Multi-Drug Resistant Gram Negative Bacteria and Antimicrobial Stewardship

Brian Meister PharmD, BCPS

Gulf Breeze Hospital

Objectives

- Definition and evolution of gram negative resistance
- Epidemiology of gram negative resistance
- Treatment of resistant organisms
- Stewardship role of hospital pharmacist

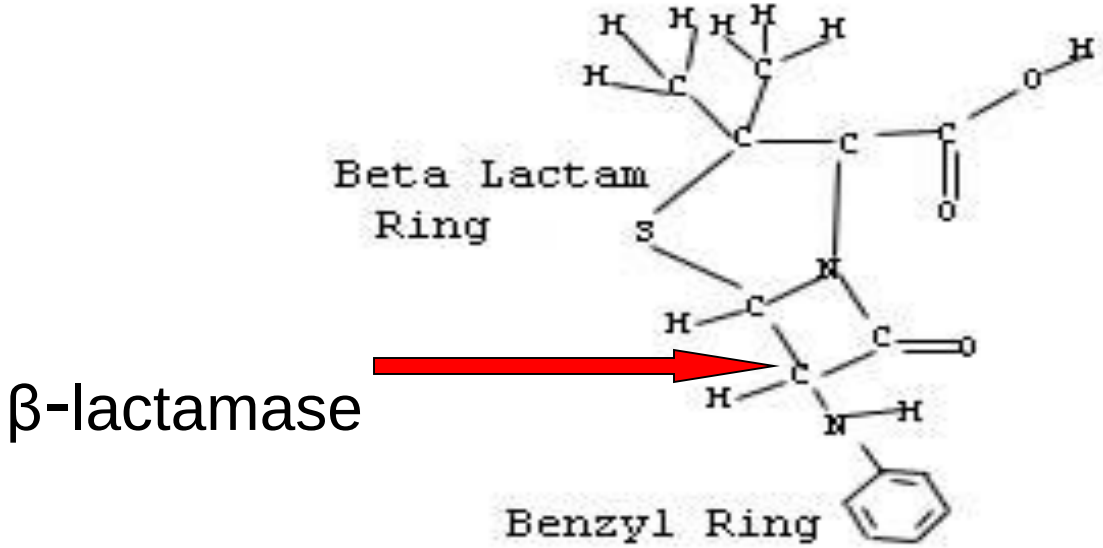
Abbreviations

- Beta - β
- Extended Spectrum β-Lactamase - ESBL
- Trimethoprim/sulfamethoxazole - TMP/SMX
- Aminoglycoside-modifying enzymes - AME
- Penicillin - PCN
- *Klebsiella pneumoniae - K.Pneumoniae*
- Temoniera - TEM
- Sulphydryl variable - SHV
- Cefotaxime resistant - CTX-M
- Oxacillin resistant - OXA
- *Escherichia coli - E. coli*
- Minimum Inhibitory Concentration - MIC
- Antibiotic - Abx
- Urinary tract infection - UTI
- Penicillin binding proteins - PBPs

Abbreviations [cont.]

- Carbapenem-resistant Enterobacteriaceae - CRE
- *Klebsiella pneumoniae* carbapenemase - KPC
- Metallo-β-lactamase - MBL
- New Delhi metallo-β-lactamase - NDM
- Intensive Care Unit - ICU
- Multi-Drug Resistant - MDR
- Vancomycin Resistant *Enterococci* - VRE
- Skin & soft tissue infection - SSTI
- Methicillin-Resistant *Staphylococcus aureus* - MRSA
- Complicated intra-abdominal infection - cIAI
- Community-acquired pneumonia - CAP
- Central nervous system - CNS
- Culture - Cx
- Diabetes mellitus – DM
- Epsilometer test (Etest)

