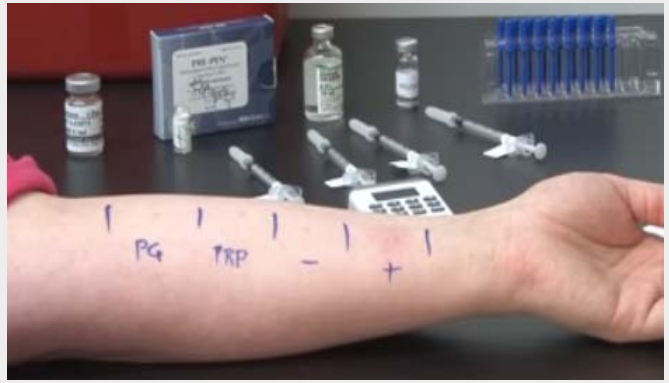
Trubiano JA. *JAMA Intern Med.* 2020;180(5):745-752

# Penicillin Allergy Skin Testing

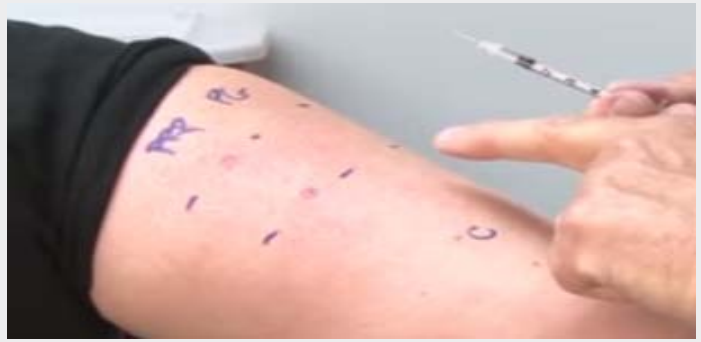
Reagents:

- **1. One ampule of PRE-PEN (Benzylpenicilloyl polylysine)** - (major determinant)
- **2. Dilute Pen G 10,000 u/mL** – (minor determinant)
- **3. Histamine** – (positive control)
- **4. Sodium chloride** – (negative control)

**Step 1. Scratch Testing**




**Step 2. Intradermal Testing**

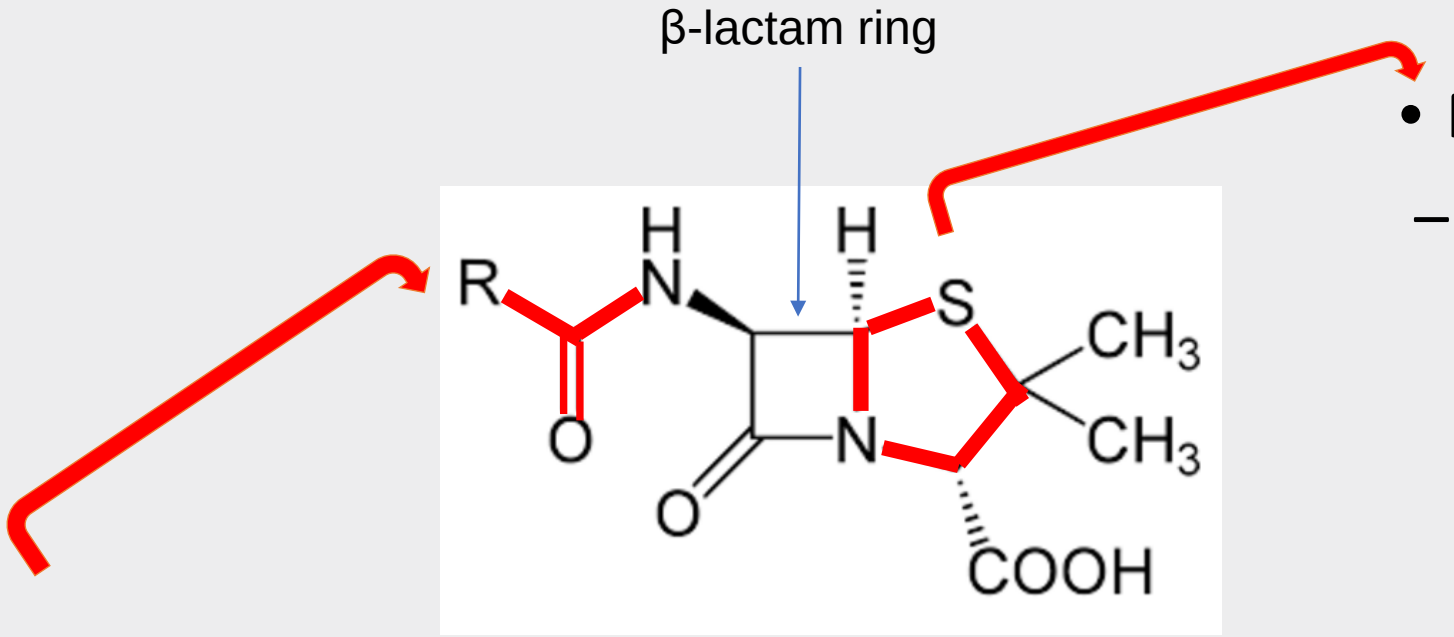


**Step 3. Direct Oral Amoxicillin Challenge**

# Penicillin Desensitization

- Reserve for infections where Penicillin is DOC (e.g. Syphilis)
- New term “temporary induction of drug tolerance” (TIDT)
- Controlled anaphylaxis theory
  - Drug administered at increasing concentrations and rates that will cause mast cells to degranulate at rates slower than required to induce a systemic reaction
- TIDT administration & observation needs to be done in the ICU!
- PRN rescue medications (eg antihistamines/corticosteroids) need to be available in event of allergic symptoms

# Immunochemistry of Pencillin Allergy




- **Major Moiety** (95%):
  - Benzylpenicilloyl

**Minor Side Chain** (5%):

-Penicillin G (benzylpenicillin)

Penicilloate, and penilloate

*Clin Rev Allergy Immunol* 2013 Aug;45(1):131-42.

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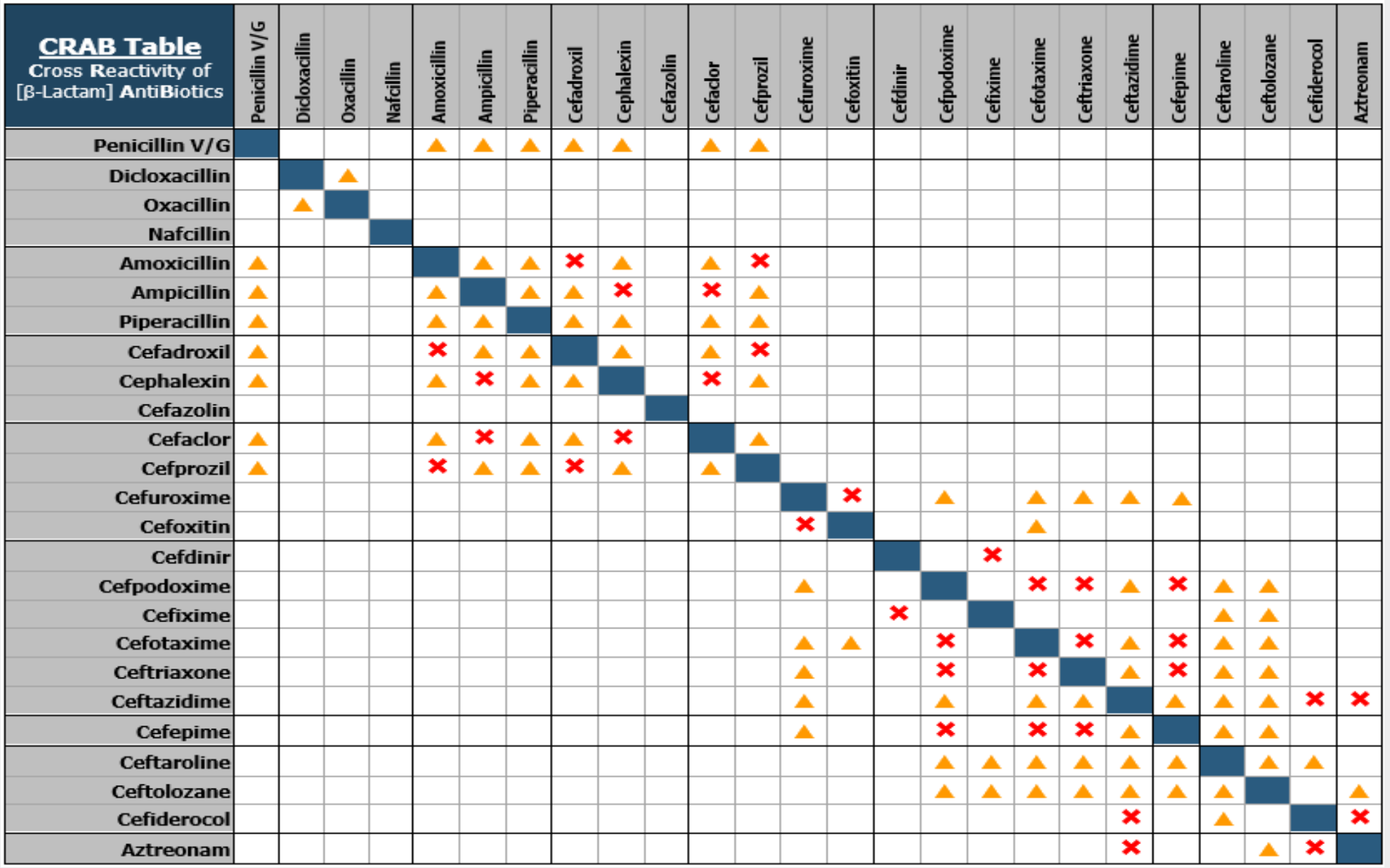


**AVOID** if history of **legitimate** IgE mediated reaction; increased risk of cross-reaction due to identical $R_1$ side chain.

