07 – Core Concepts: Antibacterial Drugs II Gram Negative Organisms
08 – Antibacterial Drugs II: Key Points and Questions That Could Be on The Exam

Speaker: David Gilbert, MD

IDBR INFECTIOUS DISEASE BOARD REVIEW AUGUST 20-24 2022

Antibacterial Drugs Active vs Gram Negative Bacteria: Part 1

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Disclosures of Financial Relationships with Relevant Commercial Interests

- Consultant: Biomerieux
- Research Grant on Diagnostics from Biofire

Structure of Presentation of Testable Topics

- First, "Hot" General Principles
- Then, discuss antibacterials from the perspective of targeted /identified gram-negative bacteria
- My Part 1 is here; Part 2 is available anytime on line
- Dr.Boucher will focus on antibacterials active vs gram-positive bacteria

What determines antibiotic choice ?

- It's not just in vitro susceptibility and allergy history.
- Preferred choices: Effective in clinical use and Guideline recommended
- Alternative preferred choices:
  - Active in vitro, part of an active drug class, but:
    - Broad spectrum, toxicity, and/or limited clinical use
- Variable choices.
  - Active in some but not all settings
  - Maybe effective in combination
  - Low barrier to development of resistance

Reasons Drug is not Recommended

- Resistance of target organism(s) in vitro
- Poor penetration of drug to site of infection
- Severe and/or frequent toxicity
- Risk of severe hypersensitivity reaction
- Insufficient supportive clinical efficacy data

"Pass the plasmid please "

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Major Gene-Expressed Mechanisms of Resistance to Antibacterials

- Enzymatic inactivation
- Target site absent: intrinsic resistance
- Target site modification or protection of target site (high level of resistance)
- Excessive non-lethal binding sites
- Reduced cell wall permeability (porin closure)
- Drug efflux pumps (low level resistance)
- Multiple mechanisms may be present

Combination vs Mono-Antibacterial Therapy

- Combination therapy:
  - Decreases risk of selection of resistant subpopulations
  - Empirically in patient at risk of infection due to MDR GNB ;
    - Increases likelihood of at least one active drug
  - Required for efficacy: e.g. Enterococcal Infective Endocarditis ; M.tbc.
  - Adjunctive:
    - Addition of clindamycin for toxic shock toxin
    - Addition of rifampin for penetration of biofilms on prostheses

Three clinicald examples of need for bacteriocidal therapy

1. Febrile Neutropenic Patients
2. Infective endocarditis
3. Bacterial meningitis

PK/PD.

- Concentration-dependent killing and long persistent (post-antibiotic) effect ?
  - *AGs, daptomycin, and FQs*
- Killing dependent on time above MIC, no persistent [post-antibiotic] effect?
  - *Penicillins, cephalosporins, aztreonam, and carbapenems*
- Killing depends on time above MIC and a persistent Post-Antibiotic effect?
  - *Vanco., macrolides, tetra, linezolid, clinda*

Variables in Dosing

- Allergy
- PK/PD
- Body weight
- Elimination:
  - Renal
  - Liver: e.g.: Induction/inhibition cytochrome P450 enzymes
- Dose related toxicity; Use of TDM

Beta-Lactams

- Penicillins
- Cephalosporins
- Carbapenems
- Monobactams (e.g.,Aztreonam)
- Share: presence of a beta-lactam ring, potential for causing seizures, and allergenicity

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To survive bacteria are constantly mutating

- More than 4500 beta-lactamases reported
- Promiscuity is rampant among bacteria
- Not unusual to detect more than one mechanism of resistance: e.g.,
  - Target change &/or Target Protection
  - Active efflux pumps
  - Decrease in cell wall permeability
  - Phenotypic antibiotic suscept. Testing does not identify specific mechanism(s) of resistance
- IF patient fails clinically and/or failure to eradicate pathogen, whole genome sequencing can identify specific mechanisms
- NO surprise: it is hard to write "resistance " test questions

Ambler Molecular Classification of Beta-Lactamases*

Class	Subtypes	B-L-ase Inhibitor	Substrates
A	ESBLs + serine carbapenemases (e.g. KPCs)	Clavulanic, Avibactam, Rele & Vaborbactam	ESCs Carbapenems
B (BAD!)	Metallo-carbapenemases	EDTA(lab testing only)	All beta-lactams except aztreonam & Cefiderocol
C	AmpC	Tazo and Avibac.	Cephalosporins
D	Oxa-48 Some ESBLs Serine carbapenemases (e.g., KPCs)	Avibactam Clavulanic Avibactam & Vaborbactam	Penicillins, Carbapenems, ESCs, & Aztreonam ESCs and Carbapenems

*Ambler: Based on nucleotide sequencing

Antibacterial activity of Piperacillin-Tazobactam

- Active vs.:
  - Majority of *Enterobacterales (formerly Enterobacteriaceae*)
  - *Bacteroides fragilis*
  - Maybe *Pseudomonas aeruginosa* if HIGH dose and prolonged infusion
  - Failed vs ESBL producing *Enterobacterales* as compared to meropenem (Merino trial)
- Better than ampicillin-sulbactam for empiric therapy due to 50% resistance of *E.coli*

ARQ #1

PREVIEW QUESTION

- A 63 y.o. male has COVID-19 pneumonia with a BAL-documented super-infection due to *E.coli*.
- The *E.coli* is reported resistant in vitro to ceftriaxone, cefazolin, and aztreonam.