β-lactamase

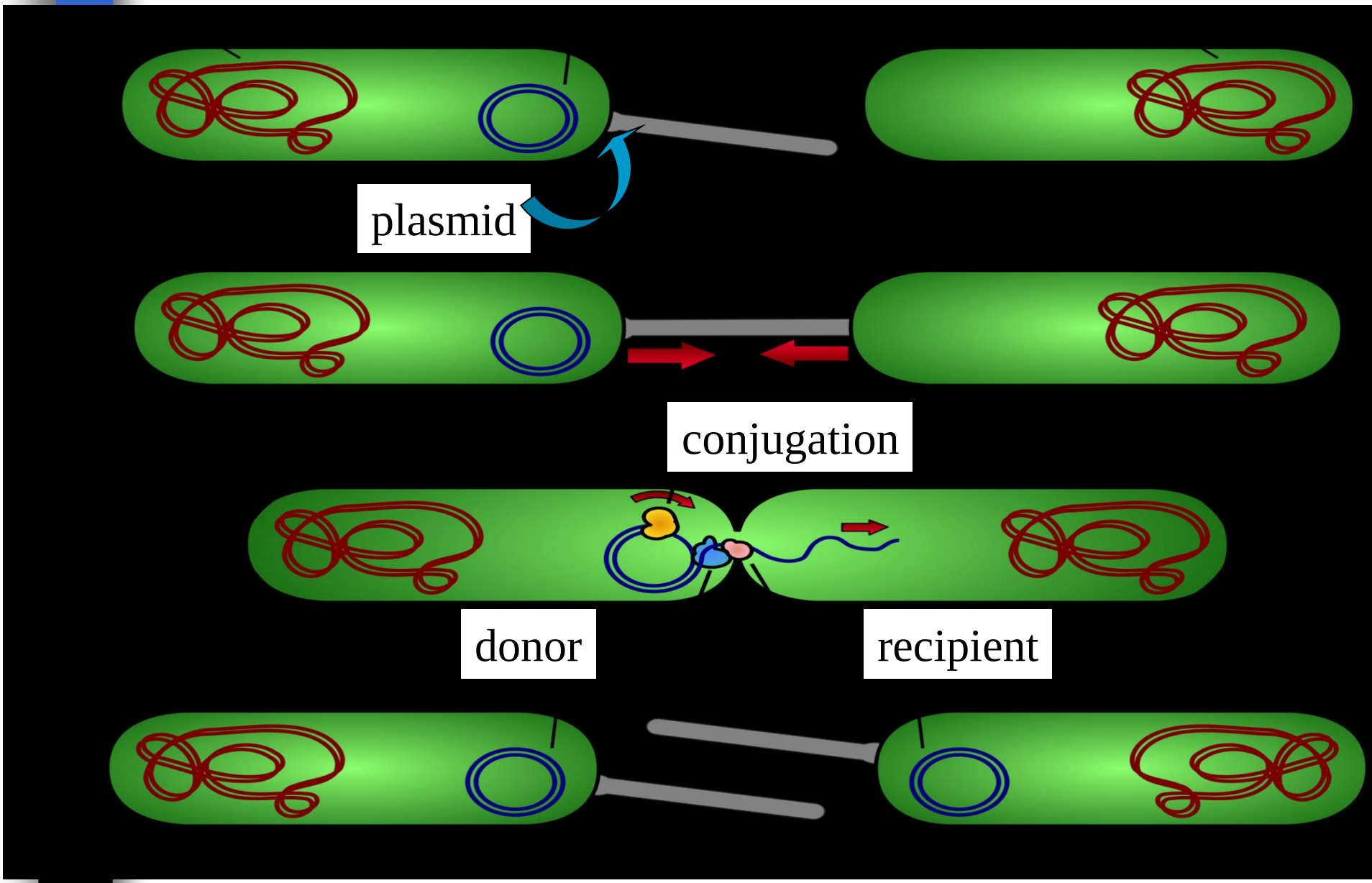


- **Enzymes that inactivate β-lactam antibiotics**
- **Resistant to penicillins and 1st generation cephalosporins like cefazolin**

ESBL

- **Inactivate broad spectrum β-lactam antibiotics**
  - **Enlarging β-lactam binding site**
- **Amino acid substitution or plasmid mediated**
- **Commonly resistant to quinolones, aminoglycosides and TMP/SMX**
  - **Plasmid mediated transfer of AME**