**CAUTION!** Cross-reactivity less likely due to similar (not identical) side chain.

**SUGGEST!** Cross-reactivity unlikely due to dissimilar side chains.

Adapted from Zagursky RJ, J Allergy Clin Immunol Pract 2018;6:72-81.e1

# Case 3

A 24-year old woman with a PMH of asthma presents to the outpatient clinic with concerns fo dysuria. She completed an outpatient course for amoxicillin for a UTI 3 months ago. Urine cultures from that time, as well as cultures obtained 2 days before her current presentations, grew more than 100k CFU/ml pan-susceptible E. coli. Her PCP prescribes another course of amoxicillin, and within 60 minutes of taking the dose, the patient has full body hives. Which of the following antibiotics is best to recommend for this patient?

a) Cephalexin (PO only)
b) Cefaclor (PO only)
c) Cefuroxime (IV/PO)
d) Ertapenem (IV)

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b) Cefaclor (PO only)

**c) Cefuroxime (IV/PO)**

d) Ertapenem (IV)

# 2nd Generation-cefotetan, cefoxitin & cefuroxime

- Moderate gram negative & positive coverage including Strep and Staph (MSSA)
  - Covers anaerobes but should be confirmed by susceptibility testing first
    - Cefuroxime better for head/neck anaerobes
  - Cefotetan has increasing resistance in the Bacteroides group
  - Cefuroxime maintains susceptibility against the “new” resistant E coli (ST-131)
- Mostly indicated for UTIs, Lower RTI, SSI, Gyn infections
- Used for surgical prophylaxis in abdominal/colorectal surgeries
- Can dose escalated in obesity
  - 80kg use 1 gm
  - >80 kg use 2 gm (1.5 gm cefuroxime)
- Cefuroxime is only in this generation available IV/PO (52%)

# 3rd Gen: Ceftriaxone & Cefotaxime

- Brother/sister drugs (IV only)
- Identical spectrums of activity include:
- Excellent Strep (including pneumococcus), these are the preferred cephalosporins
  - Will need to keep a close eye on resistant (reported at ~5%)
- Good Staph (MSSA) coverage
- Excellent g(-) coverage (no pseudomonas)
- Maintain good coverage for Ecoli (~85%)
  - WARNING-inducible AmpC-lactamase resistance with Enterobacterales (SPICE organisms)
- Niches:
- Identical spectrums, can use interchangeably
  - Ceftriaxone metabolized-good for biliary/biliary tract infections
  - Ceftriaxone Q12/24hr vs Q4-8hr
  - First line agents for CNS infections-ceftriaxone high dose 2 gm IV q12H
- AE: relatively safe drug profile, interstitial nephritis
  - Ceftriaxone can cause biliary sludge-dose dependent AE
    - Reserve cefotaxime for neonates <2 months to avoid Kernicterus

# 3rd & 4th Gen Ceftazidime & Cefepime

- Spectrums are *nearly* similar
  - Ceftazidime primarily gram negative, including Pseudomonas (90%)
    - Does not have good *Strep pneumoniae* sensitivity
    - Lacks adequate Staph coverage
    - Good CNS penetration, but not preferred first line
- Cefepime
  - Addition of good Strep (including *Strep pneumoniae*) Staph (MSSA) coverage
  - Gram positive coverage is comparable to ceftriaxone/cefotaxime
  - Covers Enterobacter species better (89-96%)
    - stable to AmpC β-lactamases
  - Can dose escalate both for CNS dosing-2gm
  - Dosing for Pseudomonas is always 2g q8h!
  - Renally eliminated, requiring dose adjustments for renal impairment

# Gram Negative Beta-lactamases

# Evolution of Enterobacterales Beta-lactamases & Treatments

Wild-Type Beta lactamases

DOC: Natural Penicillins & Aminopenicillins

Standard Beta-lactamases (Tem-1, TEM-2, SHV-1*)*

DOC: Extended spectrum Penicillins, Cephalosporins

AmpC; ESBL (TEM, SHV, CTX-M)

DOC: Carbapenems, Cefepime (AmpC only)

Carbapenamase (KPC, OXA-48,MBL)

DOC: Novel Beta lactam –beta lactamase inhibitors Avycaz, Vabomere, Recarbrio, Fetroja

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# Carbapenem Resistant Enterobacterales (CRE) Worldwide

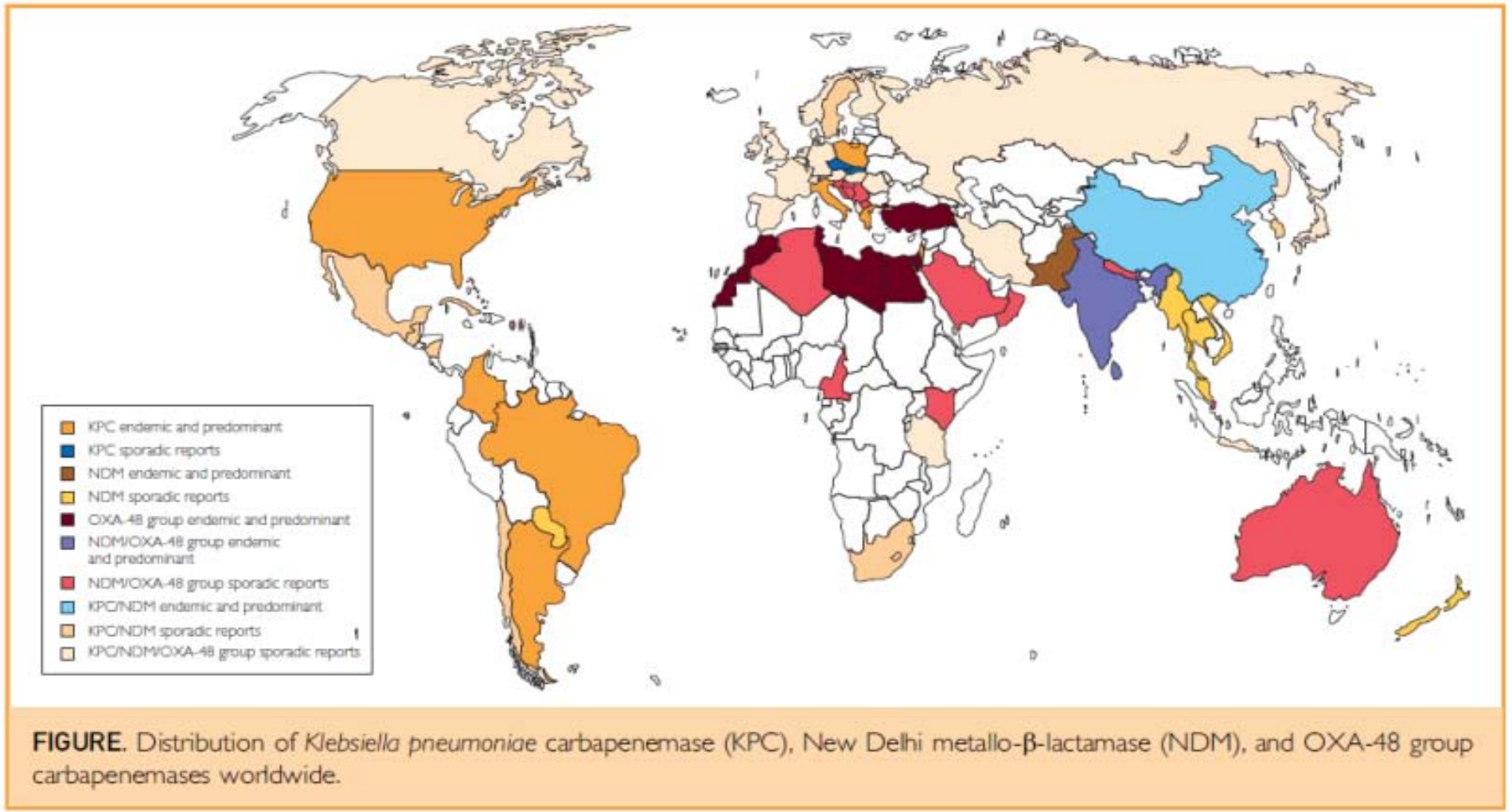


**FIGURE.** Distribution of *Klebsiella pneumoniae* carbapenemase (KPC), New Delhi metallo-β-lactamase (NDM), and OXA-48 group carbapenemases worldwide.

Vasoo S, Mayo Clin Proc. 2015;90(3):395-403.

