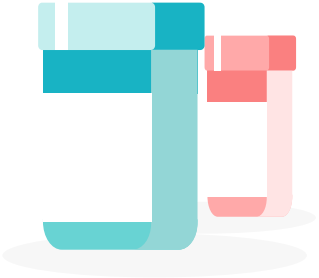
Basics of Antibiotics



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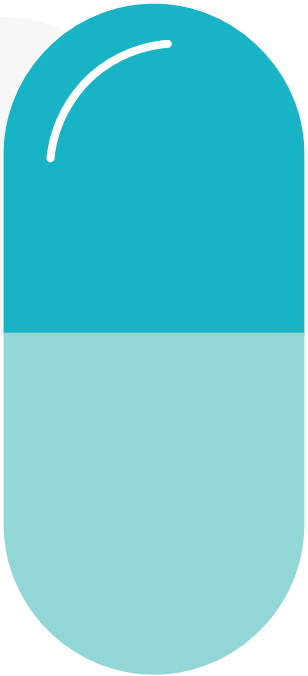
Introduction of Antibiotic



Definitions

- **Antibiotic:** is an antimicrobial drug effective against bacteria.
- **Bactericidal:** a substance that kills bacteria.
- **Bacteriostatic:** a substance that slow bacteria grow or stop bacterial reproduction.

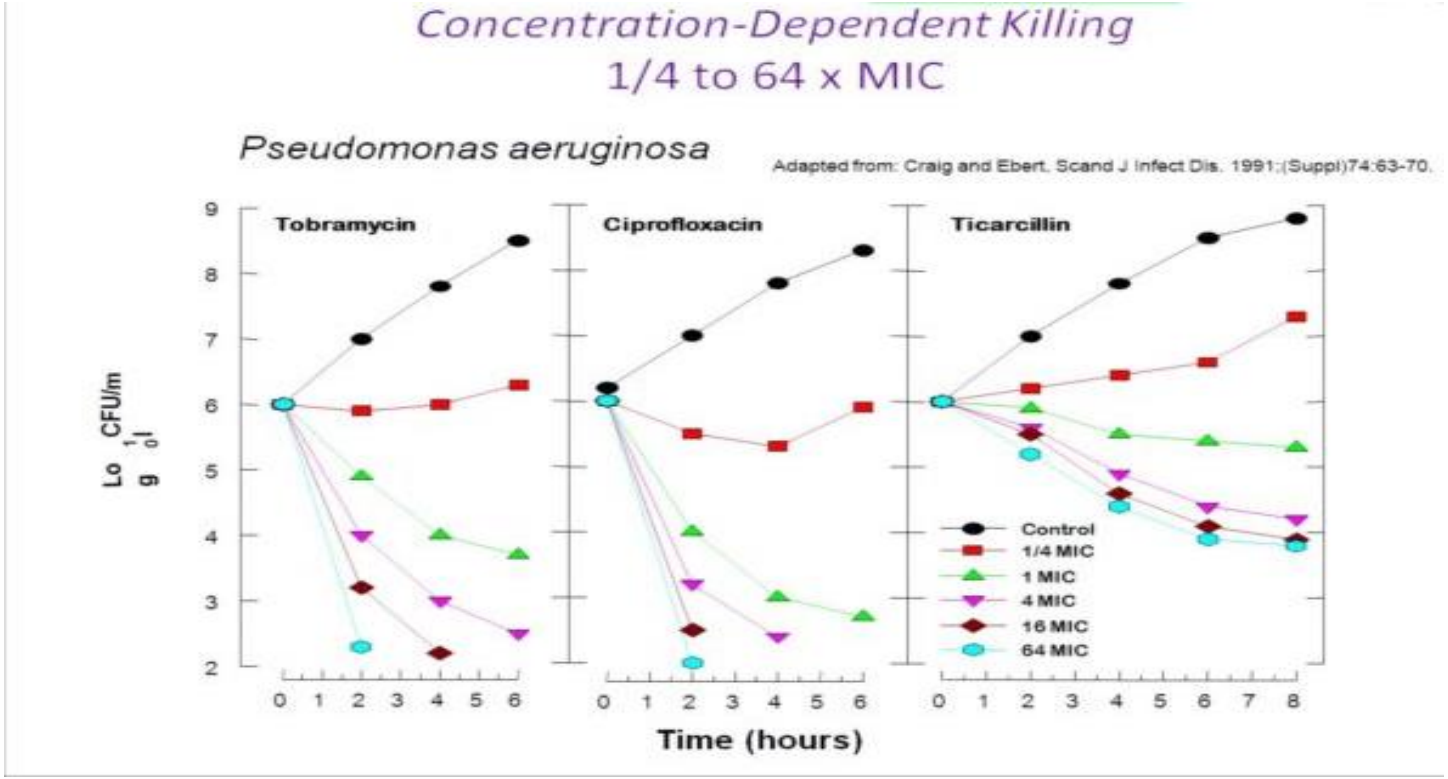
Antibacterial Killing Effect

Bacteriostatic	Bactericidal
Glycylcyclines: Tigecycline	Aminoglycosides: Tobramycin, gentamicin, amikacin
Tetracyclines: Doxycycline, minocycline	Beta-lactams (penicillins, cephalosporins, carbapenems): Amoxicillin, cefazolin, meropenem
Lincosamides: Clindamycin	Fluoroquinolones: Ciprofloxacin, levofloxacin, moxifloxacin
Macrolides: Azithromycin, clarithromycin, erythromycin	Glycopeptides: Vancomycin
Oxazolidinones: Linezolid	Cyclic Lipopeptides: Daptomycin
Sulfonamides: Sulfamethoxazole	Nitroimidazoles: Metronidazole

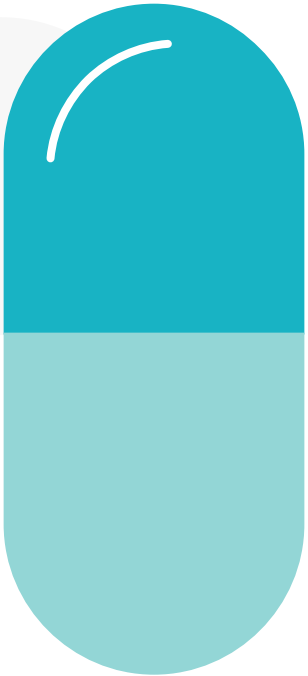
Antimicrobial Susceptibility Testing

Minimum Inhibitory Concentration (MIC)	• Lowest concentration of a given antimicrobial that will inhibit (visual) the patient's organism from growing after 18-24 h incubation
Minimum Bactericidal Concentration (MBC)	• Lowest concentration of a given antimicrobial that will kill(99.9%) of the patient's organism after 18-24 h incubation

Concentration-Dependent Killing
¼ to 64 * MIC



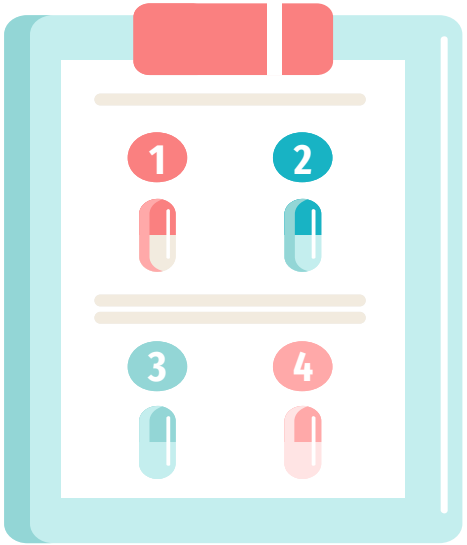
02 Pharmacology



Fundamental of Pharmacology

Pharmacokinetics : The science of the rate of movement of drugs within biological systems, as affected by liberation, absorption, distribution, metabolism, and elimination of medications

Pharmacodynamics : Deals with with the effect of a drug at its site of action, the dose-response relationship of the drug, and the influence of other factors on the drug effect.



Pharmacokinetics

Liberation: The process by which the drug is released from its pharmaceutical form (e.g capsule, tablet, suppositry, etc.)

Absorpiton: The process by which the drug reach the bloodstream.

Distribution: Measure of hydrophobicity/hydrophilicity of a drug.

Metabolism: Chemical alteration of substances (e.g, drugs) within the body by the action of enzyme and mainly take place in the liver.

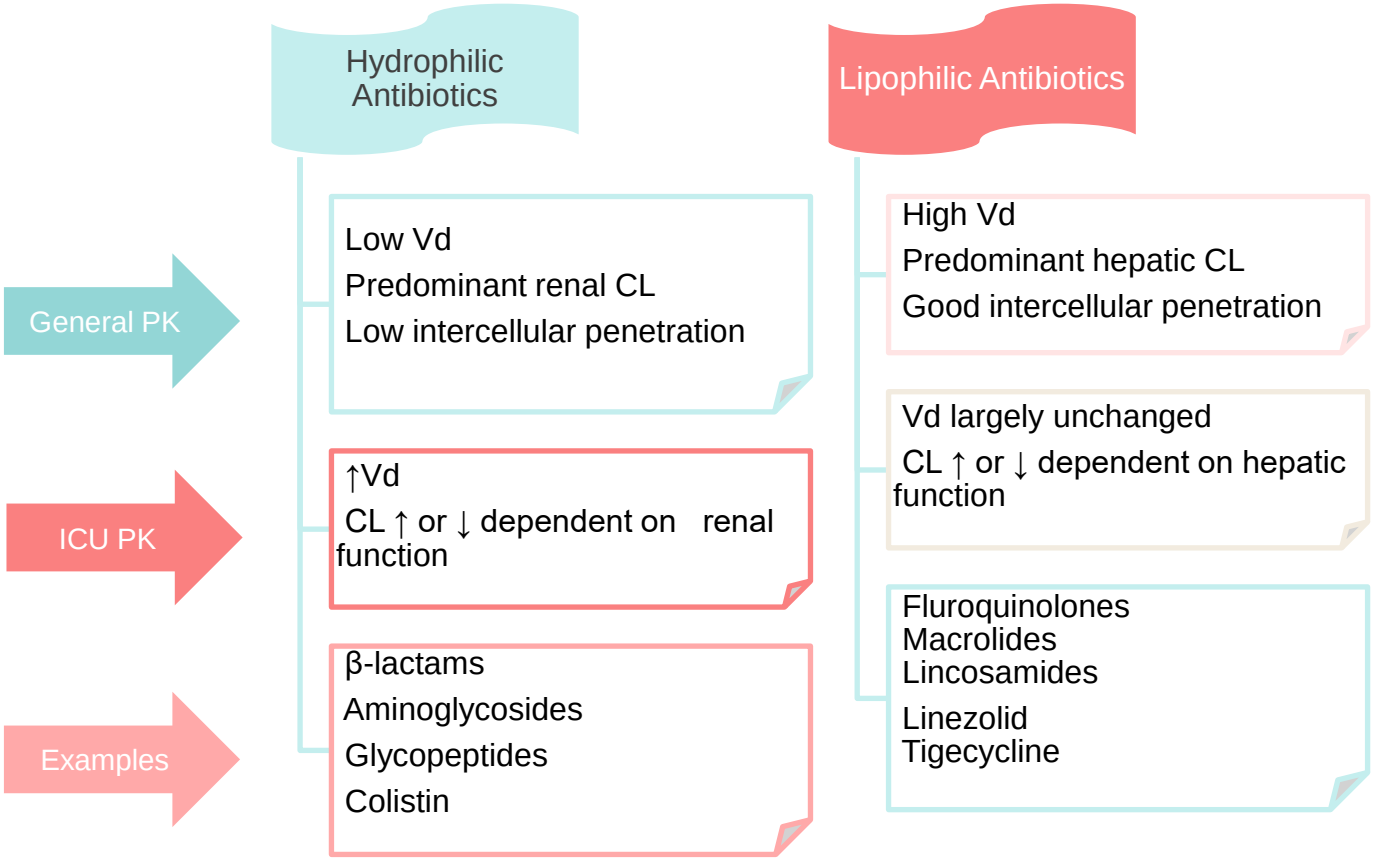
Excretion Drug clearance (CL): defined as the plasma volume that can be completely cleared of the drug in a given period of time (e.g creatinine clearance).