Plasmid transfer

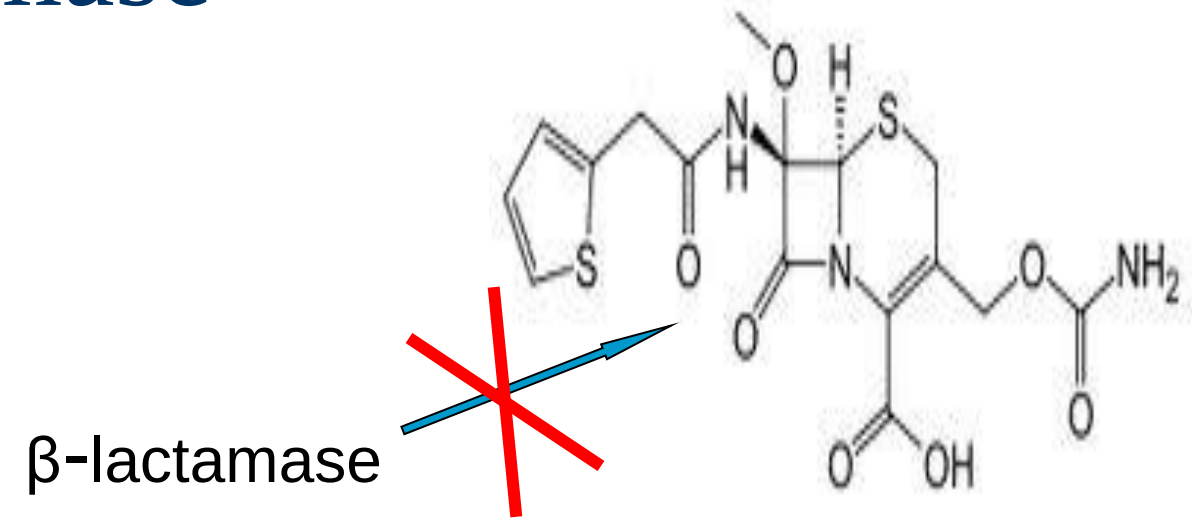


http://upload.wikimedia.org/wikipedia/commons/thumb/3/3e/Conjugation.svg/2000px-Conjugation.svg.png?uselang=fr

Evolution of β-lactamase

- 1st β-lactamase: Greece in 1960's
  - Named TEM after patient
- TEM-2 differed by 1 amino acid
  - Resistant to PCN and 1st gen cephalosporins
- Susceptible to 3rd and 4th gen. cephalosporins
  - Due to oxyimino side chain

β-lactamase



Oxyimino side chain protects the β-lactam ring

β-lactamase inhibitors

- Clavulanate
  - Amoxicillin/clavulanate (Augmentin®)
- Tazobactam
  - Pipercillin/tazobactam (Zosyn®)
- Sulbactam
  - Ampicillin/sulbactam (Unasyn®)

Evolution of ESBL

- 1st ESBL in Germany 1983
  - *K. pneumoniae*
- 1st ESBL outbreak in France 1985
  - TEM related enzymes
- Made it to U.S. in early 1990's
  - TEM related enzymes
- Amino acid substitution mechanism

Types of ESBL

- TEM: 160 types
  - TEM-10,12 and 26 are most common in U.S.
  - Some are β-lactamase inhibitor resistant
- SHV: 100 types
  - Most common ESBL in U.S.
  - SHV-5 and 12 most common

Types of ESBL

- CTX-M: 60 types
  - Plasmid transfer from another bacteria
  - Most common world wide
- OXA: more rare
  - Hydrolyze anti-staphylococcal PCN
  - Plasmid or amino acid mechanism

Epidemiology of ESBL

- 5000 *K. pneumoniae* samples
  - 45% ESBL in Latin America
  - 23% Europe
  - 7.6% U.S.
- 12000 *E. coli* samples
  - Latin America 8.5%
  - U.S. 3.3%

Risks for ESBL Infection

- Dialysis
- Ventilator
- Length of stay
- Gastrointestinal colonization
- Intensive Care Unit
- Antibiotics
- Feeding tube
- Long term care facility
- Emergent abdominal surgery
- Catheters

Most have been exposed to fluoroquinolones or Broad spectrum cephalosporins

Mechanism of Resistance

- MIC changed in 2010
  - Falsely sensitive reports
- Selective pressure
  - Enzyme resists Abx used
  - Sub-therapeutic dose or inadequate course
- Some mutations reduce spectrum
  - Check sensitivities

Treatment of ESBL

- Carbapenems 1st line
  - Imipenem, meropenem, ertapenem and doripenem
- Ceftazidime/avibactam (Avycaz®)
  - Complicated UTI
  - Intraabdominal infection with metronidazole
- Aminoglycosides
  - If susceptible, although most will not be