# 3rd Gen: Ceftazidime/Avibactam (Avycaz)

- FDA approved in 2015
  - Indication include cIAI w/ Flagyl, cUTI, HABP/VABP
- Avibactam inactivates beta lactamases (including carbapenamases), enabling ceftazidime to exert cidal activity
- Dosing is 2.5g q8h over 2h our infusion
- Spectrum of Coverage:
  - Enterobacteriaceae or *Pseudomonas aeruginosa*
    - Includes resistant organisms producing
      - AmpC
      - ESBLs
      - CRE (eg. KPC, OXA-48) but lacks MBL
- **Place in therapy: MDRO Pseudomonas & CRE infections**

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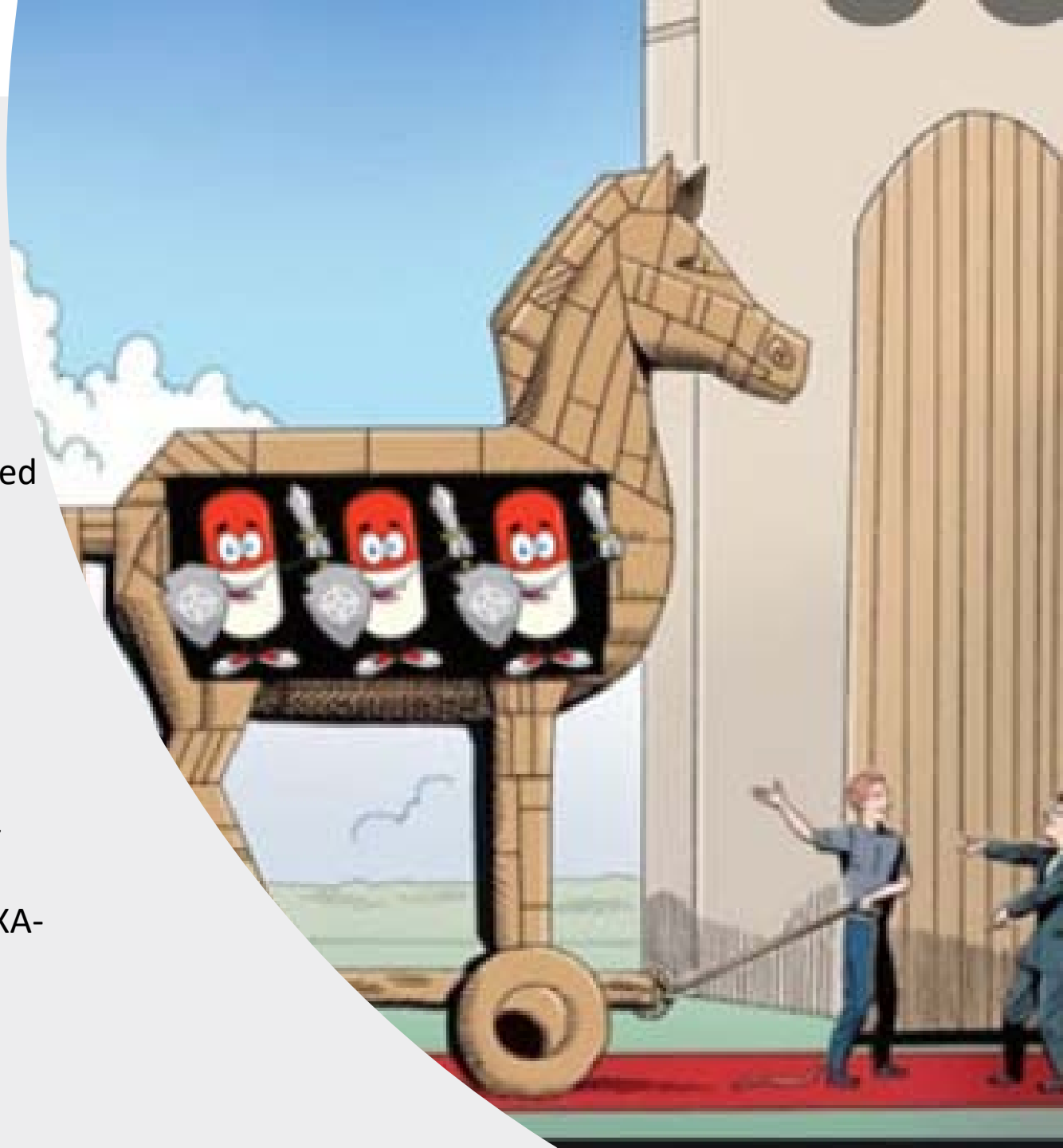
# 3.5 Gen Cefiderocol (Fetroja)

- FDA approved 2019
- Similar spectrum to ceftazidime –avibactam but expanded coverage against MDRO's (includes MBLs)
- Chelates ferric ions and uses bacterial iron transport systems to get into periplasmic space of GNB
  - Has been called a "Trojan Horse" strategy
- Dosing is 2g q6-8h with 3 hour infusion
- FDA approved for cUTI, HABP/VABP susceptible Gram-negative microorganiss: *Acinetobacter baumannii* complex, *Escherichia coli*, *Enterobacter cloacae* complex, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa* and *Serratia marcescens*.
- Exhibits in vitro carbapenemase activity against KPC, OXA-48, and MBLs
- **Place in therapy: MDRO Pseudomonas, last line!!!**



# 5th Generation: Ceftolozane/tazobactam (Zerbaxa)

- FDA approved in 2014
- Similar spectrum as Avycaz + gram positive coverage
- Indications cIAI w/ Flagyl, cUTI
- 1.5 grams  every 8 hours infused over 1 hour
  - Note 50% of serum concentration ends up in lung
  - PNA & CF exacerbation dosing is 3g q8h dosing (HAP/VAP indication)
- Spectrum of Coverage:
  - Enterobacteriaceae or *Pseudomonas aeruginosa*
    - Includes resistant organisms producing:
      - AmpC
      - ESBLs
      - No CRE coverage
- **Place in therapy: MDRO Pseudomonas**

# 5th Generation: **Ceftaroline**

- Fifth generation cephalosporin
- Broad spectrum (think ceftriaxone + MRSA coverage)
  - Gram positive coverage includes MRSA, VISA, vanco-resistant *S. aureus,* methicillin-resistant *S. epidermidis,* penicillin-resistant *S. pneumoniae,* and VRE (not *E.faecium).*
  - Gram negative coverage, (comparable to 3rd generation cephalosporins) but does not include ESBL producing or AmpC-derepressed Enterobacteriaceae or most non-fermenting gram negative bacilli. Includes *M. catarrhalis and H. influenzae(*including B-lactamase-positive strains).
  - Limited activity against anaerobes (*Bacteroides fragilis* and non-fragilis *Bacteroides* spp.*)*
- Indications for CAP and complicated skin and skin-structure infections
- Dose adjustments necessary for renal dysfunction
- **Place in therapy reserved for**:
  - Possible alternative for patients intolerant to other regimens.
  - Combination with daptomycin (synergy exists) after vancomycin failure in pSAB

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# Case 4

1. A 54-year-old man with a history of worsening hepatic insufficiency and significant ascites is admitted for suspected intra-abdominal infection. His ascitic fluid is sent for analysis and returns suggestive of bacterial peritonitis. He is initiated on empiric Zosyn therapy while cultures are pending. On day 2 ascitic fluid cultures reveal *Klebsiella pneumoniae* and blood cultures are pending with GNR growing.

Micro Reports | **Susceptibilities** | Specimen | Comments | Action List

| | A | B | C |
|---|---|---|---|
| 1 | Klebsiella pneumoniae | | |
| 2 | | MDIL | MINT |
| 3 | Ampicillin | >=32 | R |
| 4 | Amoxicillin/Clavulanate | >=32 | R |
| 5 | Piperacillin/Tazobactam | >=128 | R |
| 6 | Cefazolin* | >=64 | R |
| 7 | Ceftriaxone | >=64 | R |
| 8 | Cefepime | >=32 | R |
| 9 | Imipenem | >=16 | R |
| 10 | Ertapenem | >=8 | R |
| 11 | Meropenem | >=16 | R |
| 12 | Gentamicin | <=1 | S |
| 13 | Tobramycin | >=16 | R |
| 14 | Ciprofloxacin | >=4 | R |
| 15 | Levofloxacin | >=8 | R |
| 16 | Trimethoprim/Sulfa | >2/38 | R |
| 17 | Nitrofurantoin* | 256 | R |

Which one of the following is best to recommend for this patient?

