06 – Core Concepts: Antibacterial Drugs I

Speaker: David Gilbert, MD

Core Concepts: Antibacterial Drugs I

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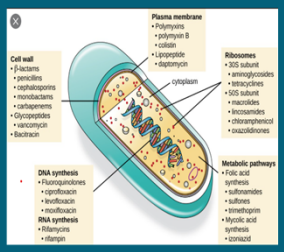
Disclosures of Financial Relationships with Relevant Commercial Interests

- Consultant: Biomerieux
- Research Grant on Diagnostics: Biofire

Overview

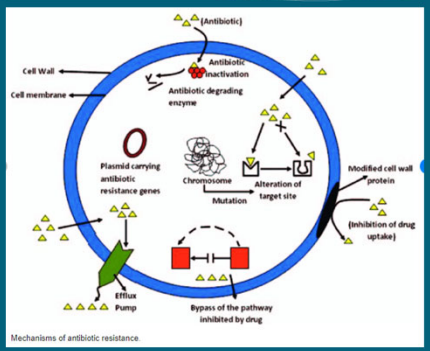
- First Lecture: Beta-lactams, FQs, AGs, Metronidazole
- Then , ARQs focused on clinical application
- A second on line lecture on to finish antibacterials used for infections due to Gram-negative bacteria: Polymyxins, Nitrofurantoin, Fosfomycin, Tetracyclines, TMP/SMX
- Dr. Boucher will discuss antibiotics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

Mechanisms of Action of Antibacterials



Major Gene-Expressed Mechanisms of Resistance to Antibacterials

- **Enzymatic inactivation**
- **Target site absent: intrinsic resistance**
- **Target site modification or protection (high level of resistance)**
- **Excessive binding sites**
- **Altered cell wall permeability**
- **Drug efflux (low level resistance)**



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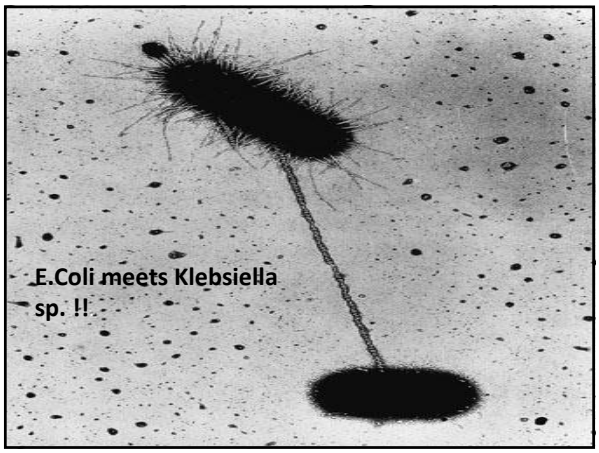

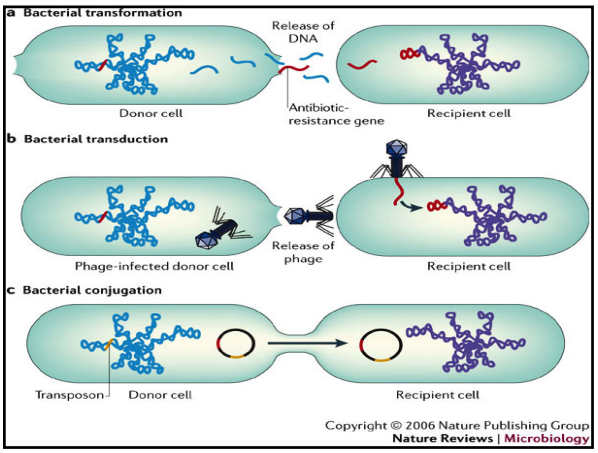

Combination vs Mono-Antibacterial Therapy

- Combination therapy:
  - Decreases risk of selection of resistant subpopulations
  - Empirically in patient at risk of MDR GNB infection;
    - 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
    - Addition of rifamycin for penetration of biofilms on prostheses

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

The best answer is usually the BETA-Lactam !