Treatment

- Tygecycline (Tygacil®)
- Colistin (Coly-Mycin®)
- Broad spectrum Cephalosporins not a good idea
  - Failure due to inoculum effect
- Piperacillin-tazobactam
  - UTI possibly
  - Urinary concentration

Carbapenems

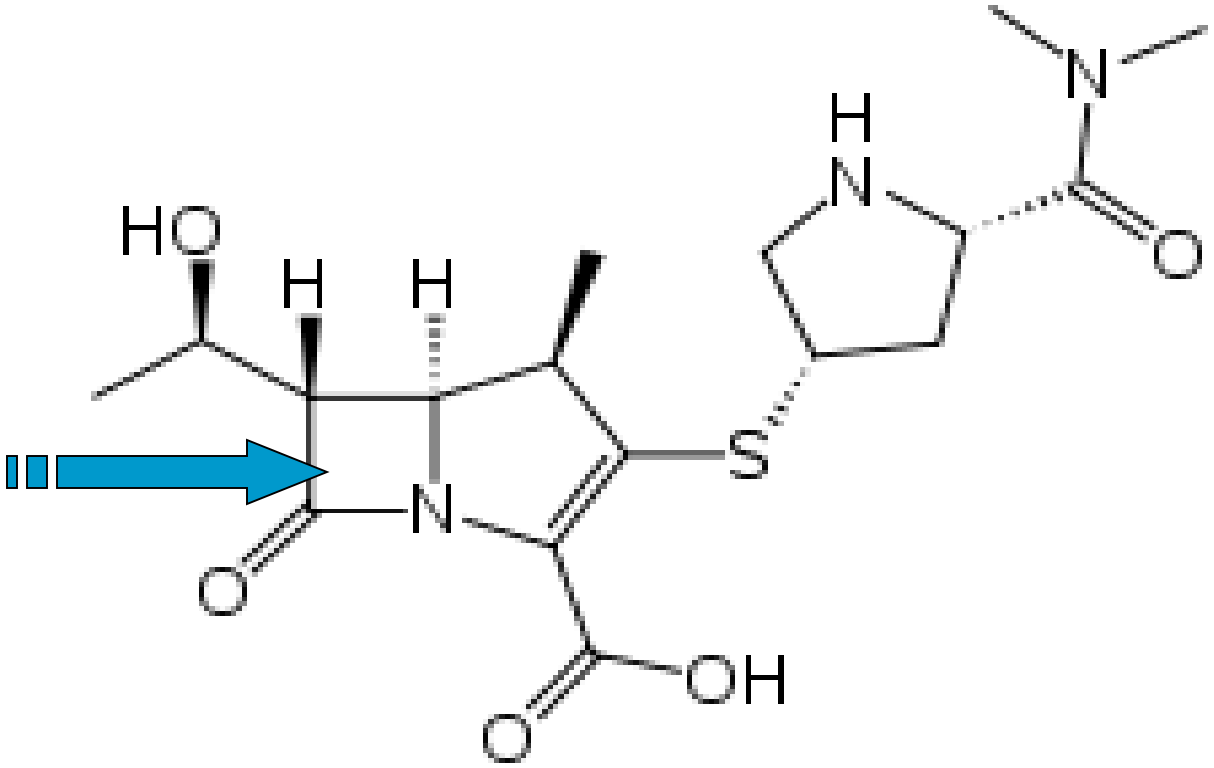
- Bind PBPs
- Inhibit cell wall synthesis
- Most cover pseudomonas
  - Ertapenem does not
- Avoid in seizure disorders
  - Class related side effect

Carbapenems

- Doripenem
- Ertapenem
  - Does not cover pseudomonas
- Imipenem
- Meropenem
- Pearls:
  - All renally dosed
  - Cover gram negatives and anaerobes

Carbapenemase

Carbapenemase



meropenem

Carbapenem Resistant Enterobacteriaceae

- First found in North Carolina 1999
  - *K.pneumoniae* resistant to all β-lactams
  - Plasmid encoded
  - Named KPC-1
- KPC requires other mutations to inactivate carbapenems