Pharmacokinetics

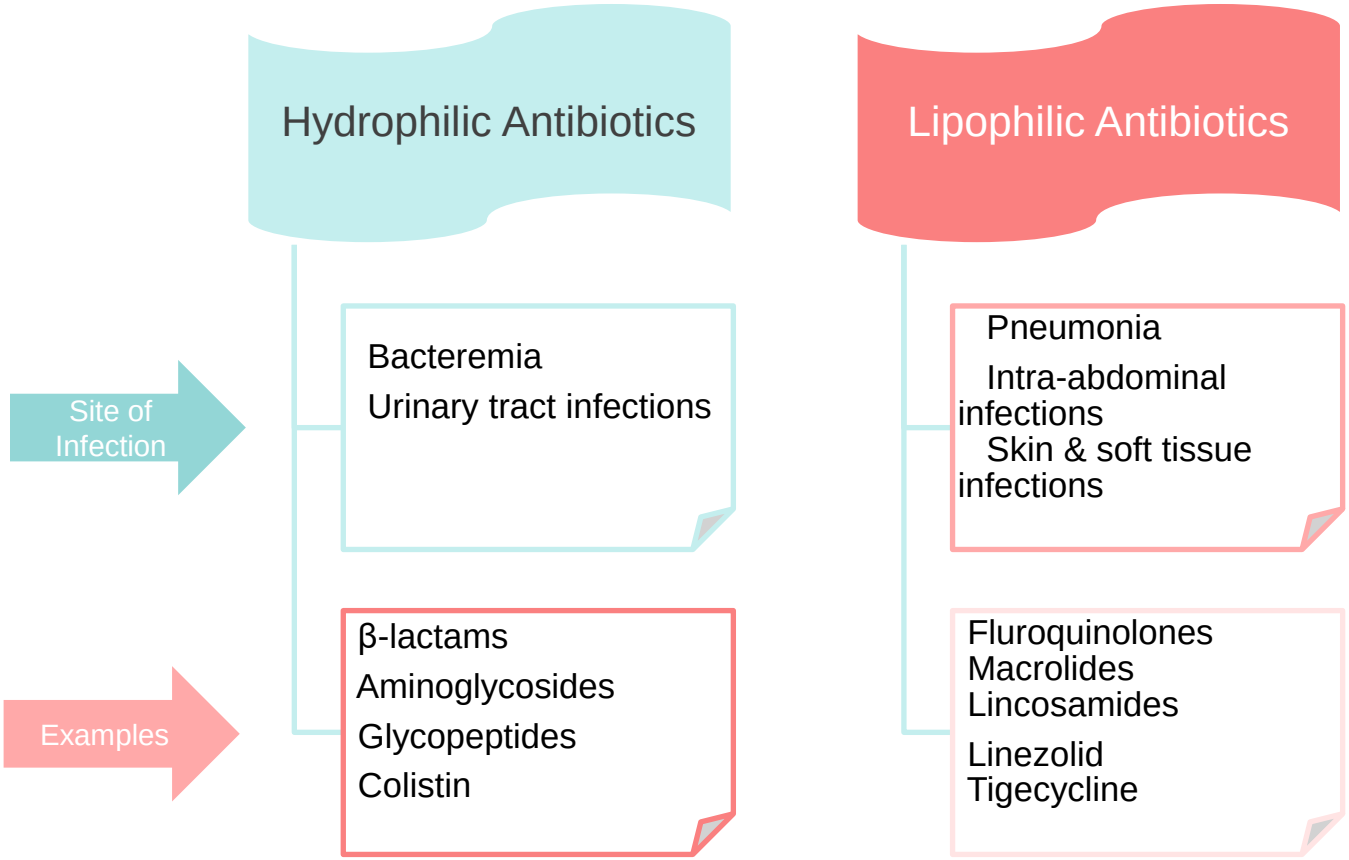
Distribution: Measure of hydrophobicity/hydrophilicity of a drug.

Vd	Low	Medium	High
Drugs	• Consisting of large molecules • Consisting of ions • Binding to plasma proteins	• Consisting of small hydrophilic molecules	• Consisting of small lipophilic molecules • Binding to tissue proteins
Compartment	Intravascular	Extracellular fluids	All other compartments, e.g. • Muscles • Adipose tissue

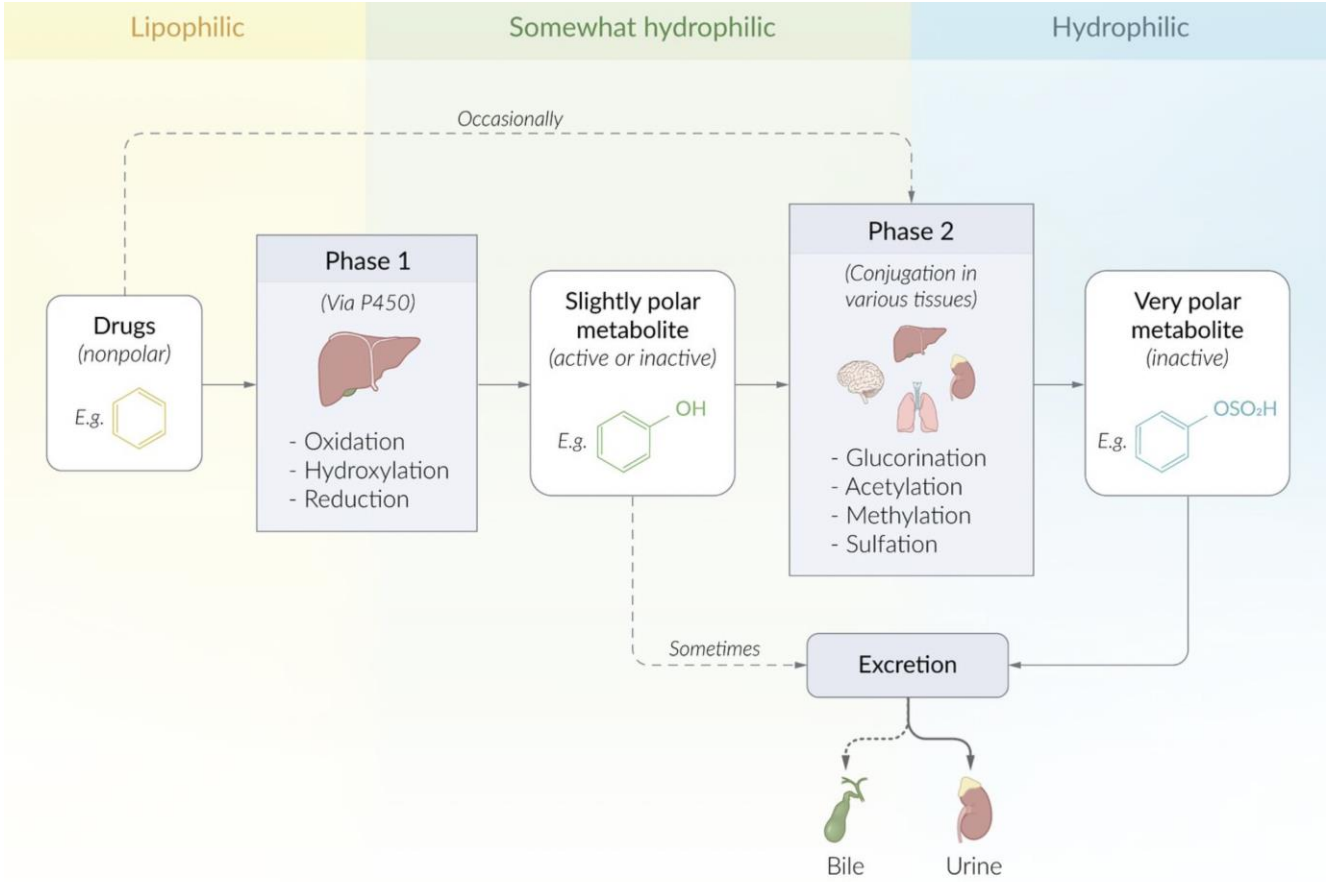
Interrelationship of Hydrophilicity and Lipophilicity of Antibiotics on Pharmacokinetics



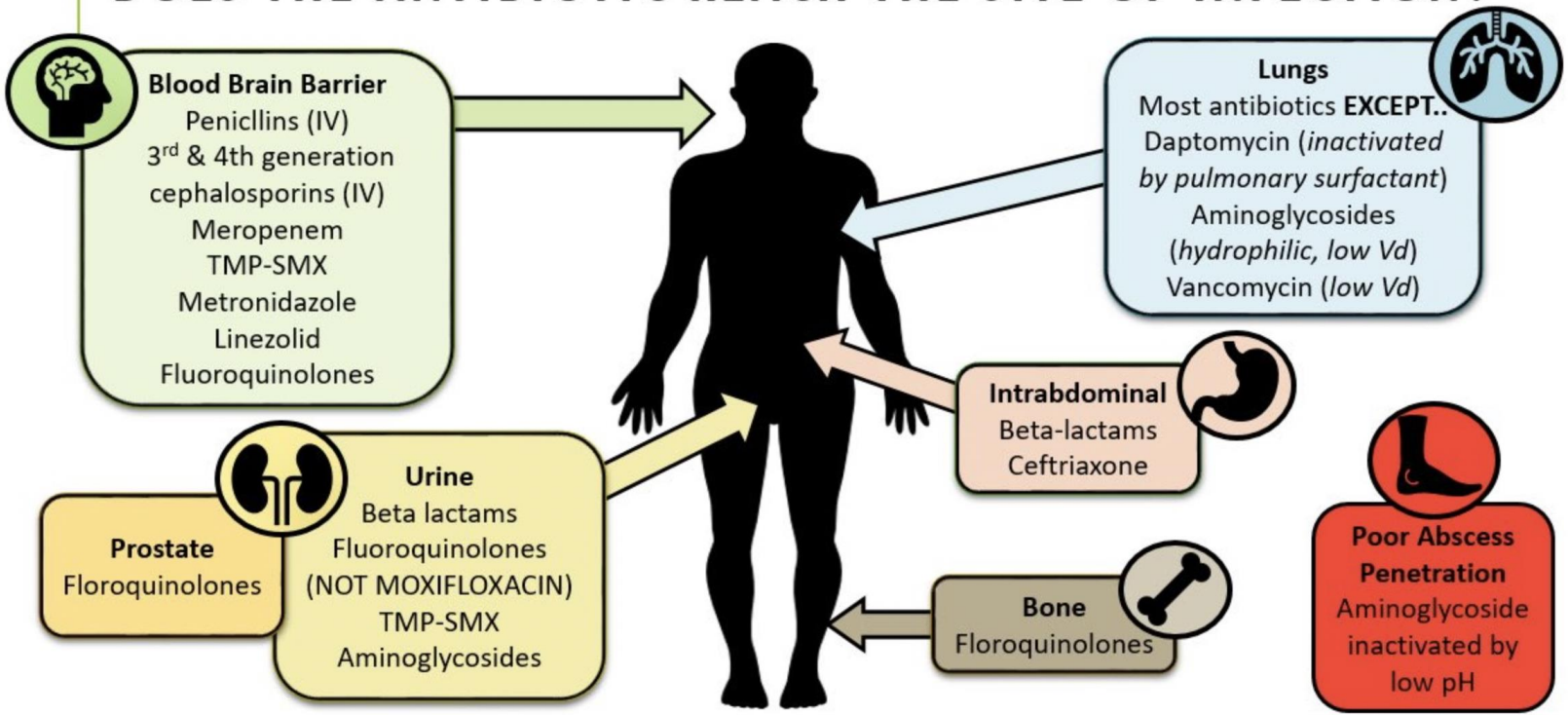
Interrelationship of Hydrophilicity and lipophilicity of Antibiotics on Pharmacokinetics



Pharmacokinetics



DOES THE ANTIBIOTIC REACH THE SITE OF INFECTION?



Pharmacokinetics

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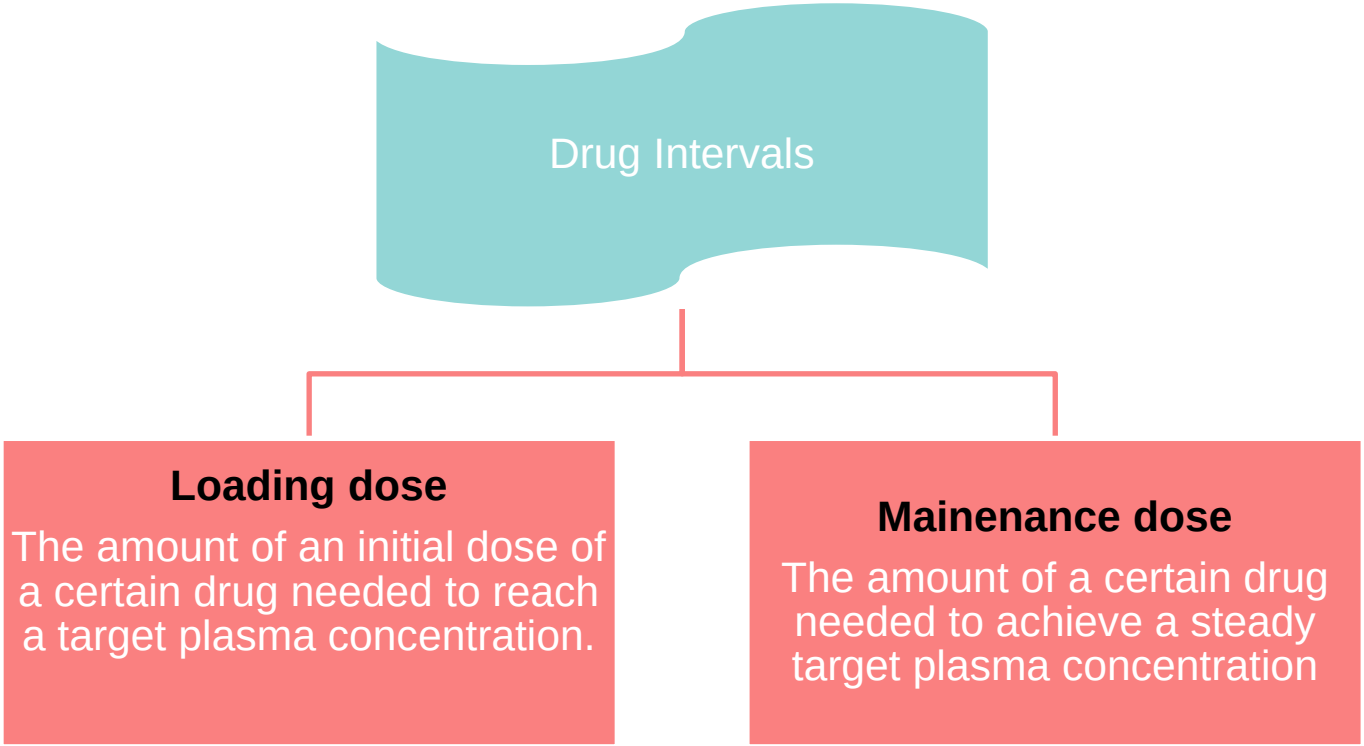
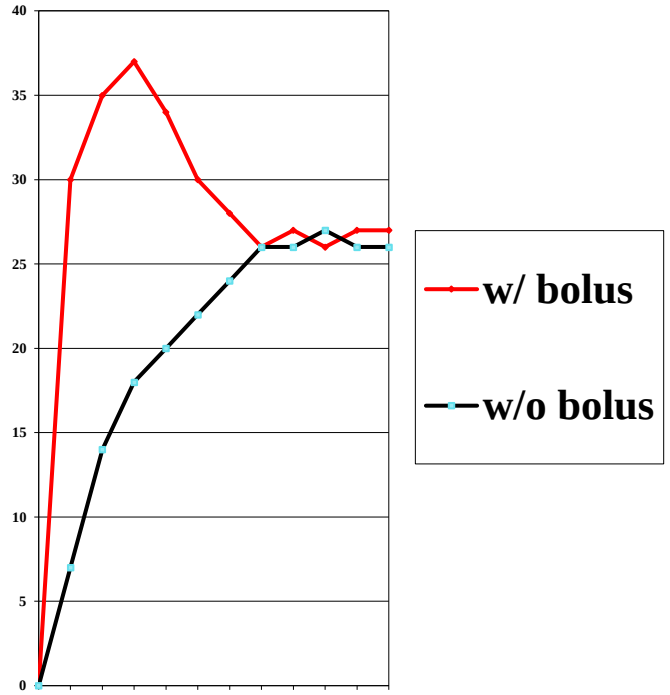