AR ? #1

PREVIEW QUESTION

- The *E.coli* is likely ESBL positive and is susceptible in vitro to the following drugs. Which drug is preferable for specific therapy ?
  - A. Doripenem
  - B. Tobramycin
  - C. Meropenem
  - D. Imipenem-cilastatin-relebactam
  - E. Piperacillin-tazobactam

MERINO Trial: P/T vs Mero for *E.coli, K.pneumoniae* ESBL Producers

- Design: PRDB.* 72 hrs from pos.culture to enroll; 30 minute infusions of Pip/tazo.
- 30 day all cause mortality:
  - Piperacillin-tazobactam: 12.3 %
  - Meropenem: 3.7 %
- Other Issues:
  - Breakpoints/inoculum effect for P/T
  - Co-production of ESBL and oxacillinase?
- Three confirmatory controlled trials in progress

* PRDB=Prospective Randomized Double-Blind

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Comparison of activity of Piperacillin-tazo. Vs Ampicillin-sulbactam

Target Bacteria	Ampicillin-sulbactam	Piperacillin-tazobactam
E.coli	+/-	++
Aeromonas sp.	+/-	+
Klebsiella sp.	+	+
ESBL producing E.coli; Klebsiella sp.	0	+/- or 0
Citrobacter, Morganella, Providencia sp.	0	+
Pseudomonas aeruginosa	0	+ (dose dependent)
Anaerobic GNB (*B.fragilis*)	+	+

In short: Prefer Pip/tazo for empiric therapy.

Ampicillin-Sulbactam

Use as a source of sulbactam in combination therapy of MDR *Acinetobacter species*

- Dose for sulbactam component for Acinetobacter* : 4 hr IV infusion of 9 gm of Amp-Sulb (6 gm Amp +3 gm Sulb) q8h

European J of Pharm. Sci. 2019; 136:104940

Piperacillin-tazobactam: AEs

- Common to All beta-lactams:
  - Allergy, seizures, neutropenia, thrombocytopenia
  - Drug-drug interactions: Rare
- Pip-tazo AE issues:
  - Sodium overload--36-90 meq of sodium in a full daily dose ; can aggravate CHF management
  - Pseudo-enhancement of vancomycin-induced nephrotoxicity with P/T + V

Cephalosporin "Generations"

Generation	Spectrum	Comment
First (Cefazolin)	*MSSA; E.coli, Kleb.sp.*	No activity versus enterococci
Second(Cefoxitin, Cefotetan)	Original target *Bacteroides fragilis*	*B.fragilis* resistance increasing
Third(Ceftriaxone[ctx])	Most of the aerobic GNBs: Enterobacterales	"Extended spectrum"
Fourth (Ceftazidime; Cefepime)	Antipseudomonal	Cefepime not porin dependent
Fifth (Ceftaroline)	Like CTX + MRSA	No activity vs. enterococci
Sixth (Ceftolozane/Tazo)	ESBL producing GNBs; Also antipseudomonal	No activity Vs. *Bacteroides* species
Seventh (Ceftaz/Avibactam)	(ESBL producing GNBs) & KPCs	Inconsistent activity vs *Bacteroides species*

Cephalosporin "Generations"

Generation	Spectrum	Comment
Eighth: Cefiderocol	Serine/Metallo Carbapenemase producing Enterobacterales and Non-fermenters*	No useful activity vs Gram positives and anaerobic bacteria

- *Non-fermenters: *Acinetobacter sp. ,Burkholderia sp., Ps.aeruginosa,*
- *Stenotrophomonas maltophilia*

What you need to know about GNB producing ESBLs:

- Phenotypic Detection by micro. lab based on:
  - Detected by In vitro "R" to penicillin, cefazolin, ceftriaxone, ceftazidime, azreonam (see Dr. Patel's lecture)
  - Partial reversal of "R" by BLIs (Clav/Tazo)
  - Similar Resistance Pattern Could be due to:(Decreased permeation + Efflux pump) or AmpC production
- Preferred therapy: Meropenem
  - Alternative: Ceftolozane-tazobactam, Cefepime (if low MIC)
  - Others: Plazomicin, FQs +/-, Polymyxins
  - Avoid Piperacillin-tazobactam

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Oral Carbapenem-Sparing Antibiotics for ESBL Producing Bacteria Causing Uncomplicated Cystitis

- **F**osfomycin
- **A**moxicillin-clavulanate
- **N**itrofurantoin

From IDSA Guidance on treatment of antimicrobial resistant gram-negative bacilli, 9/8/20. https://www.idsociety.org/practice-guideline/amr-guidance

ARQ #2

- A 45 y.o. female has a chronic Foley catheter for neurogenic bladder as a result of trauma-induced paraplegia.
- H/O multiple episodes of symptomatic cystitis and/or pyelonephritis.
- Admitted with fever, nausea and vomiting and requiring pressors and fluids for hypotension. She has no drug allergies.