Classification of carbapenemases

- Ambler classification system:
  - Class A, C and D all have serine at active site
  - Class B: zinc required for activity
    - MBL
    - NDM
  - Class D: OXA type β-lactamase
    - Found in *Acinetobacter baumannii*

Klebsiella Pneumoniae Carbapenemase

- Most prevalent carbapenemase in U.S.
- Transferable by plasmid to other bacteria
- Detected in blood, urine and respiratory cultures
- Often resistant to aminoglycosides and fluoroquinolones

Evolution of KPC

- KPC-1 in North Carolina
- KPC-2 Northeast U.S.
  - Revealed to be KPC-1
- KPC-3 outbreak in New York City
- KPC-1 to 7 Now found world wide
  - Differ by no more than 2 amino acid subs
- KPC-1 & 3 most common in U.S.

Evolution of KPC/CRE

- Mostly in *K. pneumoniae*
- Reported in *E. coli, Salmonella cubana, Enterobacter cloacae, Proteus mirabilis, Acinetobacter* and *K. oxytoca*
- Reported in 33 states
- 2005 reported in France
  - First outside U.S.

Detection issues

- Similar to ESBL detection issues
- MIC's in susceptible range
  - Imipenem and meropenem
  - Increases resistance
- Especially automated systems
  - 87% of KPC reported susceptible
- Rural facilities may not have ability to detect

Transmission of CRE

- Transferring hospitals/Long term care
- Study of hospital outbreak
  - Isolates from sinks and stethoscopes
  - None on hands of healthcare workers
- Rectal colonization
- Isolation and contact precautions recommended

Risk factors

- Length of stay
- ICU
- Ventilator
- Diabetes
- Dialysis
- Cephalosporins
- Transplant

•Prior carbapenems not necessary
•Multiple studies have shown increased mortality

Treatment

- Fosfomycin (Monurol®)
  - Synergy with aminoglycosides
  - Etest for susceptibility
- Tigecycline (Tygacil®)
  - Failures reported
- Colistin (Coly-Mycin®)
  - Resistant *K. pneumoniae* documented
- Ceftazidime/avibactam (Avycaz®)
  - Not metallo-β-lactamase
- Aztreonam
  - Limited experience in MDR bacteremia

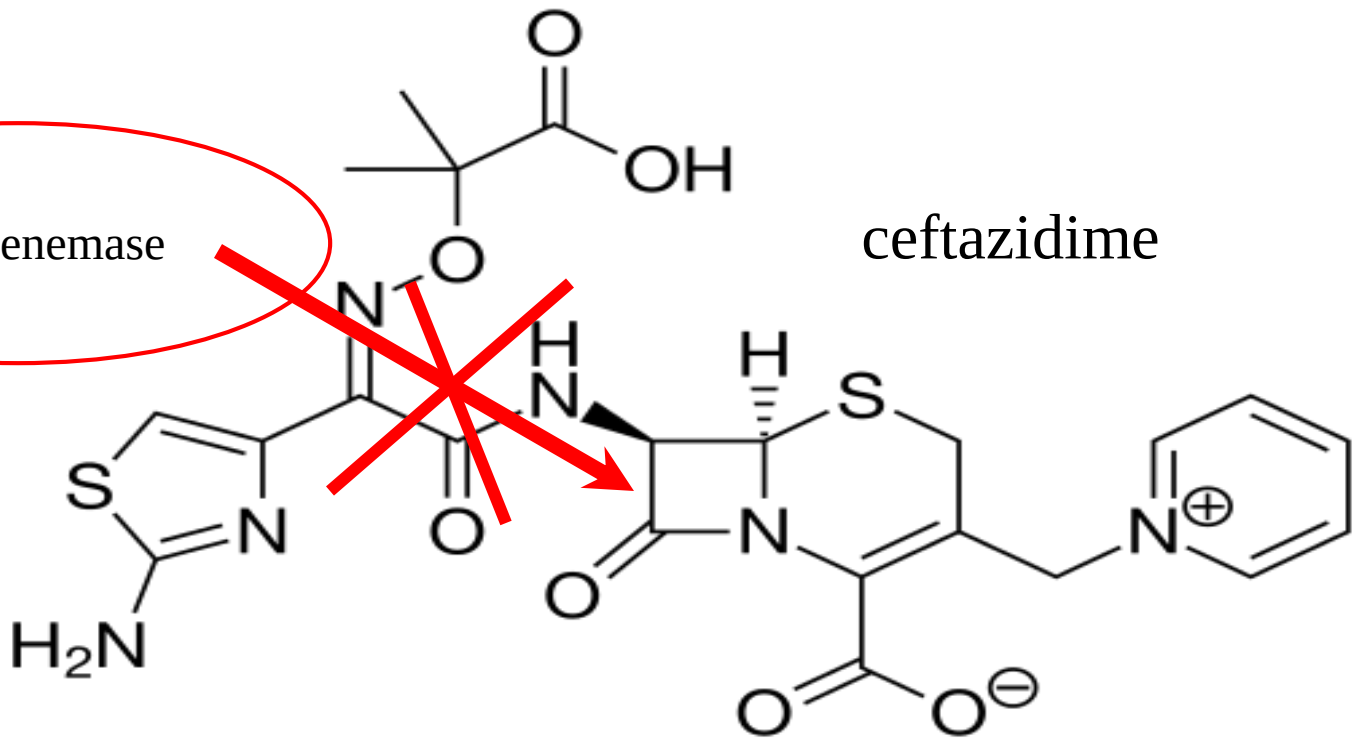
Ceftazidime/avibactam (Avycaz®)