A. Gentamicin 5mg/kg daily

B. Consult ID await further instruction

C. Avycaz 2.5g x1 and consult ID provider

D. Zerbaxa 1.5g x1 and consult ID provider

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**C. Avycaz 2.5g x1 and consult ID provider**

D. Zerbaxa 1.5g x1 and consult ID provider

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# Carbapenems

"Gorillacillins"

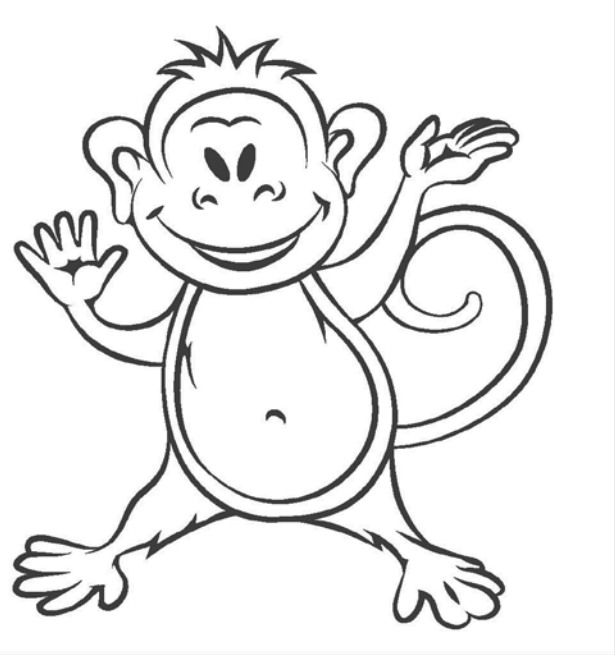
- IMIPENEM/CILASTATIN
- MEROPENEM
- ~~DORIPENEM~~
- ERTAPENEM
- MEROPENEM/VABORBACTAM (VABOMERE)
- IMIPENEM/CILASTIN/RELEBACTAM (RECARBRIO)

# Carbapenems--general principals to apply

- AKA “Gorillacillins”
  - These should be reserved as they are *the nuclear weapons*
- Broadest spectrum of the Beta lactam class
  - Gram positive includes: Strep/Enterococcus*, Staph (MSSA), g+ anaerobes
  - Gram negative coverage includes: all Enterobacteriaceae, Pseudomonas, Acinetobacter, and Extended SpetrumBeta Lactamase(EBSL) g-bacteria (Ecoli, Klebsiella)
  - Excellent anaerobic coverage both g (+) and g (-)
- MOR: carbapenemase enzymes exist (KPC, OXA-48, NDM)
  - Famously stable to AmpC β-lactamases and extended-spectrum-β-lactamases
- Low cross reactivity in PCN allergic patients (reported <2%)
- AE: seizures (elderly, h/o seizures (0.2% vs33%), higher doses and not renally adjusted, bone marrow suppression, infusion related hypotension
- Major DDI (drug-drug interactions): CYP p450 (VA-decreases levels, increasing risk for seizures)
- **Place in Therapy: DOC (drug of choice) for ESBL**

# Ertapenem

- "Monkeycillin" but still a nuclear weapon
- Spectrum of coverage very similar to Mero/imipenem:
  - exception of Pseudomonas and Enterococcus(30-50% resistance reported)
- Excellent anaerobic coverage
- Should be considered over meropenem when is Pseudomonas coverage is not needed
- FDA approved for CAP and complicated DM foot infections
- Q24hr dosing
- May need higher doses in obesity, studies have not recommended dose
- Higher rates of treatment failure in critically ill patients with hypoalbuminemia
- **Place in therapy: ESBLs & AmpC infections**



# Meropenem

- Meropenem is formulary
- We do alternative dosing strategy of 500 mg IV Q6H
- Dose escalate in obesity and MDRO's to 1g q6h
- **Place in therapy: ESBLs & AmpC infections**

# Imipenem

- Imipenem/cilastin is Nonformulary
- Degraded by dehydropeptidase so must be administered with cilastatin
- Slightly better positive activity of carbapenems (primarily Enterococcus)
- **Place in therapy: ESBLs & AmpC infections, Nocardia and Mycobacterium species.**

## Meropenem-Vaborbactam (Vabomere)

- FDA approved 2017 for cUTI
- Similar spectrum to cefiderocol but no additional pseudomonas coverage or MBL
- Dosing is 1.25g q6h over 30 min infusion
- Additional Spectrum of Coverage for:
  - MDRO Enterobacterales
    - AmpC
    - ESBLs
    - CRE (eg. KPC)
  - **Place in therapy: CRE infections**

## & Imipenem-Cilastin-Relebactam (Recarbrio)

- FDA approved 2019 for cUTI & cIAI
- Similar spectrum to cefiderocol but no MBL
- Dosing is 1.25g q6h over 30 min infusion
- Additional Spectrum of Coverage for:
  - MDRO Enterobacterales or *Pseudomonas aeruginosa*
    - AmpC
    - ESBLs
    - CRE (eg. KPC, OXA-48)
  - **Place in therapy: CRE infections & MDRO pseudomonas**

# Case

1. V.Y. is a 64-year-old woman (height 5’2”, weight 65 kg) who is admitted to a rehabilitation facility. She was hospitalized for 2 weeks after a fall resulted in a C7 fracture and spinal cord injury with dysphagia, neurogenic bowel and bladder, sacral pressure ulcer s/p flap, and spasm of muscle. V.Y. has no known drug allergies. Her Tmax over last 24 hours is 100.6°F, heart rate 78 beats/ minute, blood pressure 130/74 mm Hg, and respiratory rate 16 breaths/minute. She has a solitary kidney, SCr 0.8 mg/dL, and a neurogenic bladder requiring intermittent straight catheterization. Urinalysis showed 50 WBCs, positive for nitrites and leukocyte esterase with many bacteria. V.Y. has history of urinary tract infections caused by ceftriaxone resistant + E. coli. She was last treated for a UTI 5 months ago.
2. Which one of the following would be the best empiric treatment for V.Y.?
   A. Zosyn.
   B. Levofloxacin.
   C. Bactrim.
   D. Ertapenem

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   A. Zosyn.
   B. Levofloxacin.
   C. Bactrim.
   **D. Ertapenem**

# Fluoroquinolones – general principles

- Concentration-dependent bactericidal activity
- Drug of choice for CAP & complicated UTIs
- Spectrum of coverage:
  - Gram negative: good coverage
  - Gram positive:
  - Good Strep coverage, Levofloxacin and Moxifloxacin are preferred for Strep but are not be best choice for *S. aureus* (MSSA and MRSA)
- Anaerobes: Moxifloxacin provides coverage. No anaerobic coverage for Cipro or levo (add metronidazole).
- Pseudomonas: Some coverage with Cipro and Levo
- Atypicals: Good coverage but levo and moxi are first line DOC for CAP
- Adverse events: generally well tolerated
- Occasional: GI intolerance, *C. difficile*-associated colitis, hypo/hyperglycemia
- Rare: Tendon rupture (increased incidence in age >60, concurrent use of corticosteroids, kidney, heart, and lung transplant recipients), QTc prolongation
- Drug interactions:
  - Divalent or trivalent cations(antacids, sucralfate, vitamins, minerals) interfere with absorption
  - Avoid oral g-tube administration (use IV formulation)
- Avoid other QTc prolonging drugs (amiodarone, procainamide, propafenone, flecainide, etc), or in pts with hypokalemia/hypomagnesia, bradycardia, or cardiomyopathy

# Fluoroquinolones

- **Ciprofloxacin**
  - Best clinical and in vitro data for activity against *P. aeruginosa*
  - Good experience for nosocomial pneumonia, osteomyelitis, chronic prostatitis, and UTIs
    - Although, E. Coli ST 131 resistant to fluoroquinolones
  - Other FQ (levo and moxi) preferred for infections due to S. pneumonia.
- **Levofloxacin**
  - Good in vitro activity and clinical experience against *S. pneumonia* and atypical agents of pneumonia.
  - FDA approved for PCN-resistant S. pneumonia , monotherapy for CAP and nosocomial pneumonia
  - 100% bioavailable
- **Moxifloxacin**
  - Spectrum similar to levofloxacin
  - Includes enhanced activity against S. pneumonia
  - Best anaerobic and mycobacteria activity among fluoroquinolones
  - Poor pseudomonal coverage
  - Lower urinary drug concentrations
    - Should not be used for UTIs
- **Delafloxacin (Baxdela)**
  - Good pseudomonal, mycobacteria, and G (+) coverage
  - Claim to fame – only FQ w/ MRSA coverage

# FDA Warning on FQ Antibiotic use

1. FDA recommendations state that risks of serious side effects with fluoroquinolones generally outweigh benefits for patients with the following:
   - Acute bacterial sinusitis
   - Acute exacerbation of chronic bronchitis
   - Uncomplicated UTI

| Fluoroquinolone Boxed Warning | |
|---|---|
| **July 2008** | • increased risk of tendinitis and tendon rupture |
| **February 2011** | • increased risk of exacerbating muscle weakness related to Myasthenia gravis |
| **August 2013** | • increased potential risk for irreversible peripheral neuropathy |
| **July 2016** | • increased CNS effects ((i.e. anxiety, depression, hallucinations, suicidal thoughts, confusion) |
| **July 2018 (new labeling change)** | • new mental health side effects updated to include disturbances in attention, disorientation, agitation, nervousness, memory impairment and delirium<br>• serious blood sugar disturbances, particularly risk of coma with hypoglycemia |
| **January 2019** | • Increased risk for ruptures or tears in the aorta |

# Case

1. A 54-year-old woman with a history of worsening renal insufficiency, A-fib (on amiodarone/warfarin), aortic dissection, admitted with dysuria and flank pain. She is initiated on empiric Zosyn therapy while cultures are pending. On day 2 urine cultures reveal E. coli.