ARQ #2

- After culture of blood and urine, empiric therapy with ceftazidime.
- Within a few hours, the blood culture is reported positive for *Enterobacter cloacae*

ARQ 2

- Which one of the following would you recommend ?
  - A. Pending phenotypic susceptibility, continue ceftazidime
  - B. No need to wait, de-escalate now to ceftriaxone
  - C. Switch to empiric ceftolozane-tazobactam
  - D. Switch to empiric ceftaroline

AmpC enzymes hydrolyse all cephalosporins except: ceftolozane/tazo, ceftaz/avi, and cefiderocol

- Comes two ways:
  - Gene On plasmid, constitutive synthesis, easy to detect resistance in vitro
    - Found in *E.coli and Klebsiella species*
  - Gene In chromosome of KEC:
    - K: *Klebsiella(Enterobacter) aerogenes*
    - *E: Enterobacter cloacae*
    - *C: Citrobacter freundii*
    - In high % of KEC, AmpC is repressed

Chromosomal AmpC Genes

- Need exposure to a cephalosporin for de-repression of AmpC gene; Initial isolate may test susceptible to early generation cephalosporins
- KEC bacteria most frequently involved.
- Due to rarity, have dropped rest of the SPACE/SPICE acronyms

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Bottom Line on AmpC

- If presence of a KEC organism, even if susceptible in vitro, Avoid treatment with all cepholosporins except Ceftolozane/tazo, ceftaz/avi, or cefiderocol
- Empiric therapy of a KEC organism infection: Ceftolozane/tazo or Meropenem
- Avoid piperacillin-tazobactam

ARQ 3

PREVIEW QUESTION

- Which one of the following would you recommend as therapy for a "difficult to treat resistant" *Pseudomonas aeruginosa* outside of the urinary track ?
  - A. Meropenem-vaborbactam
  - B. Ceftolozane-tazobactam
  - C. Cefepime
  - D. Ceftazidime
  - E. Ertapenem

ARQ #4

- 60 y.o. female smoker, admitted, intubated, and ventilated due to severe COPD with Acute Respiratory Failure.
- Chest X-Ray: New bibasilar infiltrates and Emphysema
- Empiric ceftriaxone and azithromycin
- Sputum positive for both rhinovirus and *Klebsiella pneumoniae* resistant to both ceftriaxone and azithromycin
- Also "Resistant" to: all fluoroquinolones, aminoglycosides, pip/tazo, and all carbapenems

ARQ #4

- Which one of the following antibiotics is most likely to have activity vs. this likely KPC infection ?
  - A. Tigecycline
  - B. Ceftazidime-avibactam
  - C. Aztreonam
  - D. Ceftolozane-tazobactam

Cefiderocol

- First cephalosporin stable in presence of GNB producing metallo-beta-lactamases
- PI: "For complicated UTI due to susceptible GNB with no other treatment options"
- Spectrum of activity includes:
  - XDR Enterobacterales
  - XDR Non-fermenters (Steno, Pseudo, Acineto)
  - No activity vs gram + bacteria or anaerobic bacteria

Cefiderocol Warning

- Found an increase in all cause mortality in patients Rx with cefiderocol (24.8%) vs BAT (18.4%) in critically ill patients with infection due to carbapenem resistant GNB.
- See package insert for warning and details

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Testable Cephalosporin AEs

- Cross Allergenicity: Ceftazidime, Cefiderocol, and Aztreonam have same side chain
- Ceftriaxone: Crystals in Biliary tree (Pseudo-cholelithiasis)
- Cefepime: Non-convulsive status epilepticus
- No Drug-Drug interactions

Carbapenem Family

Carbapenem	Comment(s)
Imipenem-cilastatin	Avoid in meningitis patients: seizure potential
Meropenem	Less potential for inducing seizures
Ertapenem	Not active vs *Ps.aeruginosa and other non-fermenters*; Once daily therapy
Doripenem	⬆mortality vs Imipenem in VAP trial
Meropenem-vaborbactam and Imipenem-cilastatin-relebactam	Active vs Klebsiella producing carbapenemases (KPCs); Not active vs metallo or Oxa 48 carbapenemases

Carbapenems: Spectrum of antibacterial activity

Active versus:	NOT ACTIVE versus
MSSA and Enterobacterales + ESBLs	*MRSA*
*Pseudomonas aeruginosa#**	*Stenotrophomonas maltophilia*
Bacteroides fragilis	*Acinetobacter (variable)*
Enterococcus faecalis	*Enterococcus faecium*
Listeria monocytogenes	

Resistant to ertapenem.