Beta-Lactams

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

To survive bacteria are constantly mutating

- More than 2800 beta-lactamases reported
- Promiscuity is rampant among bacteria
- Not unusual to detect other mechanisms of resistance: e.g.,
  - Target change &/or Target Protection
  - Active efflux pumps
  - Decrease in 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, hard to write "resistance " test questions

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Ambler Molecular Classificaton of Beta-Lactamases*

Class	Subtypes	B-L-ase Inhibitor	Substrates
A	ESBLs KPCs;serine carbapenemases	Clavulanic Avibactam & Vaborbactam	ESCs Carbapenems
B (BAD!)	Metallo-carbapenemases	EDTA(lab testing only)	All beta-lactams except aztreonam & Cefiderocol
C	AmpC	None	Cephalosporins
D	Oxa-48 Some ESBLs Serine carbapenemases (e.g., KPCs)	None 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 (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*

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

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*

- 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

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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	Carbapenemase producing Enterobacterales and Non-fermenters*	No useful activity vs Gram positives and anaerobic bacteria

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

What you need to know about GNB producing ESBLs:

- Phenotypic Detection by micro. lab based on:
  - 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

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. !!!!

Parenteral Carbapenem Sparing Cephalosporins Active vs GNB producing ESBL and/or AmpC

	Cephalosporin active Vs:	
	AmpC producers	ESBL producers
Ceftazidime	Variable	Variable
Cefepime	If low MIC ; Big dose	I low MIC; Big dose
Ceftolozane-tazobactam	YES	YES
Ceftazidime-avibactam	YES (OK; $$$$$)	YES (OK; $$$$$)
Cefiderocol	YES (BIG OK; $$$$$)	Yes (BIG OK; $$$$$)

OK = OVERKILL

Reference: Curr Opin Infect Dis 2020;33: 78

Oral Carbapenem-Sparing Antibiotics for ESBL Producing Bacteria Causing Cystitis

- Fosfomycin
- Amoxicillin-clavulanate
- Nitrofurantoin

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Testable Cephalosporin AEs

- Cross Allergenicity: Ceftazidime 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*; 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 maltophila*
Bacteroides fragilis	*Acinetobacter (variable)*
Enterococcus faecalis	*Enterococcus faecium*
Listeria monocytogenes	

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

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 Blamase

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
- In vitro resistance of GNB is a phenotypic marker for production of ESBLamases
  - In vitro active 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

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 be susceptible to ceftazidime and cefepime
  - Ceftazidime –avibactam. Interest in combination therapy
  - Not currently testable!

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Cefiderocol

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

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*

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; Eravacycline if IAI

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

*"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

IN SUMMARY: Rx

- ESBL production: Meropenem
- AmpC induced production risk: Avoid cephalosporins; Meropenem
- Serine-based Carbapenemase: Ceftazidime –avibactam, Meropenem-vaborbactam, or Imipenem-cilastatin-relebactam
- Metallo-based carbapenemase production: Ceftazidime-avi + Aztreonam

PK/PD.

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

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---RISK vs Benefit

FQ Pharmacology

- Parenteral:
  - Higher doses for *Ps.aeruginoa*
  - Excreted in urine
  - High concentrations in prostate
- Oral:
  - Bioavailability of 59-95%
  - Chelation by divalent cations decreasing 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

- Antibacterial 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
- 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*
- Second are the cephalosporins
- Third is clindamycin

FQs and Acute Liver Injury

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

FQs and Neurologic AEs

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

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), electrolyte abnormalities.
- Moxifloxacin: Highest association; Delafloxacin the lowest.

FQ Drug-Drug Interactions

- Cipro inhibition of cytochrome P450 resulting in impaired drug elimination
- NSAIDs plus FQs displace GABA from its 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

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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 not 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
  - Long post-antibiotic effect
- Result is improved antibacterial activity and less risk of toxicity
- EXCEPTION: Combination therapy of enterococcal endocarditis with TID AG therapy

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, and Carbapenems
- 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

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

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

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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.

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 %
- Issues:
  - Breakpoints/inoculum effect for P/T
  - Co-production of ESBL and oxacillinase
- Three confirmatory controlled trials in progress

* PRDB=Prospective Randomized Double-Blind

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

Empiric therapy for Enterobacter (Klebsiella) sp.

- Avoid cephalosporins (except ceftolozane/tazo), penicillins, BL/BLIs due to induction of Amp C resistance, and documented poor clinical outcomes in patients &/or animal models.
- Carbapenems current choice

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

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