Loading Doses

- Loading doses allow rapid achievement of therapeutic serum levels
- Same loading dose used regardless of metabolism/elimination dysfunction



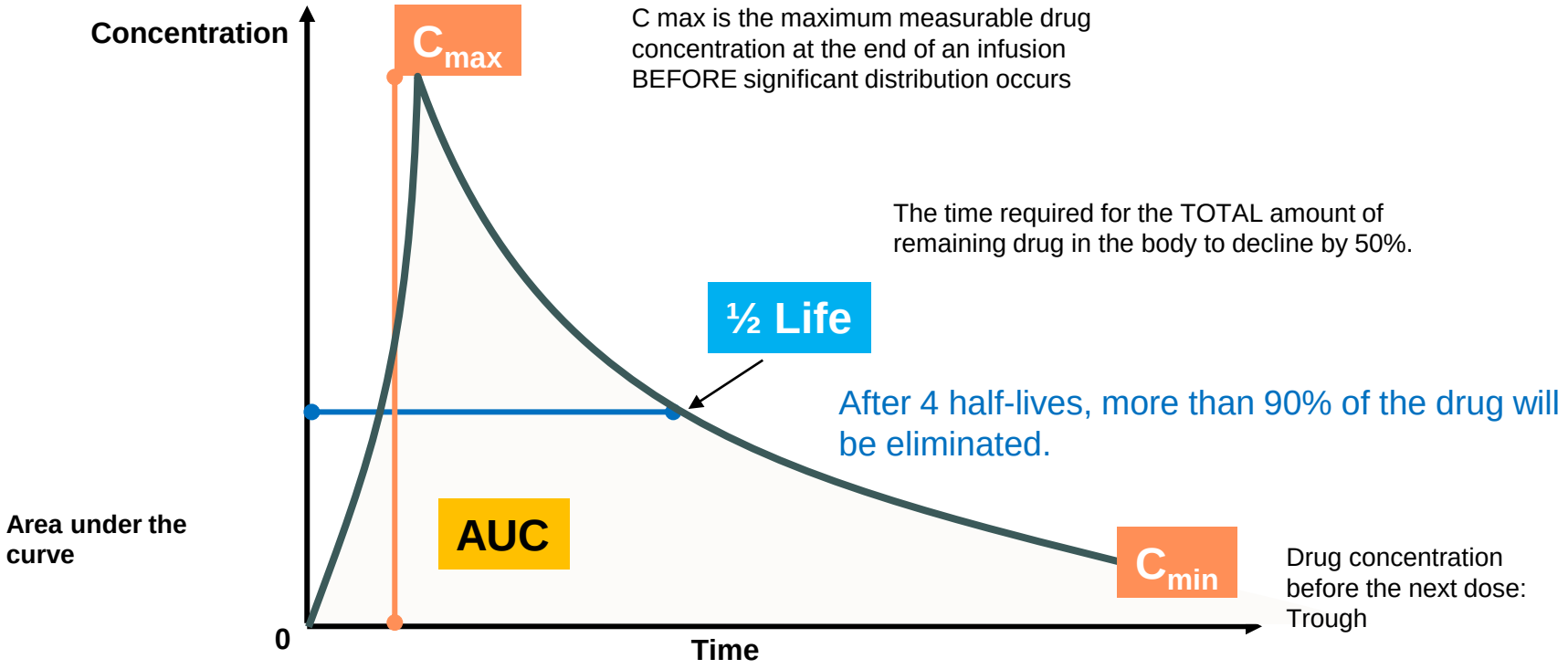
Pharmacokinetics

Deals with the effect of a drug at its site of action, the dose-response relationship of the drug, and the influence of other factors on the drug effect.

Overview of drug-receptor interactions

	Competitive antagonist	Noncompetitive antagonist	Partial agonist
Potency	• Decreased	• Unchanged	• Independent
Efficacy	• Unchanged	• Decreased	• Decreased
Drug example	• At $GABA_A$ receptor: ◦ Diazepam (agonist) PLUS ◦ Flumazenil (competitive antagonist)	• At alpha-1 and alpha-2 receptors: ◦ Norepinephrine (agonist) PLUS ◦ Phenoxybenzamine (noncompetitive antagonist)	• At opioid μ-receptor: ◦ Morphine (full agonist) PLUS ◦ Buprenorphine (partial agonist)

Pharmacodynamic Parameters



Deals with with the effect of a drug at its site of action, the dose-response relationship of the drug, and the influence of other factor on the drug effect.

Pharmacodynamic Parameters of Antibiotics

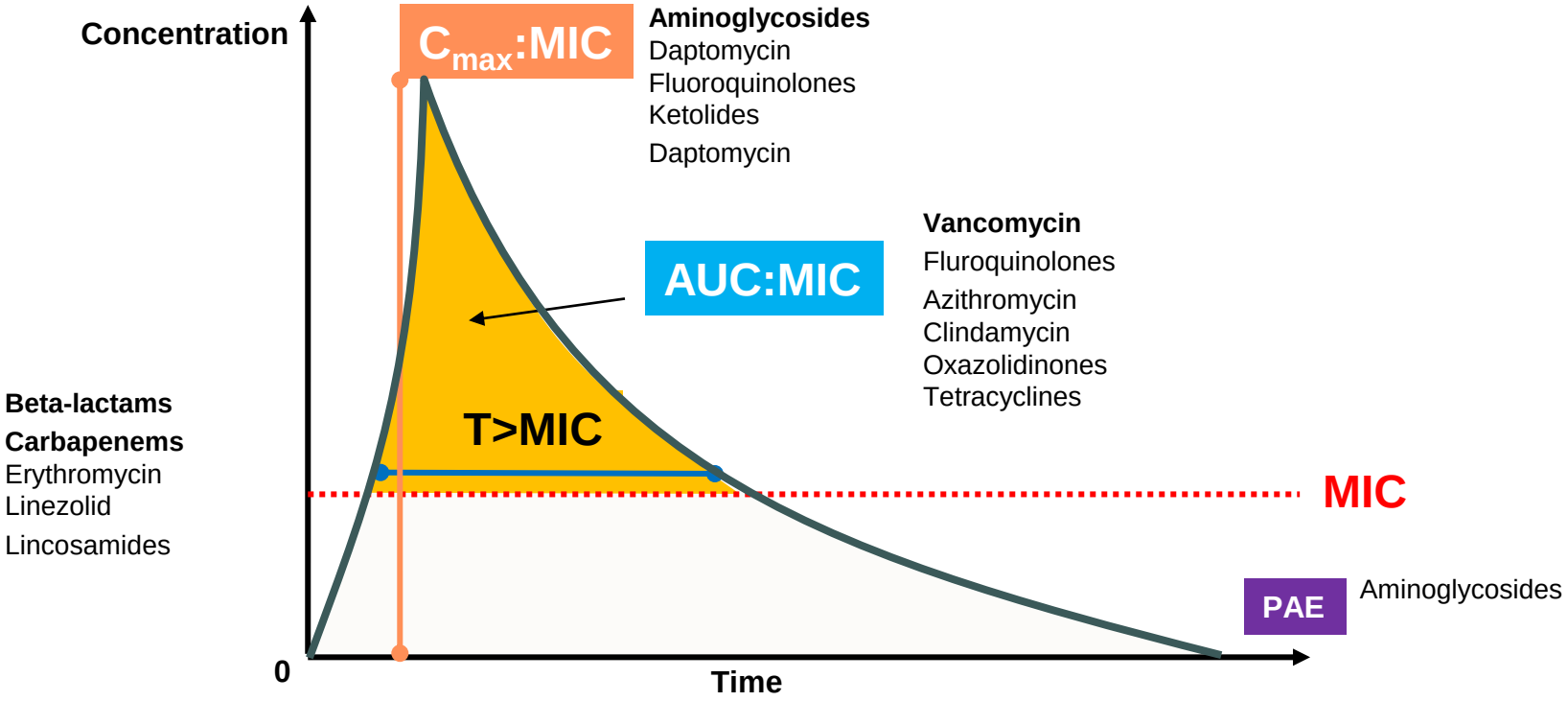


Table 1. Pharmacodynamic properties that correlate with efficacy of selected antibiotics

Antibiotics	β-lactams Carbapenems Linezolid Erythromycin Clarithromycin Lincosamides	Aminoglycosides Metronidazole Fluoroquinolones Telithromycin Daptomycin Quinupristin/dalfopristin	Fluoroquinolones Aminoglycosides Azithromycin Tetracyclines Glycopeptides Tigecycline Quinupristin/dalfopristin Linezolid
PD kill characteristics	Time-dependent	Concentration-dependent	Concentration-dependent with time-dependence
Optimal PD parameter	T > MIC	C_{max}:MIC	AUC_{0-24}:MIC

MIC, minimum inhibitory concentration; AUC, area under curve; PD, pharmacodynamics; C_{max}, maximum concentration.