Micro Reports | **Susceptibilities** | Specimen | Comments | Action List

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|---|---|---|---|
| 1 | Escherichia coli | | |
| 2 | | MDIL | MINT |
| 3 | Ampicillin | >=32 | R |
| 4 | Amoxicillin/Clavulanate | >32 | R |
| 5 | Piperacillin/Tazobactam | 8 | S |
| 6 | Cefazolin | 8 | R |
| 7 | Ceftriaxone | <=1 | S |
| 8 | Cefepime | <=1 | S |
| 9 | Gentamicin | <=1 | S |
| 10 | Tobramycin | <=1 | S |
| 11 | Ciprofloxacin | <=0.25 | S |
| 12 | Trimethoprim/Sulfa | <=20 | S |

Which one of the following is best antibiotic de-escalation strategy for this patient?

A. Ampicillin/sulbactam 3g intravenously QD

B. Ciprofloxacin 500mg PO BID

C. Ceftriaxone 1g intravenously QD

D. Trimethoprim/Sulfa 1 DS PO twice daily and reduce warfarin dose by 50%

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**C. Ceftriaxone 1g intravenously QD**

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# Aminoglycosides

- Gentamicin
- Tobramycin
- Amikacin
- Plazomicin

# Aminoglycosides –general principles

- Pharmacy to dose Aminoglycosides at BUMCP – providers enter consult
- MOA: Inhibit 30S ribosomal subunit
- Used for serious gram negative infections
  - Pseudomonas, E. coli, Enerobacter, Klebsiella, Proteus, Morganella, Providencia, and Serratia
- Concentration dependent bactericidal activity.
  - Efficacy predicted by peak/MIC ratio
  - Dosed once daily to maximize peak levels
  - Do not use QD dosing in patients with unstable renal function, CrCl<30 ml/min, meningitis, or increased Vd (pregnancy, ascites, edema).
- Produce prolonged postantibiotic effects
  - Antibiotic is bacteriostatic for 30-60 min after the concentration decreases below the MIC
- Toxicities commonly include nephrotoxicity and ototoxicity
  - Toxicity is saturable at high drug levels from QD dosing produce less adverse events than smaller doses given more frequently, which would result in prolonged elevated drug concentrations.

# Aminoglycosides - spectrum

- Good gram negative coverage: *H. flu*, *Enterobacteriaceae*, *Pseudomonas areuginosa*
  - *Pseudomonas:* Tobra better than Gent
- Gram positive:
  - Used synergistically against some *Staph, Strep, Enterococci*, and *Listeria monocytogenes*species
    - Dose at 1 mg/kg IV Q8H (goal peak 3-5 mcg/ml) along with beta-lactam antibiotics for synergy.
    - Tobramycin not active against Enterococci; Gentamicin is active.
- No activity against anaerobes or atypicals

# Aminoglycosides

- **Tobramycin**:
  - less nephrotoxicity, but more ototoxicity than gentamicin
  - Better susceptibilities to pseudomonas than gentamicin
- **Amikacin** is active against many gram negative bacteria that are resistant to gentamycin and tobramycin
  - Typically reserved for documented resistant infections to Gentamycin or Tobramycin.
  - Levels are send outs with typically ~24 hr turn around.
- **Plazomicin**
  - FDA approved for cUTI as once daily regimen
  - Only studied in CrCl ≥30ml/min
  - Expanded coverage for CRE & MBL

# Case

AZ is a 22-year-old woman of Caucasian origin diagnosed with CF with a history of 2-3 exacerbations per year (previous cultures w/ MRSA & Pan-S pseudomonas) presents to the hospital an with acute exacerbation. Which following would be the best course of action?

A. Consult ID provider for antibiotic selection dosing recommendation
B. Initiate Zosyn 4.5g x1, 3.375 q8h intravenously + consult pharmacy to dose vancomycin/tobramycin
C. Initiate Cefepime 2g q8h intravenously + pharmacy to dose vancomycin/tobramycin
D. Consult pharmacy to dose vancomycin/tobramycin + CF prolonged infusion β-lactam protocol

# Anti-MRSA Agents

- VANCOMYCIN
- LINEZOLID
- DAPTOMYCIN

# Vancomycin

- Pharmacy to dose vancomycin at BUMCP – providers enter consult
- Spectrum of activity: Strep, Staph (including MSSA/MRSA), and some gram positive anaerobes
  - Higher rates of failure when MRSA MIC is at breakpoint of 2
- Dosed by Pharmacy Consult
  - Goals determined by indication, risk for MRSA (troughs 12-18 mcg/mL, AUC/MIC 400-600)
  - Selects out for emergence of vancomycin resistant Enterococcus, VISA/VRSA
- Vancomycin ~~Red Man Syndrome~~ Infusion Reaction
  - flushing over chest/face +/-hypotension & pruritis
  - usually avoided by slowing the infusion to 120 minutes (standard is 30-60 min) + Benadryl pre-med
- Can be nephrotoxic in combo with other drugs such as high dose Zosyn, aminoglycosides, diuretics etc.
  - When used alone nephrotoxicity is associated with >4g daily dose & >7 day duration of therapy

# Linezolid

- Spectrum of activity
  - Primarily gram-positive bacteria including MRSA and VRE
  - Active against penicillin resistance Strep pneumoniae
  - Can be used in some of the drug resistant mycobacteria(non-TB) infections
- Should not be used to treat Staph bacteremia, only approved for VRE bacteremia
- MOA: Inhibits protein synthesis at the 50s ribosome
  - Bacteriostatic(most bacteria including Staph)
  - Bacteriocidal(Streptococci)
- Controversy over better penetration into lungs than vancomycin
- IV and PO available-100% bioavailable
- Major DDI w/ SSRI can cause serotonin syndrome (incidence ≤4%)
- No hepatic or renal adjustment required
- AE: severe thrombocytopenia (14d), usually reversible at discontinuation, optic neuritis and peripheral neuropathy
- WARNING-drug resistance to MRSA and VRE have been reported

# Daptomycin

- Similar spectrum of activity & need to be reserved for documented resistant infections
- MRSA, VRE or VISA/VRSA
- Daptomycin 10 mg/kg needed for VRE with MIC of 4
- Primary indications: complicated SSSI and non-resolving bacteremia
  - Daptomycin is FDA approved for R sided endocarditis
- Requires baseline CK level and weekly monitoring
- Bactericidal activity against Staph
- Daptomycin is inactivated by lung surfactants and should NOT be used to treat PNA
- Order baseline CK

# Case

G.P. is a 57-year-old man who has received a diagnosis of osteomyelitis of the tibia after a traumatic injury. The surgical bone culture reveals MRSA susceptible to all antimicrobials on the test panel (other than oxacillin). The vancomycin is S (MIC is 2 mcg/mL). G.P. has no known drug allergies.

Which one of the following is best to recommend for G.P.?

A. Levaquin 750mg QD x 8 weeks.
B. Vancomycin 15 mg/kg intravenous q12 hours x 8 weeks.
C. Daptomycin 6 mg/kg intravenous x1 dose & consult ID provider.
D. Linezolid 600 mg intravenous twice daily plus rifampin 300 mg orally twice daily x 8 weeks

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# *Clostridium difficile Treatment*

- METRONIDAZOLE
- PO VANCOMYCIN
- FIDAXOMICIN

# Metronidazole (Flagyl)

- No longer considered first line for C difficile
  - Per CDI guidelines, consider in nonsevere CDI in resource limited settings
- Use in C diff is 500mg Q8h IV for fulminant CDI
- Provides excellent anaerobic (Bacteroides) coverage
- Peripheral neuropathy reported to occur with >14 day use

# PO Vancomycin

- First line for non-severe, severe, or fulminant Cdiff
  - WBC >15, hypotension, ileus, megacolon or pseudomembranes on imaging, increasing SCr above baseline (x2), low albumin (<3)
  - Can be used for 1st recurrence with prolonged taper and pulsed regimen
  - Expensive for outpatient course
- Inpatient uses compounded solution, cheaper and just as effective
  - New formulation Firvanq approved Jan 2018
- Starting dose is 125 mg QID, in severe cases dose are escalated to 500mg QID

# Fidaxomicin

- First line for non-severe & severe CDI (not Fulminant CDI)
- Is a poorly absorbed, macrocyclic antibiotic with activity against Gram-Positive aerobes and anaerobes, including *Clostridium difficile*
- Only studied in non-severe & severe disease
  - Found to be non-inferior to vancomycin the primary efficacy endpoint, clinical cure.
  - Superior in preventing recurrent CDI compared to PO vancomycin
  - NNT to prevent 1 recurrent CDI is 5

- $$$ A 10-day course costs $3,000. ~$15,000 spent to prevent one CDI recurrence.
  - BUMCP criteria of use reserves for patients with risk factors for recurrence CDI and able to get insurance approval/prior authorization
    - Risk factors include: Concomitant broad-spectrum antibiotic used for another diagnosis or suspected infection, severely immunocompromised (e.g. hematologic cancer with neutropenia expected >30 days, BMT, early SOT), and age ≥ 65 years

# Case

1. AP is a 70 year old woman with a PMH of complicated diverticulitis, rheumatoid arthritis, and MDRO history. AP presents with some discomfort in the lower abdomen and is started on meropenem. On the 3rd day of admission, she develops profuse watery diarrhea (>3x per day). A clostridium difficile GDH/toxin test comes back positive (no previous hx of GDH). Her Scr is 1.0 and WBC of 25,000. Classifying this as a severe CDI, what is the best treatment option?