*Resistance can emerge during therapy via porin closure and efflux pumps

AZTREONAM (monobactam)

- Only beta-lactam with NO activity vs. Gram positive bacteria: e.g., *S. pneumoniae*
  - Safe with IgE mediated Pen/Ceph.allergy & aerobic GNB infection; cross allergenicity with ceftazidime
- The In vitro resistance of GNB is a phenotypic marker for production of ESBLamases
  - Has In vitro activity vs GNB that produce metallo-carbapenemases; however, inactivated by concomitant production of ESBLs
    - Use Ceftazidime-avibactam plus aztreonam to treat GNB co-producing ESBL and metallo-Carbapenemase
    - Reference: Clin. Inf. Dis. 2021; 72: 1871

IN SUMMARY: Beta-Lactams

- ESBL production: Meropenem
  - Ceftolozane-tazo. backup
- For risk of inducible AmpC production : Meropenem (Ceftolozane-tazo backup)
- Serine-based Carbapenemase (KPCs): Ceftazidime –avibactam, Meropenem-vaborbactam, or Imipenem-cilastatin-relebactam
- Metallo-based carbapenemase production: Ceftazidime-avi + Aztreonam

Fluoroquinolones (FQs)

- Family: Ciprofloxacin, Levofloxacin, Moxifloxacin, Delafloxacin
- The GOOD: Broad Spectrum of Activity, Large volume of distribution, High oral bioavailability
- The BAD: Increasing "R", Serious AEs(C.diff.) Many Drug-Drug interactions; FDA Safety Warning.
  - Conclusions:
    - Uncomplicated infections(bronchitis)---AVOID
    - Severe infections--- weigh RISK vs Benefit

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FQ Pharmacology

- Parenteral:
  - Higher doses for *Ps.aeruginoa*
  - Excreted in urine
  - High concentrations in prostate gland
- Oral:
  - Bioavailability of 59-95%
  - Chelation by multi-valent cations decreases bioavailibility:
    - Calcium
    - Iron
    - Zinc, Magnesium, Aluminum

Preferred FQs vs: ?

- For aerobic GNB: Ciprofloxacin
- For *Pseudomonas aeruginosa*: Ciprofloxacin
- For respiratory pathogens: Levofloxacin, delafloxacin , and Moxifloxacin
- For Anaerobic bacteria: Moxifloxacin
- For Mycobacteria: Moxifloxacin
- For MRSA : Delafloxacin

Resistance ("R") to FQs

- FQ Antibacterial activity due to blockade of DNA replication via binding to DNA Gyrase and Topoisomerase enzymes
- Multiple mech. Of "R":
  - Mutations of enzyme targets
  - Efflux pumps, altered cell wall permeation
  - Target protective proteins, drug acetylation
- Frequent Concomitant "R" of GNB to beta-lactams via:
  - Production of ESBLs
  - Production of Carbapenemases

FQs and *Clostridioides difficile*

- Most common drug class to cause *C.difficile colitis*
- Second are the cephalosporins
- Third is clindamycin

FQs and Acute Liver Injury

- Compared to clarithromycin, there is an increased risk for acute liver injury within 30 days of prescription use of moxifloxacin or levofloxacin (ORs 2.2 and 1.85)
- No identified increased risk after use of ciprofloxacin

QTc Prolongation: Potential Risk with all FQs except Delafloxacin

- >500 msec., or > 60 msec prolongation from baseline, increases risk of torsades de pointes & ventricular fibrillation.
- Low serum K and/or Mg ; Concomitant drugs increase risk: e.g., mefloquine, haldol, fosphenytoin.
- None of FQs are high risk used alone; problem: concomitant drugs (cytochrome P-450 inhibition) and/or electrolyte abnormalities.
  - Moxifloxacin: Highest association; Delafloxacin the lowest.