Pharmacodynamic Therapeutic Goals of Antibiotics

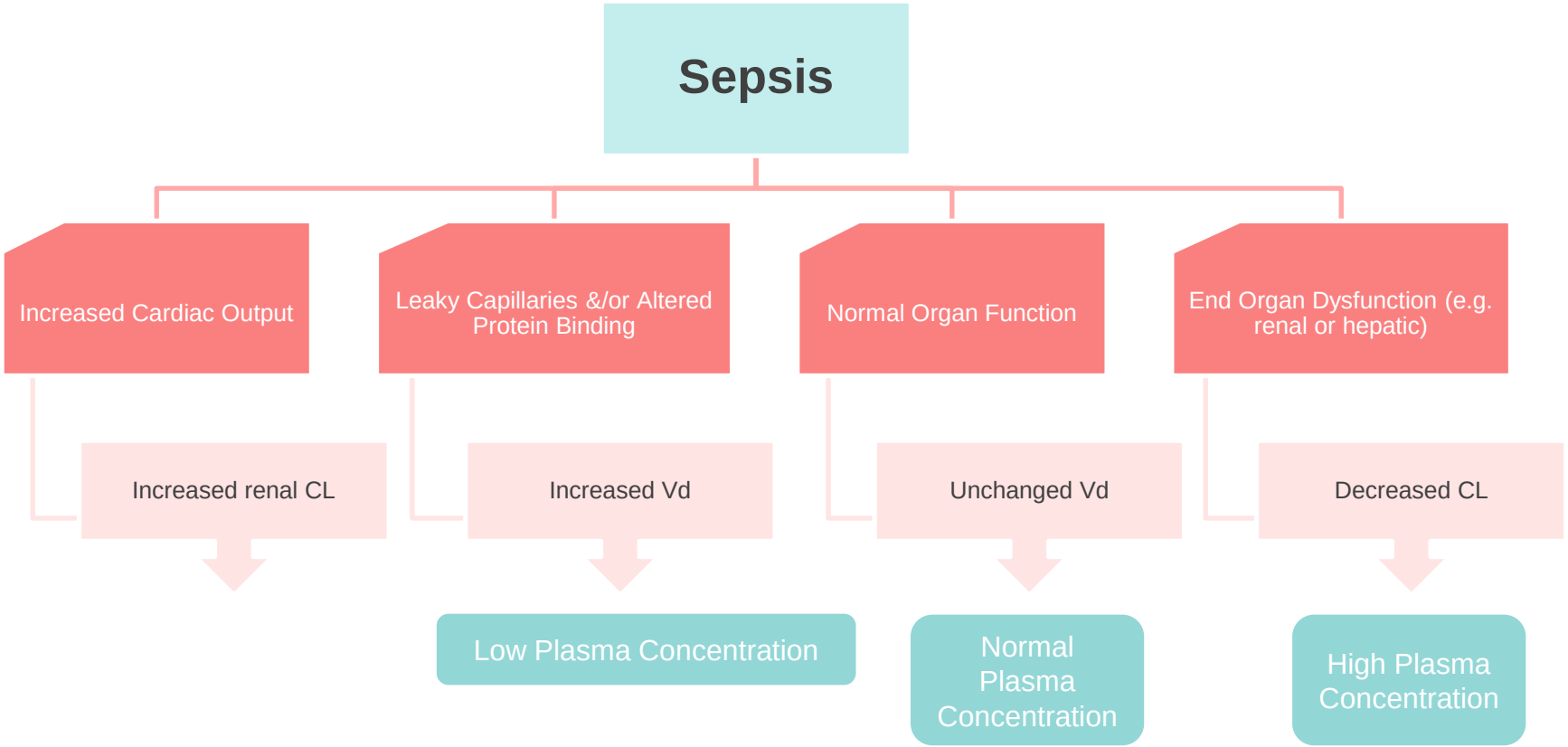
Parameter correlating with efficacy	Cmax:MIC	T>MIC	AUC:MIC	PAE
Antibiotic	**Aminoglycosides** **Colistin** Daptomycin Fluoroquinolones Ketolides	**Carbapenems** **Cephalosporins** **Penicillins** Erythromycin	**Vancomycin** **Fluroquinolones**	**Aminoglycosides** **Fluroquinolones**
Organism killing	**Concentration-dependent**	**Time-dependent**	**Concentration/time-dependent**	**Post-antibiotic effect**
Therapeutic goal	**High dose:** **C_{max}/MIC>10**	**Higher frequency, prolonged duration** **C_{min}>MIC**	**Optimize exposure to antibiotic:** **C_{max}/MIC>10 and C_{min}>MIC**	**Lower frequency**

TABLE 1. SUMMARY OF ANTIBIOTICS THAT DISPLAY CONCENTRATION-DEPENDENT OR TIME-DEPENDENT KILLING CHARACTERISTIC AND THE REQUISITE PHARMACODYNAMIC EXPOSURE

ANTIBIOTIC CLASS *Antibiotic*	KILLING CHARACTERISTIC	PHARMACODYNAMIC PARAMETER [a]
Aminoglycosides	Concentration Dependent	
amikacin, gentamicin, tobramycin		*f*C_{max}/MIC > 10–12 (Gram-negatives)
β-lactams	Time Dependent	
carbapenems *(doripenem, ertapenem, imipenem, meropenem)*		40% *f*T>MIC (bactericidal activity, Gram-negatives)
cephalosporins *(e.g., ceftriaxone, ceftazidime, cefepime)*		50%–70% *f*T>MIC (bactericidal activity, Gram-negatives)
penicillins *(e.g., oxacillin, ampicillin/sulbactam, piperacillin/tazobactam)*		50% *f*T>MIC (bactericidal activity, Gram-negatives)
Fluoroquinolones	Concentration Dependent	
ciprofloxacin, levofloxacin,		AUC/MIC > 125 (Gram-negatives) [b]
moxifloxacin		*f*AUC/MIC > 30–50 (Gram-positives)
Glycopeptides	Concentration and Time Dependent	
vancomycin		AUC/MIC > 400 [b]
Glycylcycline	Time Dependent	
tigecycline		
Polymyxins	Concentration Dependent	*f*AUC/MIC >12–48 (*Pseudomonas* and
polymyxin B, colistin (polymyxin E)		*Acinetobacter*); corresponds with a Css_{avg} of 1–4mg/L when MIC=1mg/L

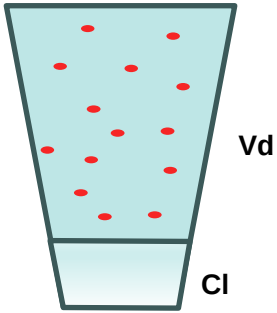
[a] Denotes common exposures based on free (f) drug concentrations, unless otherwise noted.
[b] Total drug exposure target.

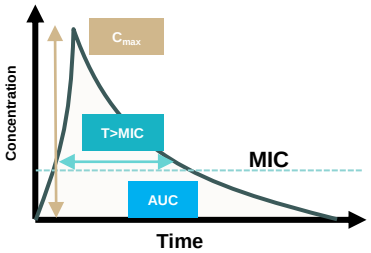
Schematic Representation of The Basic Pharmacological Changes That Can Occur During Sepsis and Their Subsequent Pharmacokinetic Effects



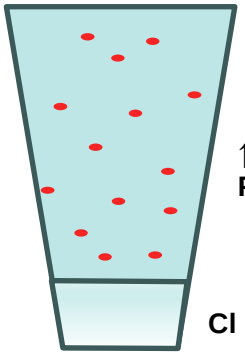
Pharmacokinetic Changes of Antibiotics in Septic Patients

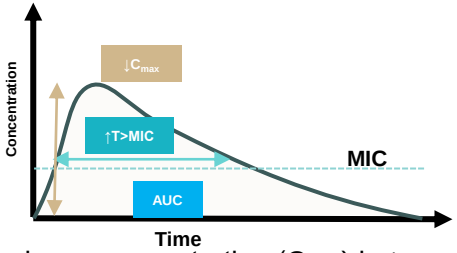
Healthy





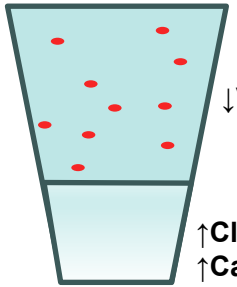
Large Volume of Distribution

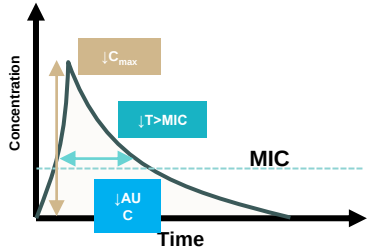




↓maximum concentration (C_{max}) but a longer half-life ($T_{1/2}$)

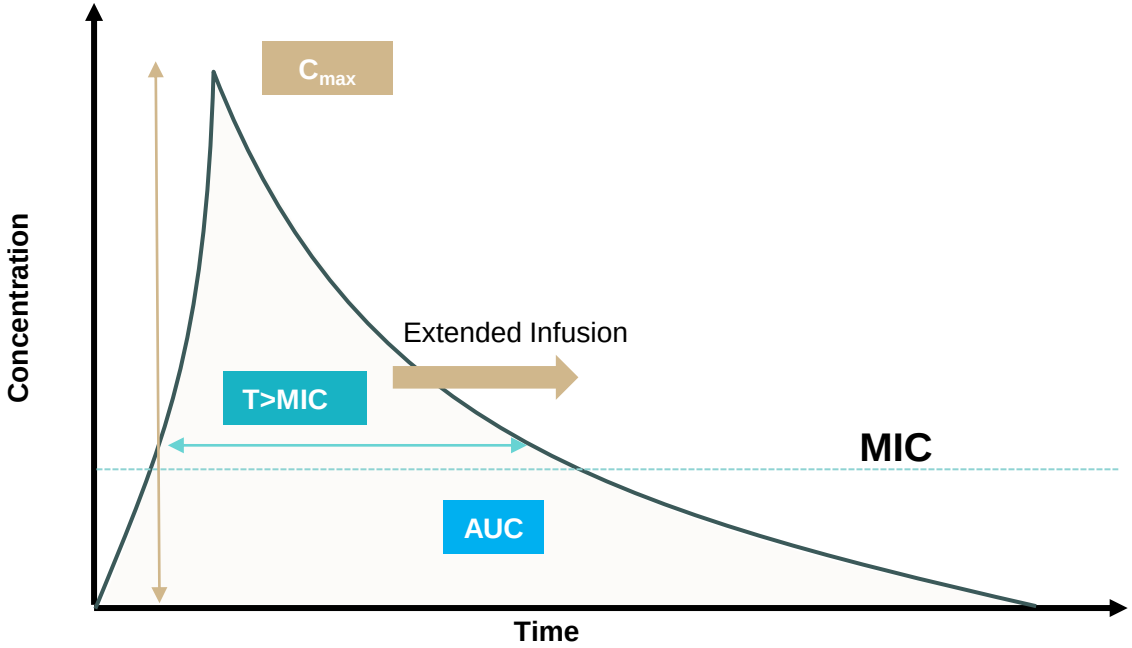
Increase Drug Clearance



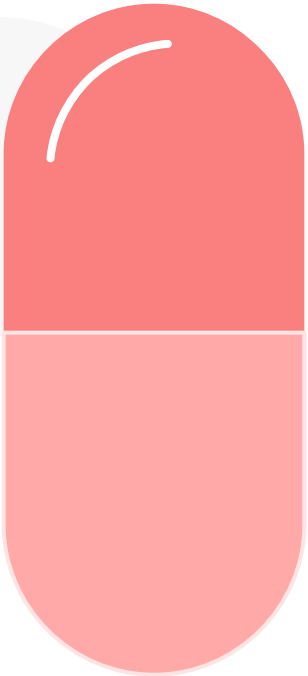


↓AUC, $T_{1/2}$ and T > MIC

Higher MIC Organisms



03 Classification of Antibiotic



Classification of Antibiotics

1.

Based on

Chemical structure

2.

Based on

Mode of Action

3.

Based on

Spectrum of Activity

4.

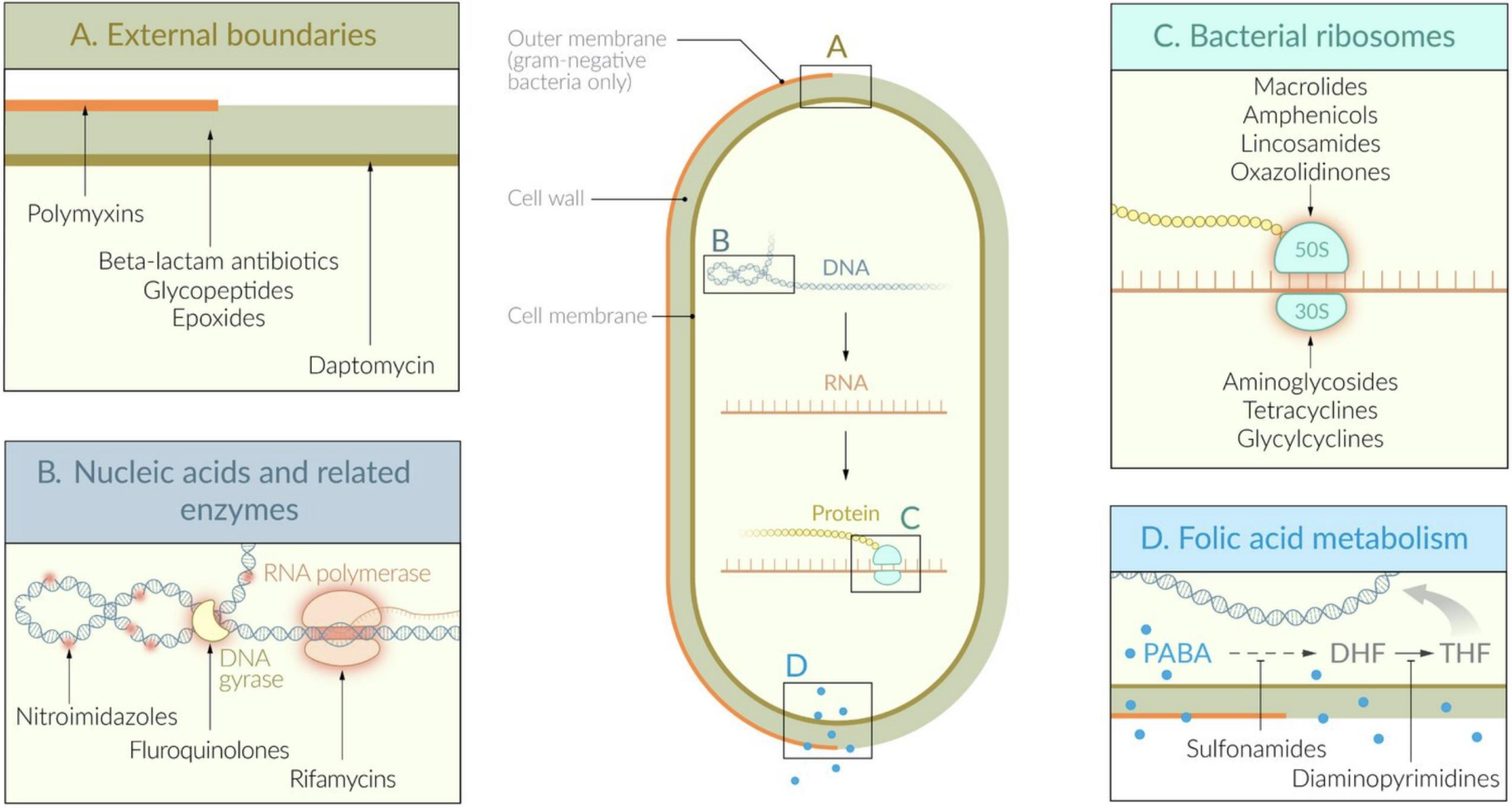
Based on

Route of Administration

Classification



1. Inhibition of cell wall synthesis
2. Disruption of cell membrane integrity
3. Inhibition of protein synthesis - 30S ribosomal subunit
4. Inhibition of protein synthesis - 50S ribosomal subunit
5. DNA gyrase inhibition
6. Disruption of DNA integrity
7. Inhibition of folic acid synthesis and reduction
8. Other