A. Metronidazole PO 500mg PO q8h x 10 days
B. Vancomycin 125mg PO q6h x 10 days
C. Fidaxomicin PO 200mg q12h
D. Vancomycin 125mg PO q6h, consult case management for Fidaxomicin 200mg q12h x10 days prior authorization to be approved.

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# Antimicrobial Duration of Therapy

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# Thank you

**Emir Kobic**
emir.kobic@bannerhealth.com
Office: 602-839-4581 | Pager: 602-201-2224

# Case

1. AT is a 49-year-old (No hx of MDROs) with uncontrolled diabetes is hospitalized with significant flank pain, chills, and a temperature of 101.3°F (38.5°C). She is very uncomfortable because of flank pain, and her vital signs are blood pressure 140/95 mm Hg, heart rate 85 beats/minute, and respiratory rate 23 breaths/minute. Her laboratory test results are remarkable only for a WBC of 11.3 x 10^3 cells/mm^3. She has no history of renal insufficiency. Which one of the following is best to recommend for this patient?

A. Piperacillin/tazobactam 4.5g x1, then 3.375g intravenously every 8 hours
B. Ceftriaxone 1 g intravenously every 24 hours
C. Aztreonam 1 g intravenously every 8 hours
D. Levofloxacin 750 mg intravenously every 24 hours

# Case

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C. Aztreonam 1 g intravenously every 8 hours

D. Levofloxacin 750 mg intravenously every 24 hours

# Aztreonam

# Duration

- Finding empiric guidelines, finding antibiogram
- Duration of therapy in UTI, BSI, PNA -> see ID Week meting
- One of the meetings is called
  - how long can we go
  - influencing ASP activities: the devil is in the details

# Intro slide

## CDI risk increases with duration

**Table. Comparison of antibiotic days for case & noncase hospitalizations**

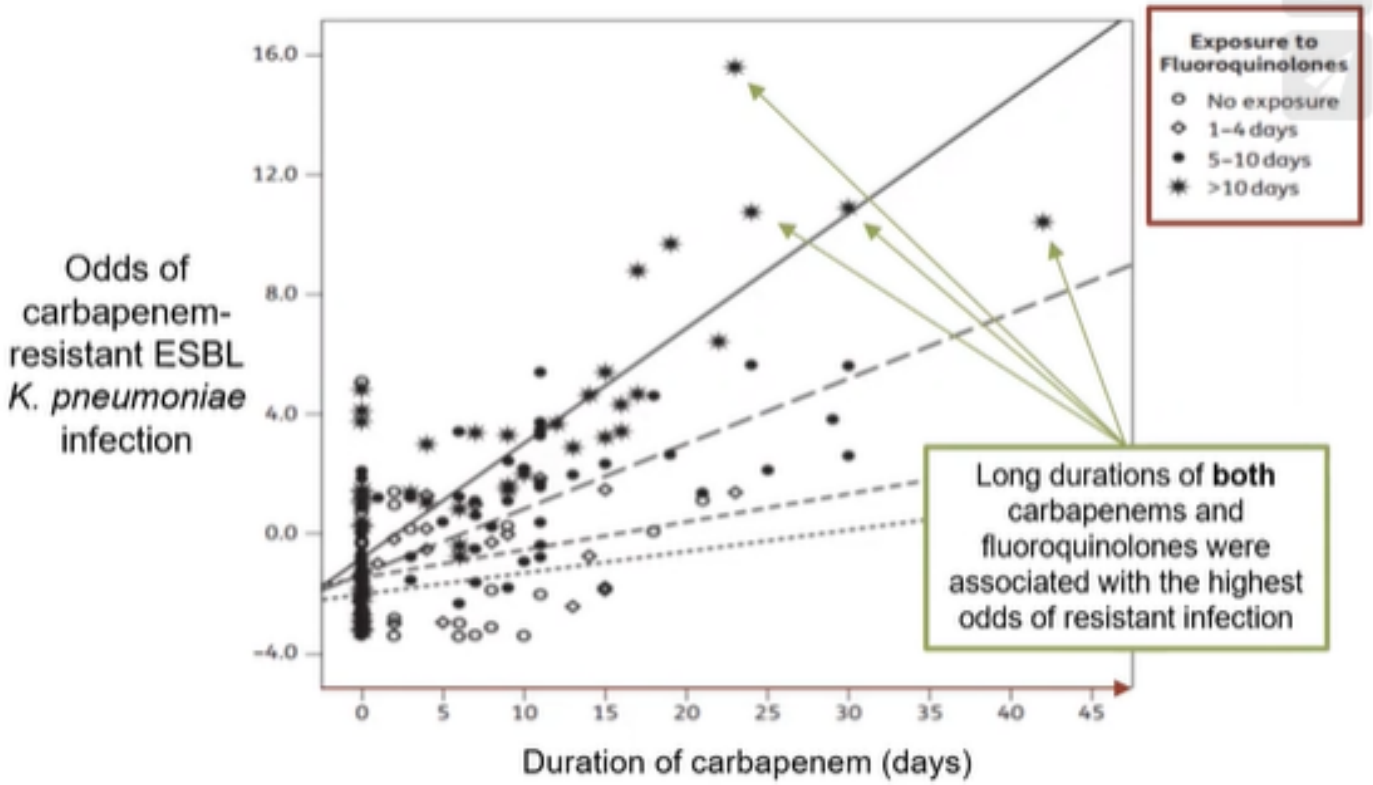
| | CDI positive n (%) | CDI negative n (%) | Adjusted hazard ratio (95% CI) |
|---|---|---|---|
| Antibiotic days, median (IQR) | 14.0 (23) | 7.0 (9) | |
| <4 | 22 (9) | 2208 (22) | Ref |
| 4 to 7 | 41 (17) | 3701 (31) | 1.4 (0.8, 2.4) |
| 8 to 18 | 87 (36) | 3097 (31) | 3 (1.9, 5) |
| >18 | 91 (38) | 1537 (16) | 7.8 (4.6, 13.4) |

**10,154** hospitalizations (7,792 unique patients) with **241** cases of CDI
Stevens et al. Clin Infect Dis. 2011 Jul 1;53(1):42-8

# Another intro slide –each day increase anti-pseudomonal resistance risk

# Linking resistance to antibiotic use

- **Resistance correlates with antimicrobial usage**
- **Resistance is higher among patients who have received prior antibiotics**




Kritsotakis et al. J Antimicrob Chemother. 2011 Jun;66(6):1383-91.

# Neutropenic fever slide

- How to find global view of agents

# Reading the MAR setting it back

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PHARMACOTHERAPY accp

# Duration of Exposure to Antipseudomonal β-Lactam Antibiotics in the Critically Ill and Development of New Resistance

Besu F. Teshome,[1,2] Scott Martin Vouri,[3,4] Nicholas Hampton,[5] Marin H. Kollef,[6] and Scott T. Micek[1,7,*]

[1]Department of Pharmacy Practice, St. Louis College of Pharmacy, St. Louis, Missouri; [2]John Cochran Division, VA St. Louis Health Care System, St. Louis, Missouri; [3]Department of Pharmaceutical Outcomes and Policy, University of Florida College of Pharmacy, Gainesville, Florida; [4]University of Florida Health Physicians, Gainesville, Florida; [5]Center for Clinical Excellence, BJC Healthcare, St. Louis, Missouri; [6]Division of Pulmonary and Critical Care Medicine, Washington University School of Medicine, St. Louis, Missouri; [7]Center for Health Outcomes Research and Education, St. Louis College of Pharmacy, St. Louis, Missouri

**Study Objective** Minimizing the duration of broad-spectrum antimicrobial exposure in the critically ill is a commonly used strategy aimed at preventing resistance. Our objective was to correlate the duration of exposure to antipseudomonal β-lactam antibiotics with the development of new resistance in critically ill patients.

**Design** Single-center, retrospective cohort study.

**Setting** A large, academic, tertiary care hospital.

**Patients** A total of 7118 adults with a discharge diagnosis of severe sepsis or septic shock who received at least one dose of cefepime, meropenem, or piperacillin-tazobactam during their hospitalization between 2010 and 2015.