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FQ Drug-Drug Interactions

- Cipro inhibition of cytochrome P450 resulting in impaired elimination of other drugs
- NSAIDs plus FQs displace GABA from GABA receptors: Lowers seizure threshold
- Rifampin and rifapentine lower serum level of moxifloxacin; of import for combined therapy of Mycobacteria

FQs and Chelation-Related AEs

- Aortic aneurysm and aortic dissection
- Tendinopathy (Tendon rupture)
  - OR 8.3 if over age 60 and
  - OR 9.1 if using oral steroid
- Arthropathy

Aminoglycoside Family

- Amikacin
- Gentamicin
- Streptomycin
- Plazomicin
- Tobramycin

AG: Spectrum of Activity

- Active vs.:
  - Aerobic gram-negative bacteria
  - Typical and atypical mycobacteria
  - Variable: *Ps.aeruginosa, S. aureus* X 24 hrs
- No activity vs.:
  - Gram-positive cocci: e.g., *S.pneumoniae*
  - Anaerobic bacteria
  - Non-fermenters: *Acinetobacter sp., Stenotrophomonas maltophilia*
- Often part of combination therapy
- Monotherapy vs Tularemia and Plague

AG: Mech. of Action & "R"

- Binds to 30s ribosome; Concentration-dependent Bactericidal activity
- Multiple mechanisms of resistance:
  - Most Frequent
    - Enzymatic alteration of drug: adenyl., acetyl., phosporyl.
      - Plazomicin is least susceptible to enzymatic attack
    - Methylation of ribosomal binding site
  - Less Common
    - Efflux pump
    - Porin closure
- Bacteria "R" to beta-lactams & FQs often have concomitant "R" to AGs

AG: Pharmacology

- Basis of once daily dosing:
  - Concentration dependent cidal activity coupled with
  - Long post-antibiotic effect
- Result is improved antibacterial activity and less risk of toxicity
- EXCEPTION: Combination therapy of enterococcal endocarditis requires TID low dose AG therapy

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AG: Shared Adverse Effects

- Nephrotoxicity: Acute tubular necrosis
- Ototoxicity:
  - Cochlear (genetic predisposition & non-reversible)
  - Vestibular (irreversible but host can compensate)
- Neuromuscular blockade (neomycin)

Metronidazole

- Antibacterial and anti-protozoan activity requires a strict anaerobic environment
- "Gold Standard" for treatment of *Bacteroides species*
  - Other Drugs active vs *B.fragilis*: Pip/tazo, Amp/sulb, Carbapenems, Erava/Omadacycline
- Other clinical Indications: Bacterial vaginosis, Amebiasis, Giardiasis, and *Trichomonas vaginitis, part of combo therapy of H.pylori*
- Metro. "R" Anaerobes: *P. (Cutibacterium) acnes, Peptostreptococci, Eikenella* and *Actinomyces*

Metronidazole: Adverse Effects

- Metallic taste; "furry" tongue
- Disulfiram (Antabuse) reaction (N/V, flushing, tachycardia, dyspnea) after alcohol use
- Prolonged use: peripheral, autonomic , and/or optic neuropathy
- Aseptic meningitis
- After 3 weeks: confusion and cerebellar dysfunction

Is the patient's encepalopathy due to your antibiotic therapy ?

Antibiotic	Time to onset	Syndrome
Beta-Lactams	Within days *	Seizures; abnormal EEG
FQs, Macrolides	Within days	Delusions/Hallucination; normal MRI
Metronidazole	Weeks	Cerebellar dysfunction with abnormal MRI

* High serum concentrations due to renal insufficiency

Reference: Neurology 2016; 86:963

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What do you need to know ?

- In the USA there are roughly 210 FDA-approved antibacterials
- As of 2020, there are 43 anti-bacterials in the clinical development pipeline*
- What do you need to know for the certifying examination ?

* WHO;2021. License: CC BY-NC-SA 3.0 | GO

Main Points

- Based on relative safety and efficacy, prefer beta-lactam antibiotics
- Due to adverse effects, Aminoglycosides, Fluoroquinolones, and Polymyxins are often in an alternative role
- Selection of preferred therapy is based on many variables----not just the MIC
- Due to complexity of resistant genotypes, need phenotypic antibiotic resistance testing

Genotypic Resistance: Pro and Con

- Pro: May allow customized choice of antibacterial therapy that may result in improved safety and efficacy with less promotion of resistance
- Con:
  - Gene presence does not necessarily equal gene activity
  - At present, not widely available, slower than phenotype
  - Expensive

1. The new antibiotic pipeline is at a low ebb which increases the import of antibiotic stewardship.
2. Increasing antibiotic resistance is an existential threat.
3. Stewardship requires decreased use of empiric antibiotic therapy and an increase in specific/directed antibiotic therapy.