A. External boundaries
Polymyxins
Beta-lactam antibiotics
Glycopeptides
Epoxides
Daptomycin
B. Nucleic acids and related enzymes
RNA polymerase
DNA gyrase
Nitroimidazoles
Fluroquinolones
Rifamycins
Outer membrane (gram-negative bacteria only)
Cell wall
Cell membrane
A
B
DNA
RNA
Protein
C
D
C. Bacterial ribosomes
Macrolides
Amphenicols
Lincosamides
Oxazolidinones
50S
30S
Aminoglycosides
Tetracyclines
Glycylcyclines
D. Folic acid metabolism
PABA
DHF
THF
Sulfonamides
Diaminopyrimidines

Inhibition of Cell Wall Synthesis

Antibacterial classes			Examples	Mechanism of action	Bacterial Activity	Mechanisms of resistance
β-lactams	**Penicillins**		Natural penicillins: PCN G	Binds to penicillin-binding proteins (PBPs) ↓crosslinking of peptidoglycan layers	Bactericidal	Cleavage of β-lactam ring by β-lactamases (penicillinases) PBP mutations (e.g. MRSA)
			Anti-staphylococcal penicillins: nafcillin			
			Aminopenicillins: ampicillin			
			Antipseudomonal penicillins: pip/taz			
	Cephalosporins	1st	generation (cephalexin, cefazolin)			Cleavage of β-lactam ring by β-lactamases (cephalosporinases)
		2nd	cefuroxime, cefoxitin			
		3rd	ceftazidime, ceftriaxone			
		4th	cefepime			
		5th	ceftaroline, ceftobiprole, ceftolozane			
	Carbapenems	Group I	Narrow spectrum: Ertapenem			Cleavage of β-lactam ring by β-lactamases (carbapenemases)
		Group II	Broad spectrum Meropenem, Imipenem, Doripenem			
	Monobactams		Aztreonam			Cleavage by β-lactamases (less susceptible)

Inhibition of Cell Wall Synthesis

Antibacterial classes	Examples	Mechanism of action	Bacterial Activity	Mechanisms of resistance
Glycopeptides	Vancomycin Bacitracin Teicoplanin Telavancin Dalbavancin, Oritravancin	Bind to D-alanine section of peptidoglycan precursor → inhibited peptidoglycan synthesis	Bactericidal (static against *C. difficile*)	Reduced penetration in gram-negative bacteria Change in peptidoglycan precursor structure • D-alanine-D-alanine → D-alanine-D-lactate • Glycopeptides do not bind the altered precursor
Epoxides	Fosfomycin	Inactivate enolpyruvate transferase (MurA) → inhibition of N-acetylmuramic acid formation → disruption of peptidoglycan synthesis	Bactericidal	Cleavage of β-lactam ring by β-lactamases (cephalosporinases)

Disruption of Cell-membrane Integrity

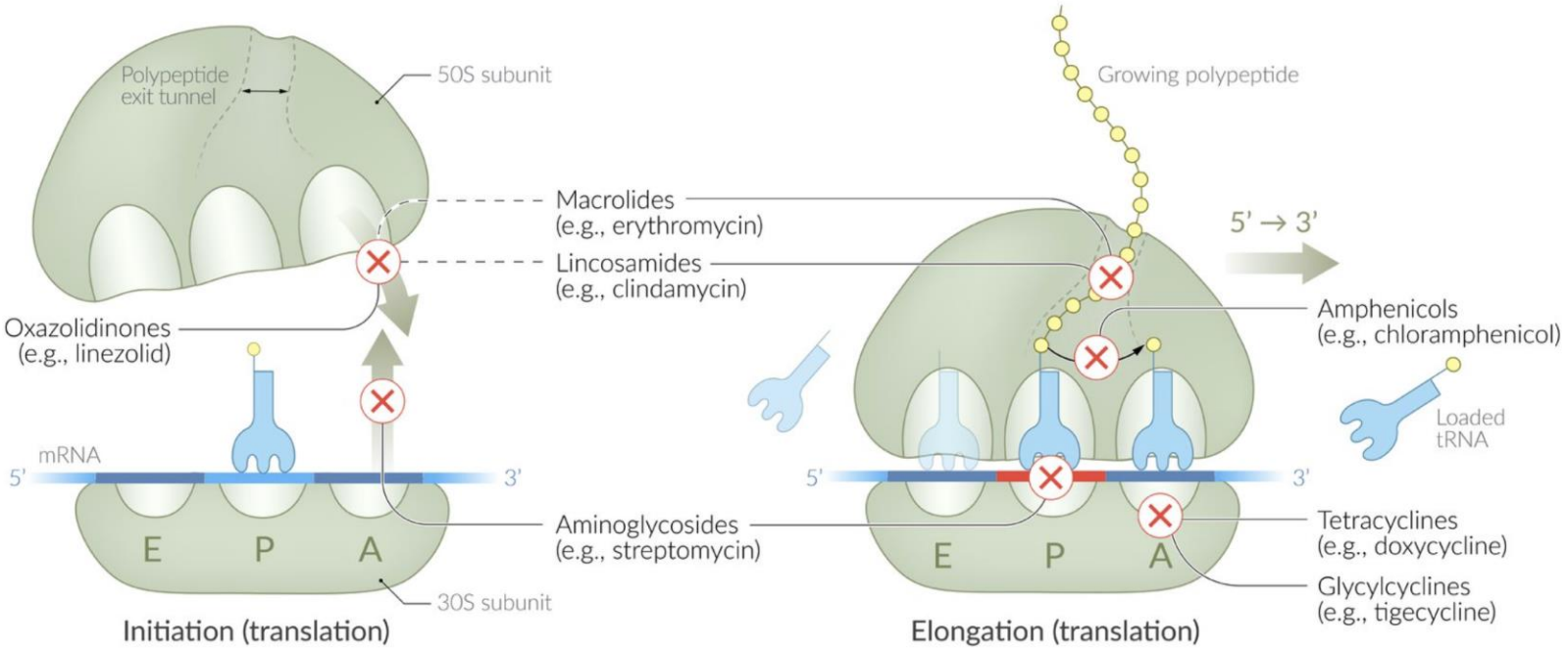
Antibacterial classes	Examples	Mechanism of action	Bacterial Activity	Mechanisms of resistance
Lipopeptides	Daptomycin	Lipid portion binds to bacterial cytoplasmic membrane → formation of ion-conducting channels → intracellular K^+ efflux → bacteria cell membrane depolarization	Bactericidal	Not fully understood Altered cell membrane potential
Polymyxins	Polymixin E (colistin) Polymixin B	Cationic detergents (polypeptides) bind to outer cell membrane (phospholipids on gram-negative bacteria) → ↑permeability → bacterial lysis	Bactericidal	Not fully understood Altered lipid A portion of lipopolysaccharides Efflux pump

Inhibition of Protein Synthesis - 30S Ribosomal Subunit

Antibacterial classes	Examples	Mechanism of action	Bacterial Activity	Mechanisms of resistance
Aminoglycosides	Gentamicin Tobramycin Amikacin Streptomycin Neomycin	Inhibits initiation complex→ protein mistranslation	Bactericidal (static against *C. difficile*)	Reduced penetration in gram-negative bacteria Change in peptidoglycan precursor structure • D-alanine-D-alanine → D-alanine-D-lactate • Glycopeptides do not bind the altered precursor
Tetracyclines	Tetracyclines Doxycycline Minocycline Eravacycline Sarecycline Omadacycline	Block incoming aminoacyl-tRNA with amino acid → decrease protein synthesis	Bacteriostatic	Reduced cell wall penetration Removal by efflux pumps (plasmid-encoded) Production of protein that protect ribosomes
Glycylcyclines	Tigecycline			Designed to overcome the resistance of tetracyclines

Inhibition of protein synthesis - 50S ribosomal subunit

Antibacterial classes	Examples	Mechanism of action	Bacterialstatic/cidal	Mechanisms of resistance
Inhibition of protein synthesis - 50S ribosomal subunit				
Macrolides and ketolides	• Erythromycin • Clarithromycin • Azithromycin	• Bind to 23S rRNA → inhibition of transpeptidation, translocation, and chain elongation → ↓ protein synthesis	• Bacteriostatic	• Reduced penetration • Efflux pumps • Methylation of 23S rRNA binding site → inhibits binding of macrolides • Cross-resistance with clindamycin and streptogramins • Mutation of bacterial ribosome binding site
Lincosamides	• Clindamycin	• Impair transpeptidation → inhibition of chain elongation → ↓ protein synthesis • Increase opsonization and phagocytosis • Inhibit alpha toxin expression	• Bacteriostatic	• Reduced penetration • Mutation of bacterial ribosome binding site
Streptogramins	• Quinupristin-dalfopristin	• Dalfopristin binds to 23S portion of the 50S subunit → conformation change → facilitation of binding of quinupristin • Quinupristin binds to and blocks 50S subunit → inhibition of polypeptide elongation → ↓ protein synthesis [5]	• Bactericidal when used in combination • Bacteriostatic when used separately	• Alteration of bacterial ribosome binding site • Enzyme-mediated methylation • Efflux pumps
Oxazolidinones	• Linezolid	• Prevent association of 50S with 30S subunit → impairment of **initiation complex** formation → early interruption of protein synthesis	• Bacteriostatic • Only bactericidal against *Streptococci*	• Point mutation of the 23S rRNA
Amphenicols	• Chloramphenicol	• Prevent binding of amino acid-containing aminoacyl-tRNA → **inhibition of peptidyltransferase** → ↓ protein synthesis	• Bacteriostatic • Bactericidal in higher concentrations	• Reduced penetration • Enzymatic inactivation by **acetyltransferase** (plasmid-encoded)


Polypeptide exit tunnel
50S subunit
Macrolides (e.g., erythromycin)
Lincosamides (e.g., clindamycin)
Oxazolidinones (e.g., linezolid)
mRNA
5'
3'
E
P
A
Aminoglycosides (e.g., streptomycin)
30S subunit
Initiation (translation)
Growing polypeptide
5' → 3'
Amphenicols (e.g., chloramphenicol)
Loaded tRNA
5'
3'
E
P
A
Tetracyclines (e.g., doxycycline)
Glycylcyclines (e.g., tigecycline)
Elongation (translation)

DNA Gyrase Inhibition

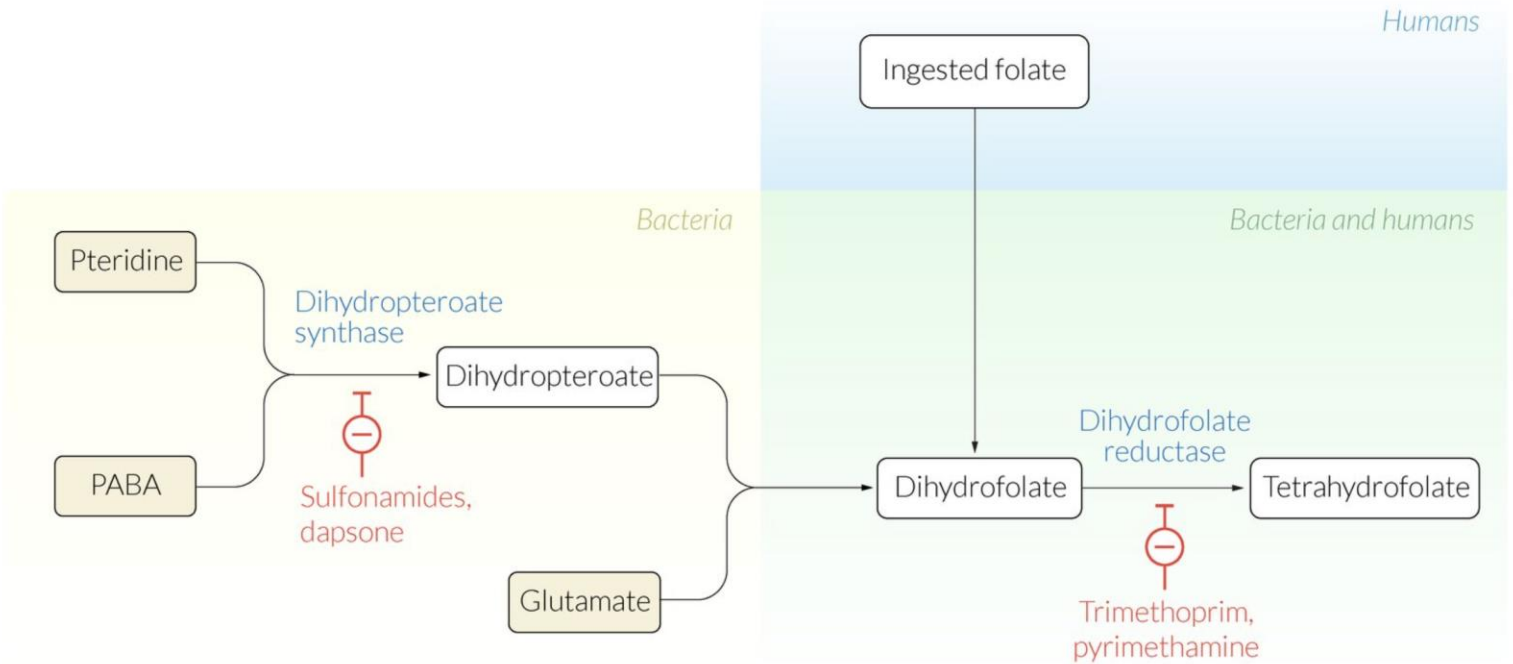
Antibacterial classes	Examples	Mechanism of action	Bacterial Activity	Mechanisms of resistance
Fluoroquinolones	Norfloxacin Moxifloxacin Gemifloxacin Ciprofloxacin Ofloxacin Levofloxacin Enoxacin	Inhibit prokaryotic topoisomerase II (DNA gyrase) and topoisomerase IV leading to inhibited DNA synthesis	Bactericidal and bacteriostatic	Mutation (chromosome-encoded) in DNA gyrase and topoisomerase IV Decreased cell wall permeability Efflux pumps (plasmid)