**Measurements and Main Results** Cohort entry was defined as the first day of any antipseudomonal β-lactam initiation, and exposure was defined as the cumulative days of any antipseudomonal β-lactam exposure during the 60-day follow-up period. The primary outcome was development of new resistance to any antipseudomonal β-lactam > 3 days after cohort entry. New resistance was defined as detection of resistance to any antipseudomonal β-lactam not identified within 180 days before cohort entry. Patients without an outcome (i.e., did not develop new resistance) or who died by day 60 were censored. Cox proportional hazards models were performed to assess the risk of development of new resistance to any antipseudomonal β-lactam with each additional day of exposure. Analyses of each individual antipseudomonal β-lactam were evaluated as secondary outcomes. Each

Results:

4% increased risk of new resistance for each additional day of anti-pseudomonal β-lactam exposure:

- Cefepime 8%
- Zosyn 8%
- Meropenem 2%

# Case

1. VY's urine cultures come back with the following susceptibility pattern Which of the following is the best treatment?

| Klebsiella pneumoniae | | | | |
|---|---|---|---|---|
| | MDIL | MINT | EDIL | EINT |
| Ampicillin | >=32 | R | | |
| Amoxicillin/Clavulanate | >32 | R | | |
| Piperacillin/Tazobactam | >=128 | R | | |
| Cefazolin | >=64 | R | | |
| Ceftriaxone | >=64 | R | | |
| Cefepime | >=64 | R | | |
| Ertapenem | >4 | R | | |
| Meropenem | 8 | R | | |
| Amikacin | 16 | S | | |
| Gentamicin | >=16 | R | | |
| Tobramycin | >=16 | R | | |
| Ciprofloxacin | >=4 | R | | |
| Levofloxacin | >=8 | R | | |
| Trimethoprim/Sulfa | >=320 | R | | |

a) Start Zerbaxa 3g q8h intravenously q8h, consult ID provider, and request Zerbaxa susceptibilities from microbiology lab.

b) Start Avycaz 2.5g intravenously q8h, consult ID provider, and request Avycaz susceptibilities from microbiology lab

c) Start Vabomere 4g intravenously q8h, consult ID provider, and request Vabomere susceptibilities from microbiology lab

d) B and C are both correct

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| Ampicillin | >=32 | R | | |
| Amoxicillin/Clavulanate | >32 | R | | |
| Piperacillin/Tazobactam | >=128 | R | | |
| Cefazolin | >=64 | R | | |
| Ceftriaxone | >=64 | R | | |
| Cefepime | >=64 | R | | |
| Ertapenem | >4 | R | | |
| Meropenem | 8 | R | | |
| Amikacin | 16 | S | | |
| Gentamicin | >=16 | R | | |
| Tobramycin | >=16 | R | | |
| Ciprofloxacin | >=4 | R | | |
| Levofloxacin | >=8 | R | | |
| Trimethoprim/Sulfa | >=320 | R | | |
| Ceftazidime/avibactam | | | 8 | S |
| Meropenem/Vaborbactam | | | 0.25 | S |

a) Start Zerbaxa 3g q8h intravenously q8h, consult ID provider, and request Zerbaxa susceptibilities from microbiology lab.

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c) Start Vabomere 4g intravenously q8h, consult ID provider, and request Vabomere susceptibilities from microbiology lab

**d) B and C are both correct**

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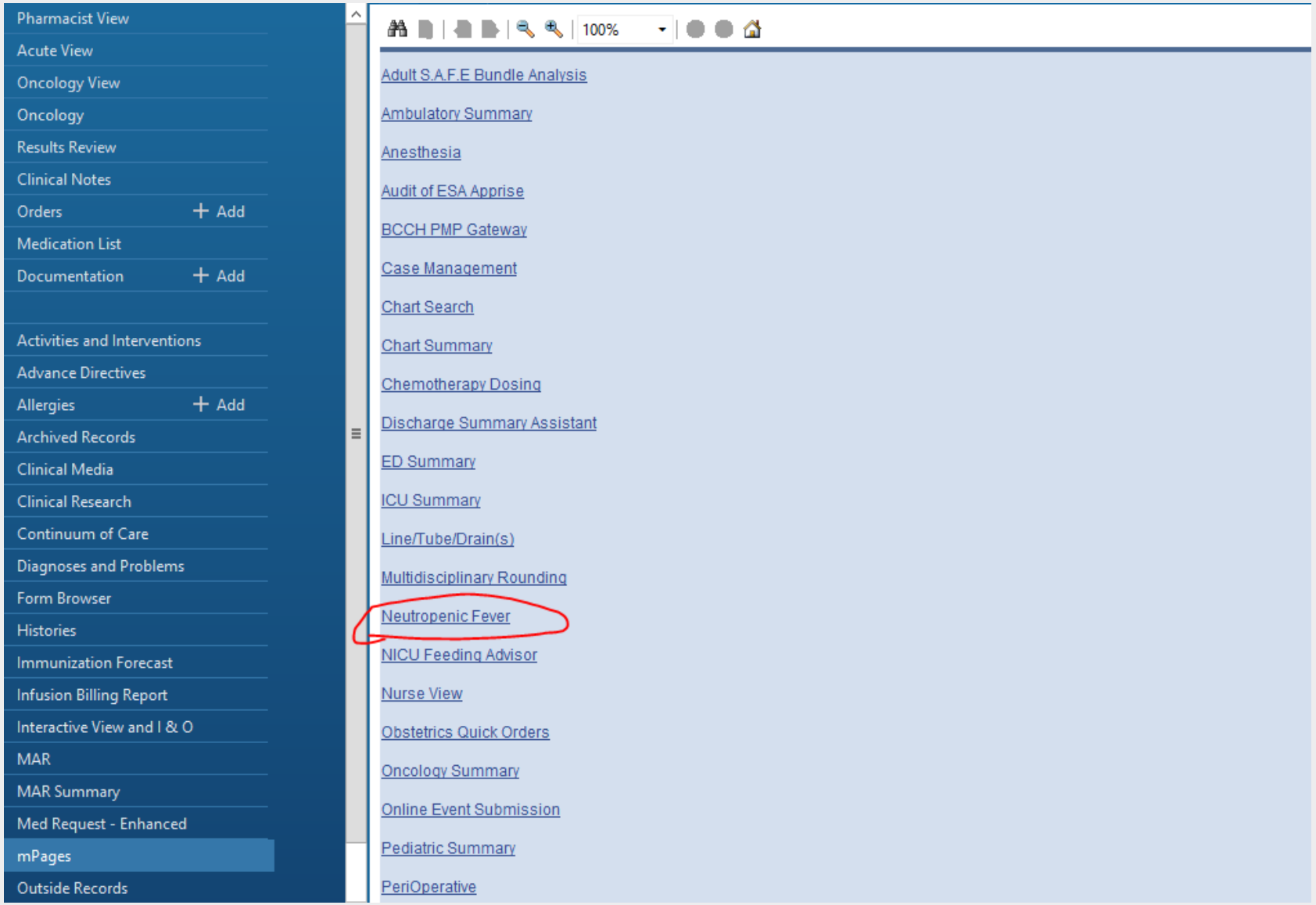
# Neutropenic fever mPage



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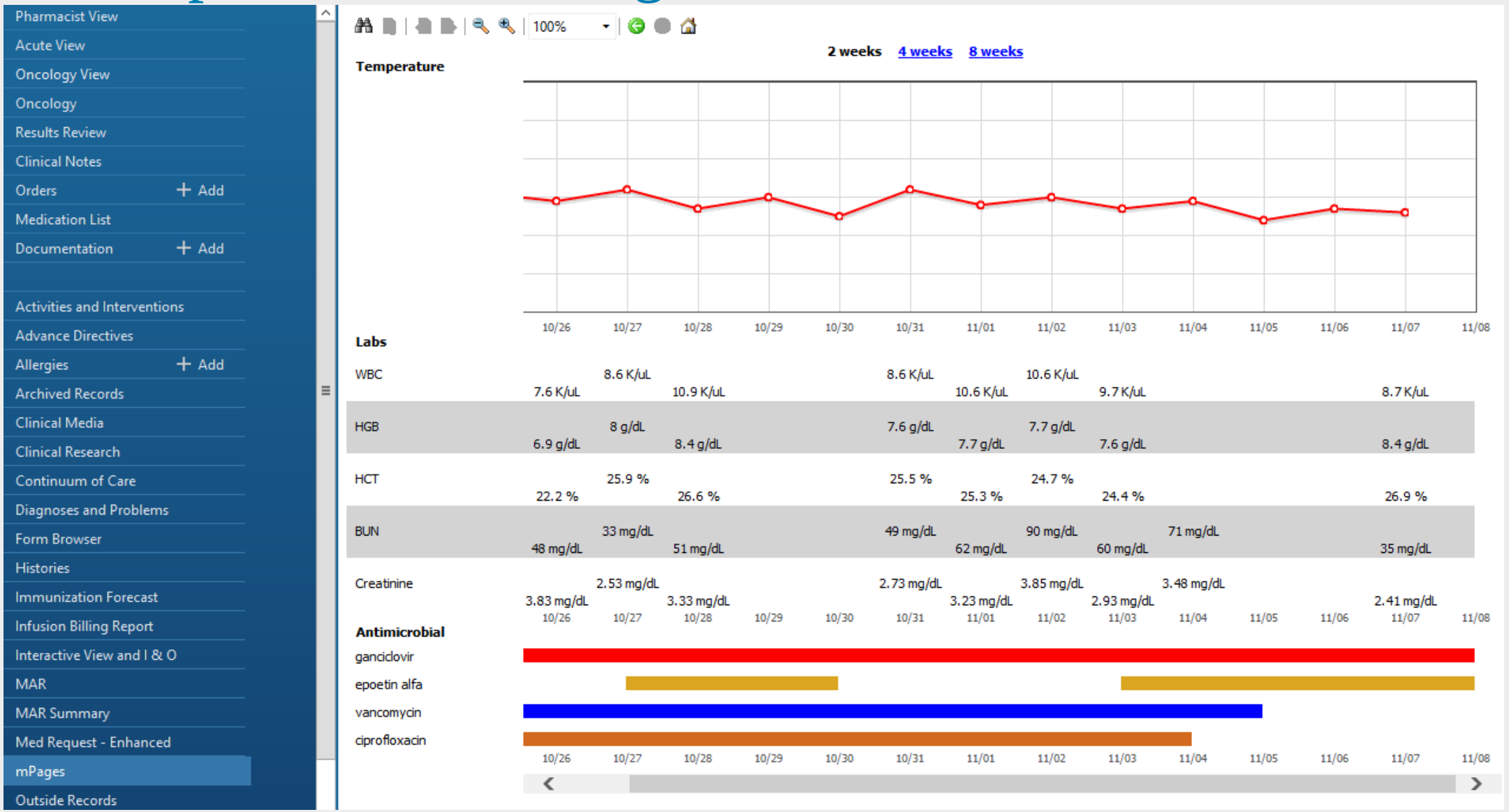
# Neutropenic fever mPage