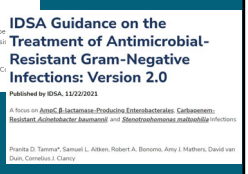
IDSA AMR Guidance – Sep 20, Nov 21, 2021


Infectious Diseases Society of America Guidance on the Treatment of Antimicrobial Resistant Gram-Negative Infections

Published by IDSA, 9/8/2020

A Focus on Extended-Spectrum β-lactamase Producing Enterobacterales (ESBL-E), Carbapenem-Resistant Enterobacterales (CRE), and *Pseudomonas aeruginosa* with Difficult-to-Treat Resistance (DTR-*P. aeruginosa*)

Pranita D. Tamma*, Samuel L. Aitken, Robert A. Bonomo, Amy J. Mathers, David van Duin, Cornelius J. Clancy


IDSA Guidance on the Treatment of Antimicrobial-Resistant Gram-Negative Infections: Version 2.0

Published by IDSA, 11/22/2021

A focus on AmpC β-lactamase-Producing Enterobacterales, Carbapenem-Resistant *Acinetobacter baumannii* and *Stenotrophomonas maltophilia* Infections

Pranita D. Tamma*, Samuel L. Aitken, Robert A. Bonomo, Amy J. Mathers, David van Duin, Cornelius J. Clancy

https://www.idsociety.org/practice-guideline/amr-guidance/

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IDSA Guidances on the Treatment of Antimicrobial-Resistant Gram-Negative Infections: Version 1.0 and 2.0

Focus on infections caused by:

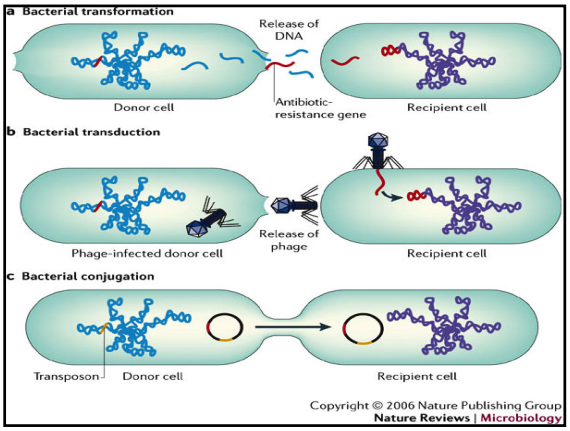
1.0
- ESBL-E: Production of ESBLs by *Enterobacterales*
- CRE: Carbapenem Resistant *Enterobacterales*
- DTR-*P. aeruginosa: Difficult to treat P.aeruginosa*

2.0
- AmpC-E: AmpC producing *Enterobacterales*
- CRAB: Carbapenem resistant *Acinetobacter baumannii*
- *Stenotrophomonas maltophilia*

Nov, 2021, https://www./

Overview

- First Lecture: Beta-lactams, FQs, AGs, Metronidazole
- A second on line lecture to finish review of antibacterials used for infections due to Gram-negative bacteria: Polymyxins, Nitrofurantoin, Fosfomycin, Tetracyclines, TMP/SMX
- Dr. Boucher will discuss antibiotics primarily active vs Gram-Positive bacteria



If choice of treatment is based on comparative
risk of adverse effect between a beta – lactam antibiotic and
other antibiotic classes active vs Aerobic GNBs,

The best answer is usually the BETA-Lactam !

Beta-Lactam Efficacy associated with time above MIC

- For Exam, pick regimen with prolonged or continuous infusion
- Supportive data for prolonged/continuous infusion for multiple beta-lactams:e.g.,
  - Ampicillin-sulbactam
  - Cefazolin
  - Cefepime
  - Ceftazidime
  - Doripenem
  - Meropenem
  - Piperacillin-tazobactam
  - Vancomycin

Ref.: Sanford Guide to Antimicrobial Therapy, 2021

The Major Families of Carbapenemases

Non-Metallo (Serine at active site)	Metallo (Zinc at active site)
KPC (Class A)	VIM (Class B)
OXA-48 et al (Class D)	New Dehli Metallo-Blasé (Class B)
	IMP (Class B)

KPC=Klebsiella-producing carbapenemases; OXA=oxacillinase; IMP=Imipenemase; VIM=Verona integron-encoded metallo Blamase; NDM= New Dehli metallo Bl amase

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FQs and Neurologic AEs

- Altered mental status
- Peripheral neuropathy
- Seizure
- Pseudotumor cerebri
- Exacerbation of myasthenia gravis

Drugs with predictive activity vs over 80% of *B. fragilis* isolates ?

Beta-lactams

- Amoxicillin-clav.
- Ampicillin-sulbactam
- Piperacillin-tazo.
- Ceftolozane-tazo
- All 6 FDA approved carbapenems
- TOTAL of 10

Non-Beta-lactams

- Metronidazole/Tinidazole
- Delafloxacin/Moxifloxacin
- Chloramphenicol
- Eravacycline
- Omadacycline
- Total of 5-7

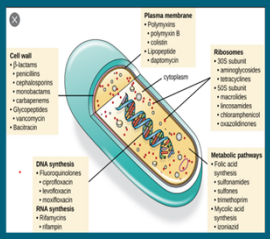
Beta-Lactam Treatment of Carbapenemase Producing GNBs