- Cephalosporin/β-lactamase inhibitor
- cIAI with Flagyl®
- Complicated UTI
  - No coverage of metallo-β lactamases
- Dosed Q8hr and renally adjusted

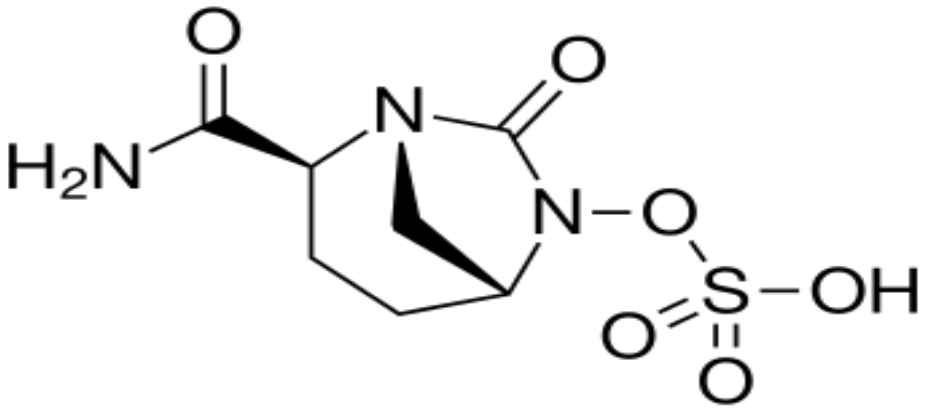
Avycaz®

Carbapenemase

ceftazidime



avibactam



Fosfomycin (Monurol®)

- Blocks formation of peptidoglycan
- In vitro activity against 93% of KPC
  - Spectrum: *Enterococcus faecium*, *Enterococcus faecalis*, *VRE*, *Pseudomonas*, *Klebsiella*, *Proteus*, *Serratia*, *Providencia*, *Enterobacter*, *E.coli*, *Citrobacter*
- Bactericidal in Urine for 36-48hrs
- No renal or hepatic adjustment

Tygecycline (Tygacil®)

- Bacteriostatic by inhibiting protein synthesis
- G-, G+ and anaerobe coverage
- Indications:
  - SSTI including MRSA but not VRE
  - cIAI
  - CAP
- Severe hepatic impairment: 50% of maintenance

Colistin (Coly-Mycin®)

- Cationic Detergent
- Adverse effects:
  - CNS toxicity, renal toxicity, respiratory failure
- Drug interactions:
  - May increase effect of neuromuscular blockers
  - Aminoglycosides, amphotericin B and vancomycin
    - Increased colistin effect / level

Aztreonam (Azactam®)

- Monobactam that binds PCN binding proteins inhibiting cell wall synthesis
- Side effects: rash, GI and injection site
- Can be used in most patients with PCN allergy