Disruption of DNA Integrity

Antibacterial classes	Examples	Mechanism of action	Bacterial Activity	Mechanisms of resistance
Nitroimidazoles	Metronidazole Tinidazole	Free radical formation leading to single-strand breaks in DNA	Bactericidal (antiprotozoal)	Reduced activation due to decreased enzymatic activity

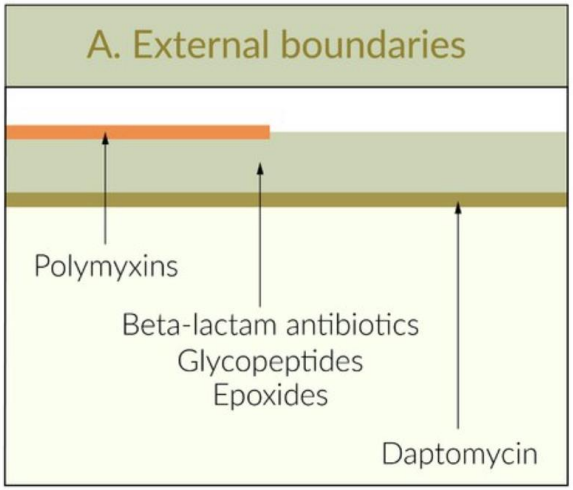
Inhibition of Folic Acid Synthesis and Reduction

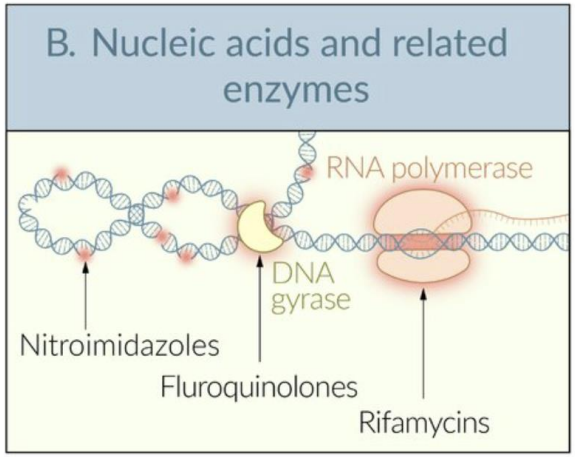
Antibacterial classes	Examples	Mechanism of action	Bacterial Activity	Mechanisms of resistance
Sulfonamides and diaminopyrimidines	Trimethoprim-sulfamethoxazole Sulfadiazine and pyrimethamine Sulfisozaxole	Prevent bacterial tetrahydrofolate formation leading to decreased DNA methylation	Bactericidal (Sulfamethoxazole Bacteriostatic (Trimethoprim)	Overproduction of para-aminobenzoate (PABA) Decreased uptake Structural changes on target enzymes Efflux pumps

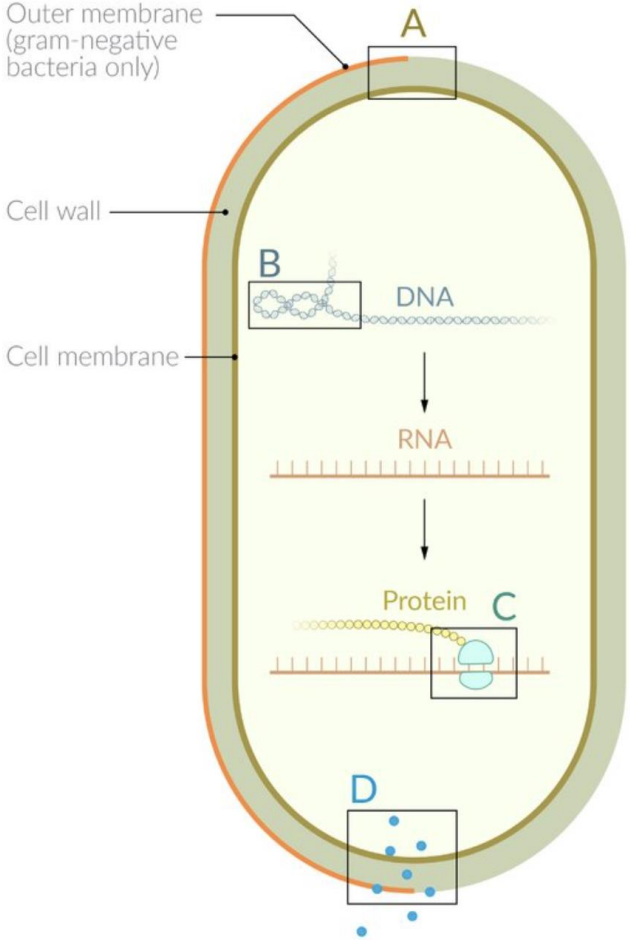

Humans
Ingested folate
Bacteria
Bacteria and humans
Pteridine
Dihydropteroate synthase
Dihydropteroate
PABA
Sulfonamides, dapsone
Glutamate
Dihydrofolate reductase
Dihydrofolate
Tetrahydrofolate
Trimethoprim, pyrimethamine

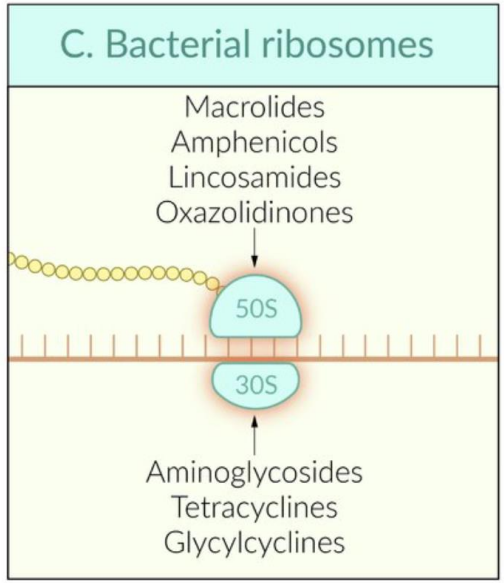
Other

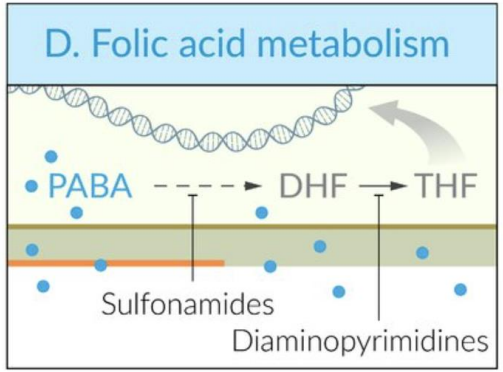
Antibacterial classes	Examples	Mechanism of action	Bacterial Activity	Mechanisms of resistance
Nitrofurans	Nitrofurantoin	Prodrug Binds to bacterial ribosomes leading to inhibition of DNA, RNA, and protein synthesis	Bacteriostatic Bactericidal in higher concentration	Enzyme-mediated reduction Efflux pumps


A. External boundaries
Polymyxins
Beta-lactam antibiotics
Glycopeptides
Epoxides
Daptomycin

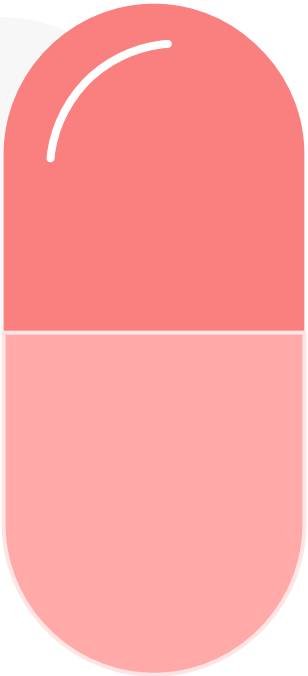

B. Nucleic acids and related enzymes
RNA polymerase
DNA gyrase
Nitroimidazoles
Fluroquinolones
Rifamycins


Outer membrane (gram-negative bacteria only)
A
Cell wall
B
DNA
Cell membrane
RNA
Protein
C
D


C. Bacterial ribosomes
Macrolides
Amphenicols
Lincosamides
Oxazolidinones
50S
30S
Aminoglycosides
Tetracyclines
Glycylcyclines


D. Folic acid metabolism
PABA
DHF
THF
Sulfonamides
Diaminopyrimidines

04 Bacterial Coverage



Penicillins

Natural Penicillins	Penicillinase-Resistant Penicillins	Amino-penicillins	Carboxy-penicillin	Ureido-penicillins	β-Lactam -β-Lactamase Inhibitor
Penicillin VK[1] **Penicillin G[1]**	**Nafcillin[4]** **Dicloxacillin[4]**	**Ampicillin[1]** **Amoxicillin[1]**	**Carbenicillin** **Ticarcillin[2]**	**Peperacillin[2]**	**Amox/Clav[3]** **Pip/Taz[3]**
Group A and B streptococci. Peptostreptococcus B anthracis Actinomycosis Corynebacterium Treponema	Inhibit penicillinase-producing staphylococci **Not active against Enterococcus, Gram negatives**	Active against the ß-lactamase negative *Escherichia coli, Proteus mirabilis, Salmonella, Shigella, and Haemophilus influenzae* Listeria GBS Enterococcus	Extended gram negatives Including pseudomonas More resistant to the chromosomal beta-lactamases of indole-positive *Proteus species, Enterobacter species, and Pseudomonas aeruginosa*.	More active against *klebsiella, enterococci* and *Bacteroides fragilis*	S. Aureus (MSSA) H. Influenzae M. Catarrhalis E. Coli Klebsiella, Bacteroides

[1]Oral dosage form available

[3]Anaerobe coverage

[2]Antipseudomonal activity notable

[4]MSSA

Cephalosporins

First generation	Second generation	Second generation (cephamycins)	Third generation	Fourth generation	Advanced generation and combination agents
Parenteral cephalosporins					
Cefazolin (Ancef, Kefzol) Cephalothin (Keflin, Seffin) Cephapirin (Cefadyl) Cephradine (Velosef)	Cefamandole (Mandol) Cefonicid (Monocid) **Cefuroxime (Kefurox, Zinacef)**	Cefmetazole (Zefazone) **Cefotetan (Cefotan)** **Cefoxitin (Mefoxin)**	Cefoperazone (Cefobid) **Cefotaxime (Claforan)** **Ceftazidime (Fortaz)** Ceftizoxime (Cefizox) **Ceftriaxone (Rocephin)** Moxalactam	**Cefepime (Maxipime)** Cefpirome (Cefrom)	**Ceftaroline (Teflaro)** **Cefiderocol (Fetroja)** Ceftobiprole (Zeftera) **Ceftolozane-tazobactam (Zerbaxa)** **Ceftazidime-avibactam (Avycaz, Zavicefta)** Cefoperazone-sulbactam
Oral cephalosporins					
Cefadroxil (Duricef, Ultracef) **Cephalexin (Keflex, Biocef, Keftab)** Cephradine (Velosef)	**Cefaclor (Ceclor)** **Cefprozil (Cefzil)** **Cefuroxime-axetil (Ceftin)** Loracarbef (Lorabid)		**Cefdinir (Omnicef)** Cefditoren (Spectracef) **Cefixime (Suprax)** **Cefpodoxime-proxetil (Vantin)** Ceftibuten (Cedax)		