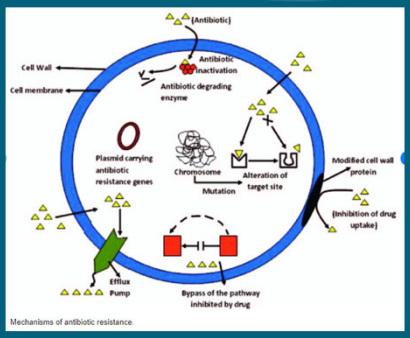
- Class A (KPCs-Klebsiella-Producing Carbapenemases):
  - Ceftazidime-avibactam
  - Meropenem-vaborbactam; Imipenem-cilistatin-relebactam
  - Cefiderocol
- Class B (Metallo-carbapenemases):
  - Ceftazidime-avibactam + Aztreonam
  - Cefiderocol
- Class D (OXA-type) carbapenemases (heterogeneous and low level enzymatic hydrolysis)
  - May not hydrolyse ceftazidime and cefepime
  - Ceftazidime –avibactam active (Avibactam binds OXA-48).
  - Reference: AAC 2021;65: e00184-21

What do you need to know ?

- Major mechanisms of antibacterial activity
- Spectrum of antibacterial activity
- Mechanisms and "language" of antibacterial resistance
- Drug Pharmacology: PK/PD, Distribution, Drug-drug interactions, Excretion, Unique toxicities (Allergy lecture to follow)
- Pertinent Clinical Microbiology (see Dr. Patel's lecture): Phenotypic patterns of resistance to beta-lactams
- Useful acronyms: SPACE-M, KPCs, NDM-CP, PEACHES

Mechanisms of Action of Antibacterials





07 – Core Concepts: Antibacterial Drugs II Gram Negative Organisms
08 – Antibacterial Drugs II: Key Points and Questions That Could Be on The Exam
Speaker: David Gilbert, MD

How do bacteria acquire genes that control resistance mechanisms?

- Transduction via bacteriophages (bacterial viruses): species specific
- Transformation: scavenge and incorporate naked DNA of dead bacteria
- Conjugation: cytoplasmic bridges between species with transfer of plasmids
- Spontaneous mutations

What is a plasmid?

- Extra chromosomal circular DNA
- Can replicate independent of chromosomal DNA
- Replication can be constitutive or induced
- Exchanged between species by conjugation
- Can carry genes for multiple antibacterial resistance determinants and virulence factors

What is a transposon?

- Mobile short stretch of DNA
- Can move between different points within a genome by a process termed transposition.
- Not capable of self-replication

What is an integron?

- Collects genes from transposons and forms chunks of DNA called cassettes
- Integrons allow transposons/cassettes to move from chromosome to plasmid DNA .
- Then the plasmid DNA can spread via conjugation from one genus to another.
- Mobile genetic elements= plasmids, transposons, integrons

Conjugative Plasmids

- Increasingly common
- Carry multiple resistance genes expressed in vitro as resistance to beta-lactams, FQs, Aminoglycosides, other drugs.

Beta-Lactam – Beta-Lactamase Inhibitor (BLI) Combinations

- The six current BLIs are: Clavulanic acid, Tazobactam, Sulbactam, Avibactam,Relebactam, and Sulbactam . Not All are beta-lactams.
- BLIs demonstrate irreversible ("suicide") binding to bacterial beta-lactamases
- To date, there are 3 BLIs combined with a penicillin, 1 combined with a cephalosporin, and 2 combined with a carbapenem.
- Sulbactam is the only BLI with clinically useful antibacterial activity: active vs. Acinetobacter sp.

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Summary: Vanco:P/T as of 2020

- Vancomycin is potentially nephrotoxic
- Piperacillin-tazobactam alone has a very low potential to cause nephrotoxicity
- The reported increased ACUTE KIDNEY INJURY with V + P/T is at least partly due to the blockade of the renal tubular secretion of creatinine by piperacillin
- Current evidence would suggest that the combination of V+P/T is no more nephrotoxic than Vancomycin alone

Ceftriaxone "R" *E. coli*

- 25% "R" of organisms in the order *Enterobacterale* worldwide; In Asia, 50% of *E.coli* are resistant to ceftriaxone
- Most common mechanisms of resistance:
  - 1. Production of Extended spectrum beta-lactamase (ESBLs)
  - 2. If *Enterobacter species*: could be Production of Amp C cephalosporinase
  - Carbapenems effective in presence of both mechanisms
- Are there any carbapenem sparing cephalosporins ?