Amtimicrobial Stewardship

- Antibiotic stewardship refers to a set of coordinated strategies to improve the use of antimicrobial medications with the goal of enhancing patient health outcomes, reducing resistance to antibiotics, and decreasing unnecessary costs

http://www.shea-online.org/PriorityTopics/AntimicrobialStewardship.aspx?sa=X&ved=0ahUKEwjMp_OS0L7JAhWJrD4KHX8EBVQQ9QEIGTAA

Antimicrobial Stewardship

- Narrowest empiric spectrum
  - Most likely pathogens
- De-escalate
  - Based on Cx
- Length of therapy
  - Least necessary

Antimicrobial Module

- Skin / Soft Tissue Source (pg 2)
- Urinary Source (pg 3)
- Gastrointestinal Source (pg 4)
- Pulmonary Source (pg 5)
- Febrile Neutropenia (pg 6)

Decision Tree Abbreviations:

- PO - by mouth
- IV - Intravenous
- Q8hr - Every 8 hrs

Skin / Soft Tissue Infection

- Ceftriaxone 1gm IV daily + Vancomycin 15mg/kg IV Q12h

If Penicillin / Cephalosporin Allergy:

- Levofloxacin 750mg IV daily + Vancomycin 15mg/kg IV Q12h

Anaerobic Coverage Indicated Add:

- Metronidazole 500mg IV Q8hr
- Metronidazole 500mg PO Q8hr

Pseudomonas Risk Factors

- Cefepime 2gm IV Q12h + Vancomycin 15mg/kg IV Q12h

If Penicillin / Cephalosporin Allergy:

- Tobramycin 5mg/kg IV daily + Vancomycin 15mg/kg IV Q12h

Anaerobic Coverage Indicated Add:

- Metronidazole 500mg IV Q8hr
- Metronidazole 500mg PO Q8hr

Urinary Source Infection

Uncomplicated

- Cefazolin 1gm IV Q 8 hours x 7 days
- Cephalexin 500mg PO BID x 7 days

If Penicillin / Cephalosporin Allergy:
- Nitrofurantoin 100mg po BID x 7 days
- Cipro 400mg IV q12hrs x 3 days
- Cipro 500mg PO q12hrs x 3 days

Complicated / pyelonephritis

- Cefazolin 1gm IV Q 8 hours x 14 days
- Ceftriaxone 1gm IV daily x 14 days

If Penicillin / Cephalosporin Allergy:
- Cipro 400mg IV q12hrs x 14 days
- Cipro 500mg PO q12hrs x 14 days

Pseudomonas Risk Factors

- Uncomplicated: Cefepime 2gm IV Q12h x 7 days
- Complicated: Cefepime 2gm IV Q12h x 14 days

If Penicillin / Cephalosporin Allergy:
- Tobramycin 5mg / kg IV daily x 7 days

MRSA Risk Factors

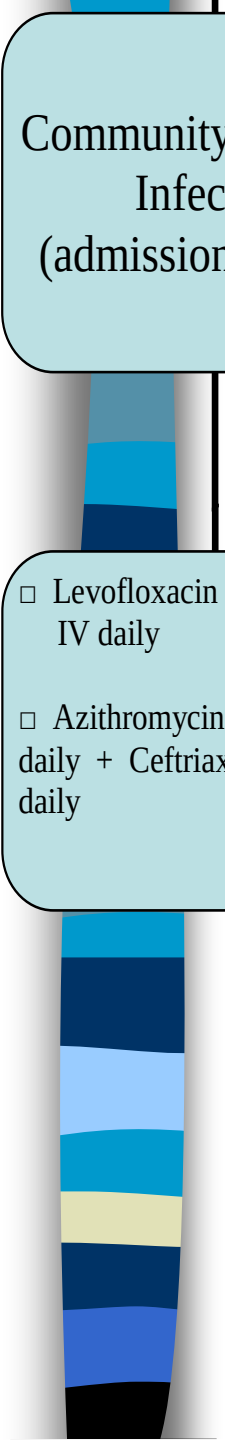
- Vancomycin 15mg/kg IV Q12h x 7 days
- Uncomplicated: Sulfamethoxazole/ Trimethoprim DS PO BID x 3 days
- Complicated: Sulfamethoxazole/ Trimethoprim DS PO BID x 7 days
- Pyelonephritis: Sulfamethoxazole/ Trimethoprim DS PO BID x 14 days

Uncomplicated Gastrointestinal Source in hemodynamically stable patient.