Cephalopsporins

1st Generation	2nd Generation	3rd Generation	4th Generation	5th Generation
Cefadroxil[1] Cephalexin[1] Cefazolin	Cefprozil[1] Cefuroxime [1] Cefoxitin[3] Cefotetan[3]	Cefixime[1] Ceftazidime[2] Cefotaxime Ceftriaxone	Cefepime[2]	Ceftibiprole[2]
Not active against enterococci				
Staphylococci (MSSA), S. pyogenes,			Gram-positives – MSSA, S. pneumoniae	
Some gram-negative rods (incl. E. coli)	Some gram-negatives (incl. H. flu, M. catarrhalis & Neisseria spp.)	Enhanced gram-negative activity: Enterobacteriaceae		

[1]Oral dosage form available

[3]Anaerobe coverage

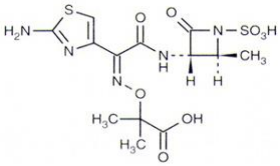
[2]Antipseudomonal activity notable

Carbapenems

	Group 1	Group 2	Group 3
Agents	Ertapenem Panipenem Tabipenem	Imipenem Meropenem Doripenem Biapenem	Tomopenem Razupenem
Activity against non-fermenters (*pseudomonas, A. baumanii*)	No	Yes	Yes
Activity against MRSA	No	No	Yes

Carbapenems

Drug	Strep spp. & MSSA	Entero-bacteriaeae	Non-fermentors		Anaerobes
			Pseudomonas	Acinetobacter	
Imipenem	+	+	+	++	+
Meropenem	+	+	++	+	+
Ertapenem	+	+	Limited activity		+
Doripenem	+	+	++	++	+
Not active against stenotrophomonas, Flavobacterium, MRSA Not active against Chlamydia, Mycoplasma, or Legionella					



Monobactams

Monobactams			
Aztreonam	**Carumonam**	**Pirazmonam**	**Tigemonam**
Aztreonam/avibactam			

Gram-negatives
E. coli, *K. pneumoniae*, *P. mirabilis*, *S. marcescens*, *H. influenzae*, *M. catarrhalis*, *Enterobacter*, *Citrobacter*, *Providencia*, *Morganella*, *Salmonella*, *Shigella*
Pseudomonas aeruginosa
No activity against gram-positives or anaerobes

Macrolides/Ketolides

Drug	Strep spp. & MSSA	Pneumococcus	Gram negative coocci	Atypicals	Entero-bacteriaeae and other Gram -	Anaerobes
Erythromycin	±*	+	±&	+	-	-
Azithromycin	±*	+	±&	+	-	-
Clarithromycin	±*	+	±&	+	-	-
Telithromycin	+	+	+	+	-	-

*Limited sterptococcus Group A-B-C-D
& Limited Neisseria gonorrhea

Fluroquinolones

Drug	Strep spp. & MSSA	Enterobacteriaeae	Non-fermentors		Anaerobes
			Pseudomonas	Acinetobacter	
Ciprofloxacin Ofloxacin	±		+	±	-
Pefloxacin	±	+	±	±	-
Levofloxacin	+	+	±	-	±
Moxifloxacin	+	+	-	-	+
Gemifloxacin	+	+/-	-	-	
Gatifloxacin	+	+	-	-	±

Aminoglycosides

Drug	*Enterococcus spp. and Staphylococcus spp*	Enterobacteriaeae	Non-fermentors		Anaerobes
			Pseudomonas	Acinetobacter	
Gentamicin*	±ƒ	++	+	++	-
Tobramycin*	±ƒ	+	+++	++	-
Amikacin*	±ƒ	++	+++	++	-
Streptomycin*	±ƒ	+	+	+	-
Neomycin	Mainly used topically or orally for gut decontamination				-
Plazomicin	±ƒ	+	+	+	-

ƒ Synergy with beta-lactams or vancomycin

*Effective against Yersinia pestis (plague), Francisella tularensis (tularemia), Brucella spp., and Burkholderia pseudomallei (melioidosis)

Tetracyclines

Chlamydia	*Staphylococcus aureus* (including MRS)	VRE (susceptible strains)	Whipple's disease
Legionellae's disease	*Borrelia recurrentis*	Melioidosis	Acne
Mycoplasma pneumoniae	Brucellosis	Nocardiosis	Meningococcal prophylaxis (minocycline0
Traveler's diarrhea	Ehrlichiosis and anaplasmosis	Tularemia	Amebiasis
Early Lyme disease	Leptospirosis	Syphilis	*Mycobacterium marinum*
Chloroquine resistant malaria	*Vibrio vulnificus*	Actinomycosis	

Clindamycin

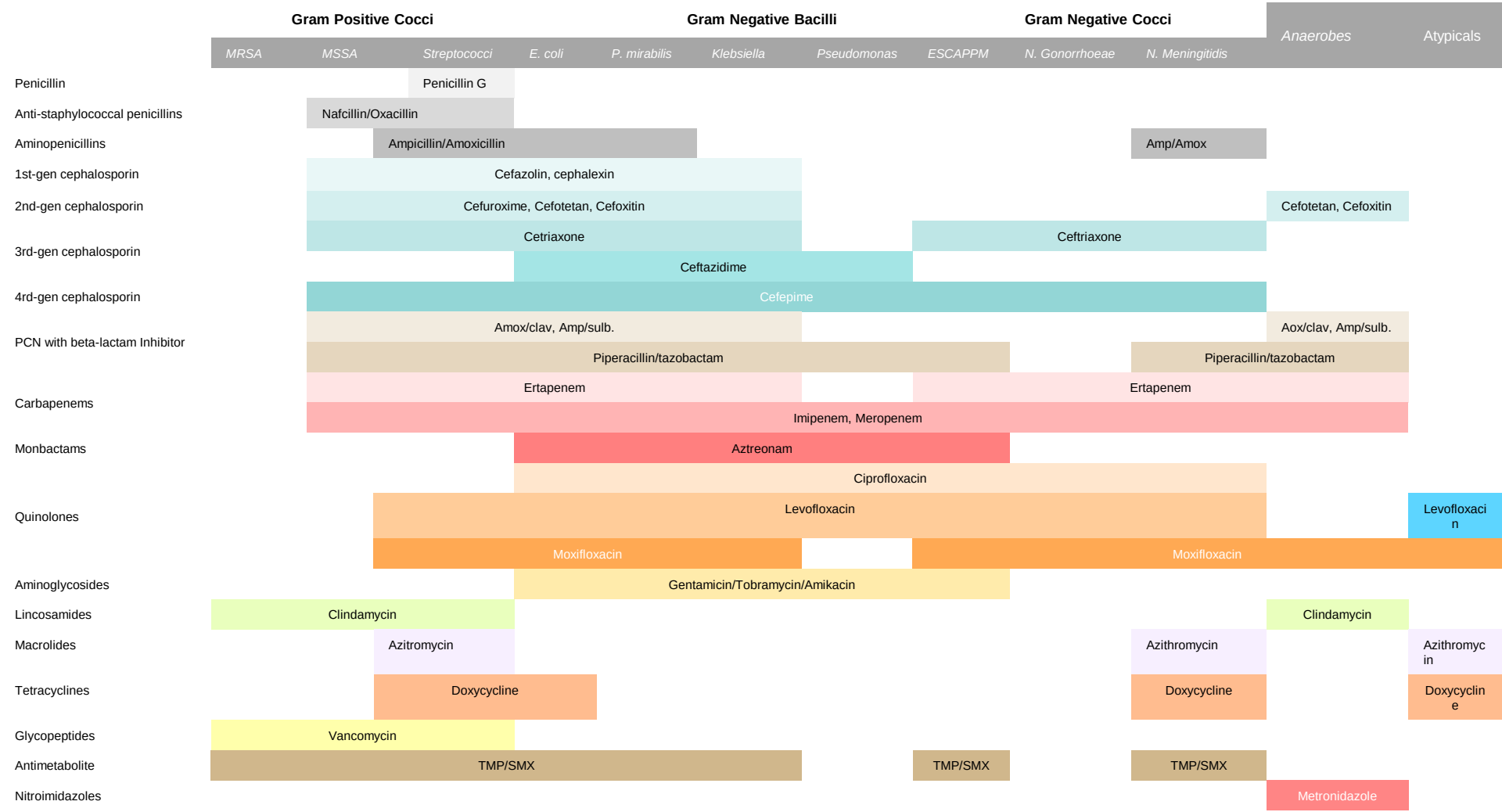
Gram Positive Organisms	Anaerobes	Others
Staphylococci (including MRSA)	*B. Fragilis (increasing resistance)*	*Toxoplasma gondii*
Viridans group streptococci	*Clostridium perfringens*	*Actinomyces israelii*
Streptococcoccus pyogenes	*Fusobacterium spp*	*Nocardia astreroides*
Streptococcus pneumoniae	*Provetella*	*Babesia spp.*
	Peptostreptococcus spp.	*Plasmodium vivax and falciparum* (in combination with chloroquine)

Trimethoprim + Sulfamethoxazole

Staphylococcus aureus (including MRSA)	Neisseria species	*Pneumocystis carinii* (now jiroveci)
Streptococcus pneumoniae	*Hemophilus influenzae*	*Actinomyces israelii*

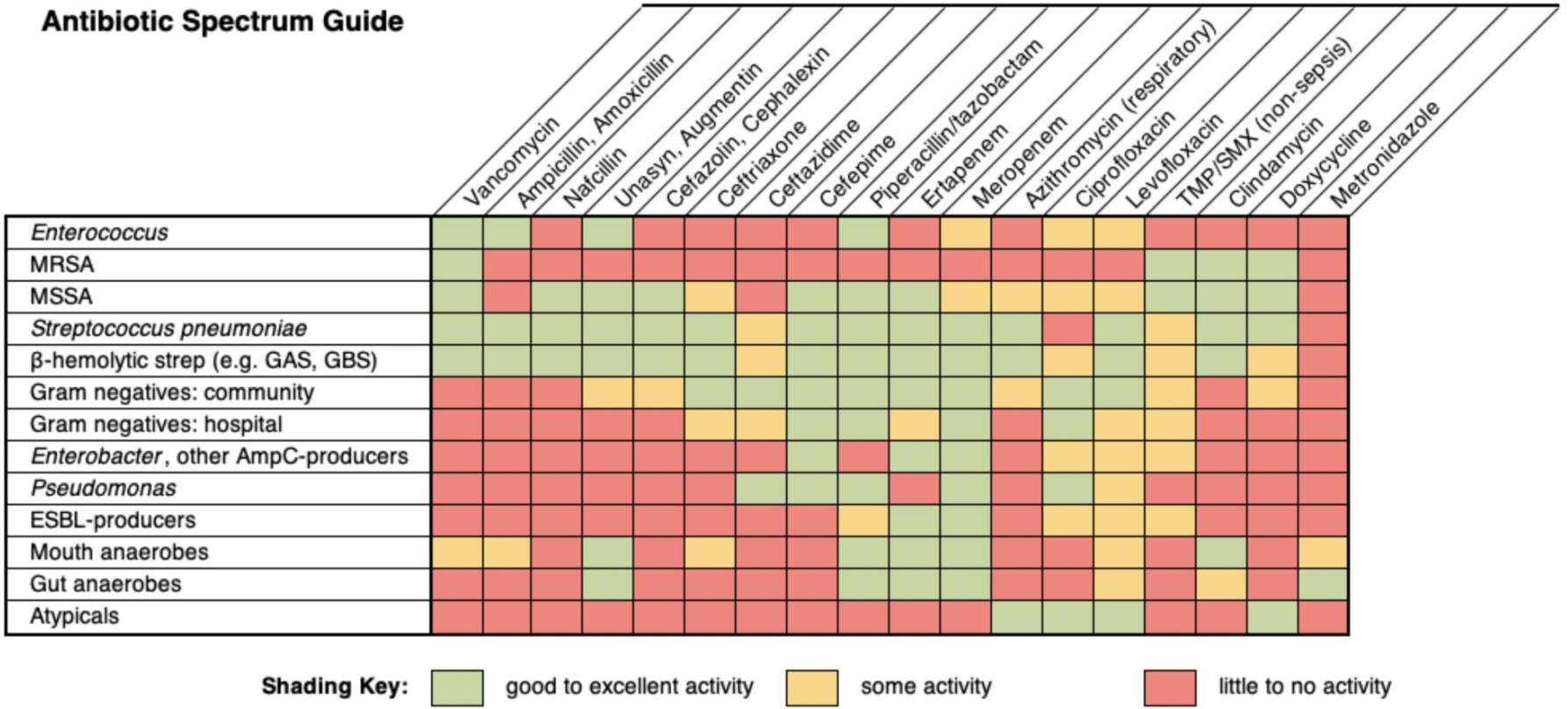
Other Antibiotics

Nitrofurantoin UTI, prophylaxis and Tx)	**Tigecycline** Gram-positive, gram-negative, and anaerobes. Bacteriostatic	**Daptomycin** Gram-positive bacteria, including methicillin-susceptible and -resistant Staphylococcus aureus (MSSA/MRSA) and vancomycin-resistant Enterococci (VRE) Not for pneumonia
Rifampin (Combination therapy for penicillin-resistant staphylococci	**Linezolid** VRE and MRSA Bacteriostatic	**Metronidazole** Bacteroides and Fusobacterium spp., peptostreptococci and Clostridia spp.