Collateral Damage from Carbapenem Therapy for ESBLs

- Selection of CP "R" strains of Enterobacterales, and/or Non-Fermenters (e.g., *Acinetobacter sp.*)
- Selection of vanco "R" enterococci, MRSA, Candida species
- Nonetheless, based on the MERINO trial, Meropenem is Drug of Choice for treatement of ESBL producing Enterobacteraceae

FDA Approved Beta-Lactam Beta-Lactamase Inhibitor Combinations

Penicillins	Cephalosporins	Carbapenems
Amoxicillin-clavulanate	Ceftolozane-tazobactam	Meropenem-vaborbactam
Ampicillin – sulbactam	Ceftazidime-avibactam*	Imipenem-cilastatin-relebactam
Piperacillin-tazobactam		

Note: so far 6 Beta-lactam inhibitors and none inhibit class B metallo-carbapenemases

* Only avibactam inhibits chromosomally-mediated AmpC ESBLs

ARQ #2

- 40 y.o. surgeon has surgical repair of torn anterior cruciate ligament of his knee. Single dose of cefazolin as prophylactic antibiotic.
- Three days later: Purulent knee exudate. GNB on gram stain. Ceftriaxone (CTX) started empirically
- At five days: Growing *Klebsiella (Enterobacter) aerogenes* suscept. To CTX
- At Ten days: Knee still inflamed. Repeat culture: *K.(E.) aerogenes* resistant to CTX

ARQ #2

- Which one of the following is the most likely explanation of the *Klebsiella(E.) aerogenes* resistance to ceftriaxone ?
  - A. Mutation in Cephalosporin cell wall binding protein
  - B. Activation of a Cephalosporin efflux pump
  - C. Activation of an inducible chromosomal cephalosporinase
  - D. Expression of constitutive plasmid cephalosporinase

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Cefiderocol

- Clinical studies:
  - Microbial eradication: Imipenem 56% ; Cefiderocol 73%
  - Day 14 mortality: Best available therapy 12 %; Cefiderochol 25%
- Has catechol side chain that utilizes iron transport system (siderophore). "Trojan horse"
- No serious AE , so far: GI 2-4%, C.difficile, Seizures
- For salvage therapy when no other option available

Aztreonam Activity vs Carbapenemase-Producing GNB

Active versus:	NOT active versus:
Metallo-Carbapenemases (Gp B)	Klebsiella-producing Carbapenemases (KPCs)(Gps A & D)
Enterobacterales(if no ESBLs)	ESBL producers
Pseudomonas aeruginosa	*Acinetobacter; Stenotrophomonas*

"Difficult to Rx" Resistance of Ps.aeruginosa *

Preferred Therapy	Alternative Therapy
Ceftolozane-tazobactam	Aminoglycoside monotherapy (Gentamicin, Plazomicin et al)
Ceftazidime-avibactam	
Imipenem-cilastatin-relebactam	
Cefiderocol	
In addition, need Source Control	

*DTRx defined as "R" to Pip/tazo, ceftazidime, cefepime, Aztreonam, Meropenem, Imipenem-cilastatin, and FQs.

Reference: IDSA 2020 Guideline on Rx of Antimicrobial Resistant Gram-Negative Infections: CID 2021;72: 1109

Primary & Alternative Rx of ESBL and Carbapenemase Producing Enterobacterales*

Resistant	Sensitive	Presumed Mechanism	Primary Treatment	Alternative Treatment
CTX & Aztreonam	Mero, P/T, Ceftolo-Tazo	ESBL**	Mero: Extended Infusion	Ceftolo-tazo, FQ, TMP/SMX
Ertapenem	Meropenem	Serine Carba-penemase	Meropenem	Ceftz-Avi
Erta + Mero	Ceftz-Avi	Serine Carbapenemase	Ceftaz –Avi	Mero-vaborbactam ; Imipenem-relabactam
Ceftaz-Avi, Cpenems, azithromycin	Cefiderocol, Plazomicin, Polymyxin	Metallo (Zn) Carba-penemase	Ceftaz-Avi + Aztreonam	Cefiderocol; Eravacycyline if IAI

*IDSA Guideline:CID 2021;72:1109; **If chromosomal, not detected until induced

Fluoroquinolones

- Broad spectrum synthetic bactericidal antibiotics that inhibit DNA synthesis of both intracellular and extracellular bacteria
- Increasing antibacterial resistance
- Increasing recognition of serious adverse events
- Benefit needs to exceed risk

If I say Amp C, you think:All cephs destroyed except ceftolozane-tazobactam or ceftazidime/avibactam.

Bacteria with Amp C Genes come 2 ways:

Chromosomal & Inducible

- M: *Morganella*
- *Y: Yersinia*
- *S: Serratia*
- *P: Pseudo/Proteus/Provid.*
- *A: Aeromonas/Acinetobact.*
- *C: Citrobacter*
- *E: Enterobacter species* (19%)

On plasmid; constitutive

- *Escherichia coli*
- *Klebsiella species*

Treatment: Carbapenem. Maybe Pip/Tazo.; Beware of cefepime with MIC of 4 -8.
AAC 2015;59:7558
JAC 2016;71:296

Microlab cannot detect unless induced by treatment. !!!!