- Ceftriaxone 1gm IV daily + Metronidazole 500mg IV Q8h

If Penicillin / Cephalosporin Allergy:

- Ciprofloxacin 400mg IV q12hr + Metronidazole 500mg IV Q8h
- Ciprofloxacin 500mg PO q12hr + Metronidazole 500mg PO Q8h



Community Acquired Infection (admission to floor)

- Levofloxacin 750mg IV daily
- Azithromycin 500mg IV daily + Ceftriaxone 1gm IV daily

Community Acquired Infection (admission to ICU)

- Azithromycin 500mg IV daily + Ceftriaxone 1gm IV daily
- Levofloxacin 750m daily + Ceftriaxone 1gm IV daily

Healthcare / Nosocomial Acquired Pneumonia (*Pseudomonas* Risk)

- Cefepime 2gm IV Q12h + Levofloxacin 750mg IV daily

If Penicillin / Cephalosporin Allergy without renal dysfunction:

- Tobramycin 7mg / kg IV daily + Levofloxacin 750mg IV daily

With renal dysfunction:

- Aztreonam + Levofloxacin

MRSA Risk Add:

- Vancomycin 15m/kg IV Q12h

Aspiration Pneumonia

- Ceftriaxone 1gm IV Daily + Metronidazole 500mg IV Q8h
- Levofloxacin 750mg IV daily + Metronidazole 500mg IV Q8h

Neutropenic Fever

Treatment:

□ Cefepime 2gm IV Q 8 hours

If Penicillin / Cephalosporin Allergy:

□ Aztreonam 2gm IV Q8h + Vancomycin 15mg/kg IV Q 12 hours

Additional antibiotics indicated:

□ Add Tobramycin 7mg / kg IV daily

□ Add Ciprofloxacin 400mg IV Q 8 hours

*fluoroquinolones should not be used in patients who have received fluoroquinolones recently or if fluoroquinoloes were used for neutropenic prophylaxis

□ Add Vancomycin 15mg/kg IV Q 12 hours

Stewardship

- Gather all the information
- Make recommendation based on patient care (present and future)
- Always remember allergies, interactions, renal/hepatic dosing
- Do not use cost as your basis of recommendation

Stewardship

- Daily antimicrobial reports
- Focus on antipseudomonals and carbapenems, etc
- Read history and physical, surgical report, cultures and radiology reports
  - Create picture of risk and likely pathogens
  - Example:
    - Gram + coverage for cellulitis
    - Gram negative coverage for UTI
    - Gram negative + anaerobes for GI

Stewardship

- Nursing home or recent hospitalization
  - Not candidates for de-escalation
- Find candidates for de-escalation
  - Surgical patients with no recent history
  - Recommend de-escalation
- De-escalate based on cultures
  - Tailor therapy to cover what grows
    - Ex: if MSSA grows, stop vancomycin

Interventions

- Hospitalist patient with DM foot
  - Ex: Pt on vancomycin and Zosyn® empirically
  - Afebrile, white blood cell count is normal and less swelling
  - Wound cx: MSSA sensitive to cefazolin
    - Recommend change to cefazolin which the culture showed sensitivity to
    - Less monitoring, narrower spectrum, etc

Intervention

- Patient started on meropenem for ESBL *E.Coli* UTI
- Urine cx: sensitive to ertapenem and aminoglycosides
- Recommend Ertapenem
  - Avoid unnecessary pseudomonas coverage
  - No drug level monitoring
  - Unfortunately cost more

Interventions

- Surgeon (not in house): leave note on chart or page
  - 35 year old status post cholecystectomy without abscess or perforation
  - No risk of MDR organisms
  - Ex: recommend de-escalate ertapenem to rocephin + flagyl IV or augmentin PO

PHARMACY NOTE

No Known Allergies

Dr. Doe

Date: 9/29/15

Patient: Meister, Brian

Room: 200

- WBC 6.9 Tmax 98.9° No abscess or perforation on C.T.
- Patient has no apparent risk of ESBL organisms

To reduce the spread of multi-drug resistant organisms due to the over use of carbapenems, could the patient be de-escalated to ① Rocephin + Flagyl if I.V. desired
② Augmentin if P.O. is possible

Thank you

Pharmacist: [signature] Pharm D

** Not a permanent part of the chart**

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