# The New Antibiotic Mantra- "Shorter is Better"

| Diagnosis | Treatment Days Short (d) | Long (d) | Result | # RCTs |
|---|---|---|---|---|
| CAP | 3-5 | 5-14 | Equal | 10 |
| VAP | ≤8 | 15 | Equal | 2 |
| Pyelonephritis | 5 or 7 | 10 or 14 | Equal | 7 |
| Intra-abd | 4 | 10 | Equal | 2 |
| GNB Bacteremia | 7 | 14 | Equal | 2 |
| Acute Exacerbation Chronic Bronchitis | ≤5 | ≥7 | Equal | >20 |
| Cellulitis | 5-6 | 10 | Equal | 4 |
| Chronic Osteo | 42 | 84 | Equal | 2 |
| Septic Arthritis | 14 | 28 | Equal | 1 |
| Ortho Implant w/ removal | 28 | 42 | Equal | 1 |
| Neutropenic Fever | AFx72h | +ANC>500 | Equal | 1 |

Spellberg. Jama 2016;176(9):1254-1255

# *Miscellaneous*

- TIGECYCLINE/ERAVACYCLINE
- COLISTIN/POLYMYXIN

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# Vancomycin ~~Red Man Syndrome~~ Infusion Reactions

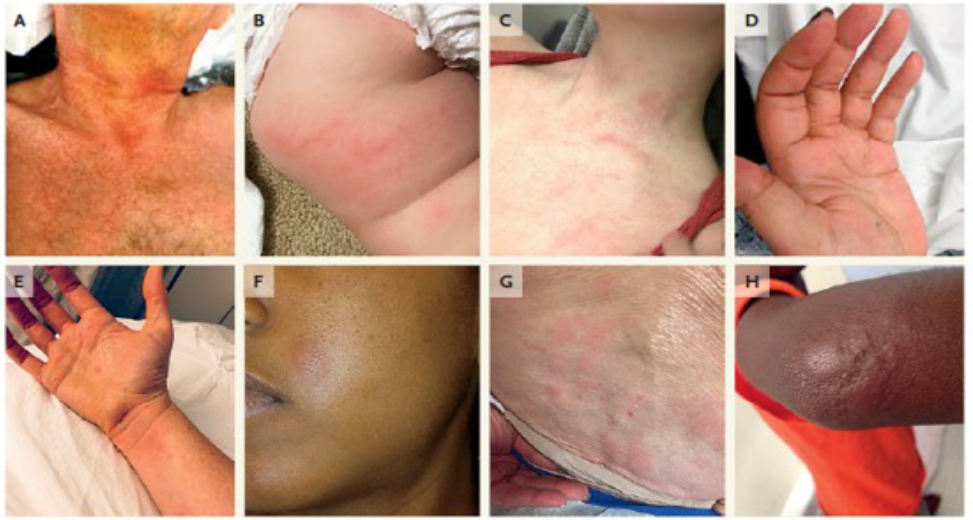
***Out with the old, in with the new*** *[more accurate and less discriminatory terminology]*

**"Red Man Syndrome" should no longer be used to describe common vancomycin infusion reactions.**

**→ Why?**

- The term "Red Man" is **discriminatory** against Native American and Indigenous people, and also enables **gender and race-related biases**.
  - Redness may be more apparent on lighter skin.*
  - Reactions may be missed altogether on darker skin.*
  - "Red Man Syndrome" is more likely to be documented for males compared to females with similar reaction features.*
  - Female reactions are more often misclassified as "allergies" leading to unnecessary avoidance of vancomycin.*

- **What is the actual reaction?** Vancomycin-induced histamine release from mast cells, which can mimic anaphylaxis but is less severe.
  - ***Common symptoms:*** pruritus, erythematous rash over face/neck/upper torso, diffuse burning, generalized discomfort
  - ***Less common, but possible symptoms:*** hypotension, angioedema, dizziness, headache, fever




**Dermatologic Findings in Patients Varying in Age, Sex, and Skin Color.**
The immediate reaction to drugs, including the vancomycin infusion reaction, can present as erythema that can be confluent or blotchy, typically involving the head and neck but also the trunk, extremities, and palms or soles (Panels A through D) or urticaria that can be localized or diffuse (Panels E through H).

## How should we document appropriately?

Under "Allergies" add vancomycin with the following:
- **Reactions:** Flushing
  *Alternative: Other (see comments)*
- **Severity:** Low
- **Reaction Type:** Intolerance
- **Comments:** Vancomycin infusion reaction

***Please review the article below for citations to the studies supporting these statements.***

Alvarez-Arango S, Ogunwole M, Sequist TD, Burk CM, Blumenthal, KG. Vancomycin infusion reaction – moving beyond "red man syndrome". *N Engl J Med.* 2021;384(14):1283-6.

*Created by Aileen Ahiskali, PharmD, BCIDP – 17 June 2021*

# MEROPENEM/VABORBACTAM (VABOMERE)

- Indication
  - Complicated UTI
- Dosing
  - 4g q8h over 3h infusion
- Spectrum of Coverage
  - Good G (+), g (-), and anaerobic coverage
  - ESBLs, AmpC, & CRE (KPC-1 & KPC-2s)
  - Lacks MBL coverage
- Vabomere should be reserved for infections with demonstrated or strongly suspected susceptibility to Vabomere.
  - Always request susceptibility from Microbiology

# Tigecycline

- Spectrum of activity: should be reserved for documented resistant pathogens
  - Gram positive included Strep and enterococcus
  - Gram negative w/ exception of Pseudomonas
  - Anaerobic, Proteus and Providencia
- Fixed dosing; 100mg x1, then 50mg q12h
- Large Vd (7L/kg) -> poor concentration in serum/urine
- Indications for use: MDR organism(primarily gram negative) including carbapenemase producing gram negatives, complicated SSSI, or complicated intra-abdominal infections
- Patient's with Child Pugh Score C require dose adjustment
- AE: highly associated with N/V (20-30%)

# Eravacycline

- Spectrum of activity: similar to tigecycline, in vitro data suggests eravacycline is 2-4 fold more potent against gram+ and 2-8 fold more potent against gram-
- Weight based dosing, 1mg/kg q12h.
- Vd (~4L/kg) -> poor concentration in urine
  - Failed 2 phase 3 noninferiority trials for cUTI
- Indications for use: complicated intra-abdominal infections
- Patient's with Child Pugh Score C require dose adjustment
- AE: Less N/V (5-10%) than tigecycline

# Colistin

- Two formulations
  - Colistimethate (Coly-Mycin)
  - Polymixin B
- Spectrum: Most MDR Gram-organisms including *Pseudomonas aeruginosa, Acinetobacter spp.,* ESBL and KPC producers
- Indication: Last resort reserved for MDR infections
- Inhalation –CF patients or nosocomial pneumonia
- Rapidly bactericidal –development of resistance is slow
- AE: **Nephrotoxicity** –up to 20% (usually reversible), neurotoxicity
- Inhaled –bronchospasm, ARDS

Banner Health

# Banner Health Pharmacy and Therapeutics Clinical Consensus Group
## Restricted Antimicrobials
### Last Updated April 2020

| Medication | Restriction Criteria |
|---|---|
| Amikacin | ▪ Short-term empiric therapy<br>o Severe, life-threatening infections when Nocardia species, Mycobacterium, or gram-negative organism with suspected MDRO or patient with history of MDRO<br>▪ Treatment:<br>o Severe, life-threatening infections for Nocardia or Mycobacterium species<br>o Gram negative MDRO organisms not susceptible to other aminoglycosides (i.e. gentamicin/tobramycin) |
| Aztreonam | ▪ Treatment of GNR infection in cases with severe PCN allergy (Anaphylaxis, which may manifest as hypotension, shock, swelling of tongue or throat, difficulty breathing, Steven Johnson Syndrome (SJS), Drug Reactions with Eosinophilia and Systemic Symptoms (DRESS), or Toxic Epidermal Necrolysis (TEN) reactions with previous PCN use)<br>▪ If allergy to ceftazidime or cefiderocol avoid aztreonam use |
| Ceftaroline (Teflaro) | ▪ MRSA (ceftaroline-susceptible):<br>o Severe infection* AND vancomycin failure** or allergy/intolerance***<br>o Can be used for synergistic combination therapy with daptomycin for refractory MRSA bacteremia****<br>▪ *Streptococcus pneumoniae* (ceftaroline-susceptible): severe infection* AND ceftriaxone resistance, intolerance or contraindications AND vancomycin failure** or allergy/intolerance***<br>▪ *Enterococcus* spp.: severe infection* for synergistic combination therapy (documented ceftaroline susceptibility not required)<br>If patient does not meet above criteria, consider alternative therapy options such |