ESCAPPM: Enterobacter spp, Serratia spp, Citrobacter freundii, Aeromonas spp, Proteus spp, Providencia spp, Morganella morganii

Bacterial coverage



https://idmp.ucsf.edu/content/antibiotic-stewardship-and-spectrum-guide

05 Contra-indications

Contraindication

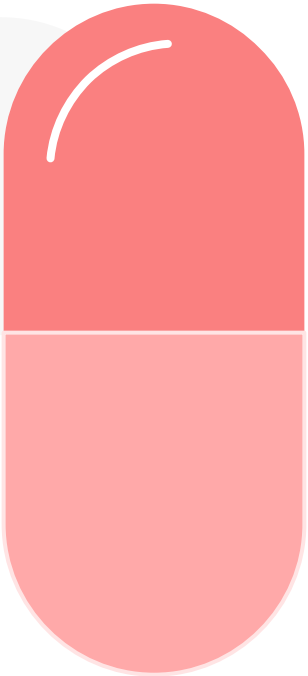
	Absolute contraindication	Relative contraindication	Safe to use

Children	• Tetracyclines: < 8 years old (except doxycycline)
	• Glycylcyclines: < 8 years old
	• Chloramphenicol
	• Fluoroquinolones
	• Sulfonamides and diaminopyrimidines: < 2 years old
	• Nitrofurans: < 1 month old
	• Ethambutol: young children who are unable to report visual changes
		• Polymyxin: < 2 years old
		• Streptogramin: < 16 years old
		• Nitroimidazole
		• Ethambutol: < 13 years old
		• Macrolides
		  ◦ Erythromycin: < 12 years old
		  ◦ Clarithromycin and azithromycin: < 6 months old
			• β-lactams
			• Epoxide
			• Lipopeptide
			• Glycopeptide
			• Aminoglycosides
			• Lincosamides
			• Oxazolidinones
			• Rifamycins
			• Isoniazid
			• Pyrazinamide
			• Dapsone

Pregnant women	• Aminoglycosides • Tetracyclines • Glycylcyclines • Chloramphenicol • Fluoroquinolones • Sulfonamides with diaminopyrimidines • Macrolides (clarithromycin and erythromycin estolate)	• Lincosamides: 1st trimester • Oxazolidinones • Nitrofurans • Rifamycins • Isoniazid • Pyrazinamide • Ethambutol • Dapsone • Glycopeptide • Polymyxin • Streptogramin • Nitroimidazole	• β-lactams • Epoxide • Lipopeptide • Macrolides (azithromycin and erythromycin)

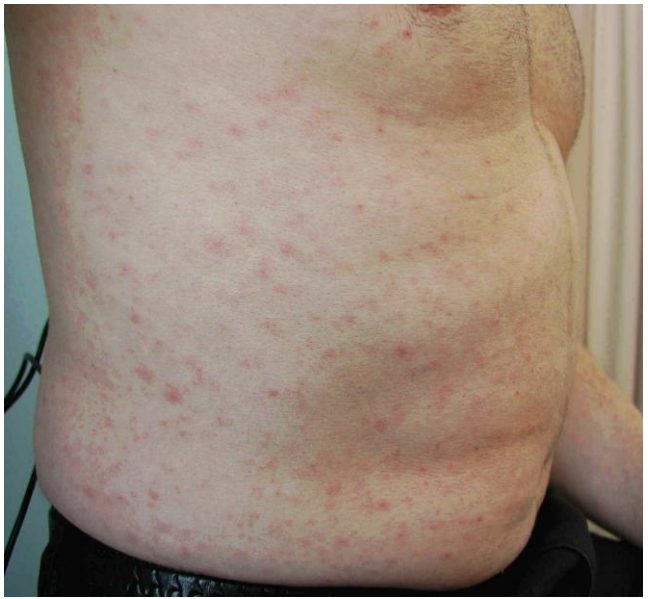
Breastfeeding women	• Aminoglycosides • Tetracyclines • Glycylcyclines • Lincosamides • Chloramphenicol • Fluoroquinolones • Sulfonamides with diaminopyrimidines • Nitrofurans • Rifamycins	• Macrolides • Oxazolidinones • Nitroimidazole • Pyrazinamide • Ethambutol • Dapsone • Glycopeptide • Epoxide • Streptogramin	• β-lactams • Lipopeptide • Polymyxin • Isoniazid
Individuals with renal failure	• Epoxides • Aminoglycosides • Tetracyclines • Sulfonamides with diaminopyrimidines • Nitrofurans	• Polymyxin • Chloramphenicol • Fluoroquinolones • Isoniazid • Dapsone • Macrolides (clarithromycin)	• β-lactams • Glycopeptide • Lipopeptide • Lincosamides • Streptogramin • Oxazolidinones • Nitroimidazole • Rifamycins • Pyrazinamide • Ethambutol • Macrolides (erythromycin and azithromycin)
Individuals with hepatic failure	• Tetracyclines • Macrolides (azithromycin and clarithromycin) • Sulfonamides with diaminopyrimidines • Nitrofurans • Pyrazinamide	• Glycylcyclines • Macrolides (erythromycin) • Chloramphenicol • Fluoroquinolones • Nitroimidazole • Rifamycins • Isoniazid • Dapsone	• β-lactams • Glycopeptide • Epoxide • Lipopeptide • Polymyxin • Aminoglycosides • Lincosamides • Streptogramin • Oxazolidinones • Ethambutol

06 Side Effects

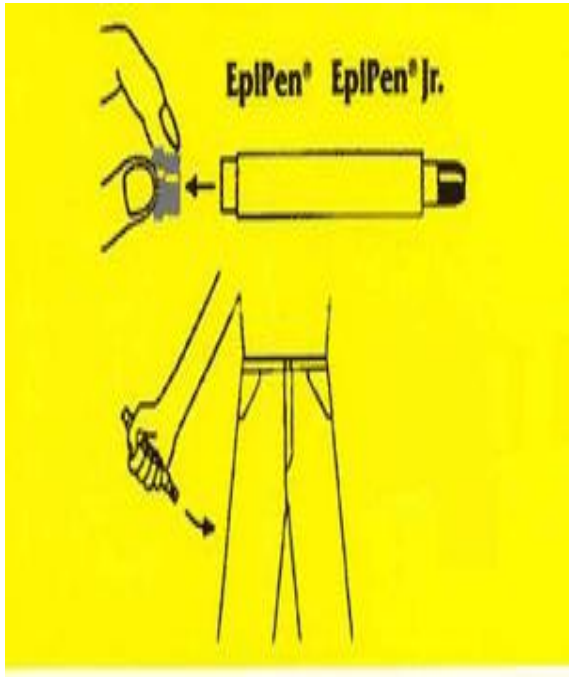


Hypersensitivity Reactions

- 5% of patients with penicillins will develop a hypersensitivity reaction (penicilloic acid).
- Rashes - most common reaction. 50% do not have a recurrent rash.
- Ampicillin - rash in 50-100% of patients with mononucleosis.
- Very little cross-allergenicity with aztreonam due to its low immunogenic potential. May be a safe alternative for pcn allergic patients.



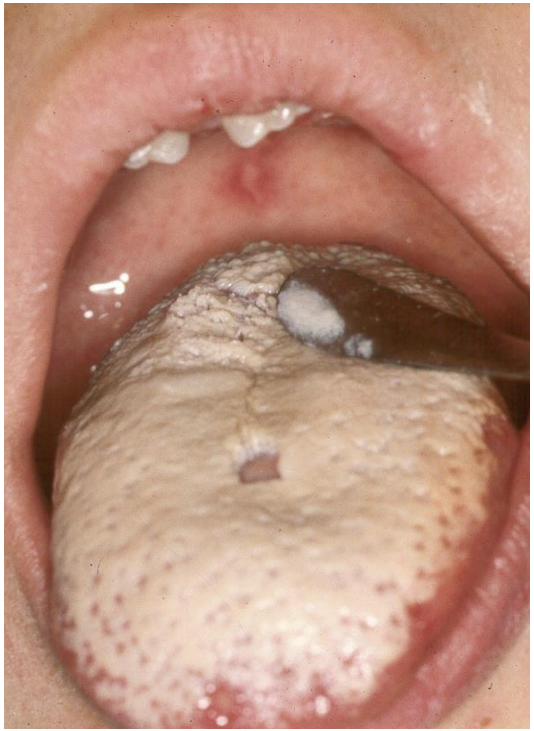
Anaphylaxis with Penicillins



- 1/10000 patients
  - Hives, angioedema, rhinitis, asthma, and anaphylaxis.
  - 10% mortality rate.
  - Anaphylaxis possible after negative skin testing.
  - Desensitization is an option if penicillin must be given.
  - Avoid all other B-lactams.

Cephalosporins

- 5-10% cross-sensitivity with pcn allergic pts.
- 1-2% hypersensitivity reactions in non-pcn allergic pts.
- Broader spectrum leads to opportunistic infections (candidiasis, C. difficile colitis).



β-Lactams

Neurologic

- notably high dose PCN & carbapenems
- Increased incidence w/ high doses &/or renal insufficiency
- Irritability, jerking, confusion, seizures

Hematologic

- Leukopenia, neutropenia, thrombocytopenia with prolonged therapy (> 2 weeks)

Gastrointestinal

- Increased LFTs
- Nausea
- Vomiting
- Diarrhea
- Pseudomembranous colitis

Interstitial Nephritis:

- Type IV hypersensitivity reaction
- Especially with nafcillin

Macrolides

Gastrointestinal	Thrombophlebitis	Cardiac	Other
• Up to 33 % • Nausea, vomiting, diarrhea, dyspepsia • Erythro > > clarithro, azithro	• IV Erythro & Azithro	• QTc prolongation • ventricular arrhythmias	• Ototoxicity (high dose erythro) • Drug-drug interaction

Pseudomembranous Colitis

- Clindamycin > cephalosporins > aminopenicillins.
    - Abdominal pain, fever, leukocytosis, bloody stool…
    - Diarrhea commonly develops on days 4-9 of treatment.
    - Typically resolves14 days after stopping the antibiotic.
    - Treat with oral vancomycin

Aminoglycosides

Ototoxic

- Associated with high peak levels and prolonged therapy.
- Pts on loop diuretics, vancomycin and cisplatin are at higher risk.
- Cochlear and vestibular.
- Concentrates in endolymph and perilymph.

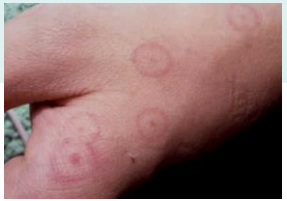
Nephrotoxic.

- Proximal tubule damage.

Trimethoprim + Sulfamethoxazole

Dermatologic:

- Rashes are common
- Ranging from photodermatitis to Stevens-Johnsons syndrome.



Hematologic

- Hemolytic anemia (G6PDH deficient pts.)
- Neutropenia
- Thrombocytopenia (up to 80% of HIV pts)

Drug interactions:

- Warfarin
- Phenytoin
- Methotrexate.

Fluoroquinolones

Gastrointestinal	CNS	Cardiac	Articular Damage:	Dysglycemias	Hepatotoxicity	Drug interactions:
• Nausea • Vomiting • Diarrhea	• Headache • Agitation • Insomnia • Dizziness • Rarely, hallucinations	• Prolongation QTc interval • Led to withdrawal of grepafloxacin, sparfloxacin	• Cartilage damag • Arthralgia	• Led to withdrawal of gatifloxacin	• Led to withdrawal of trovafloxacin	• May increase levels of theophylline, warfarin, caffeine and cyclosporine.

Aminoglycosides

Nephrotoxicity

- Direct proximal tubular damage - reversible if caught early
- Risk factors:
  - High troughs
  - Prolonged duration of therapy
  - Underlying renal dysfunction
  - Concomitant nephrotoxins

Ototoxicity

- 8th cranial nerve damage – irreversible vestibular and auditory toxicity
  - Vestibular: dizziness, vertigo, ataxia
  - Auditory: tinnitus, decreased hearing
- Risk factors: same as for nephrotoxicity

Vancomycin

Anaphylaxis

- Immune-mediated
- Rare
- Intense pruritus, tachycardia, hypotension, erythematous rash, and bronchospasm

Infusion related

- Non-immune mediated
- Red-Man Syndrome
- Intense pruritus, tachycardia, hypotension, rash involving face, neck, upper trunk, back and upper arms
  - Resolves spontaneously after discontinuation
  - Lengthen infusion (over 2 - 3 hr) and/or pretreat with antihistamines

Hematologic

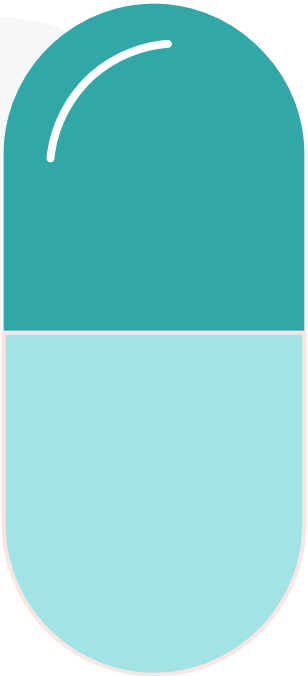
- Neutropenia
- Eosinophilia
- Thrombocytopenia

Others

- C-diff
- Hypersensitivity reaction
- Nephrotoxicity
- Ototoxicity

07

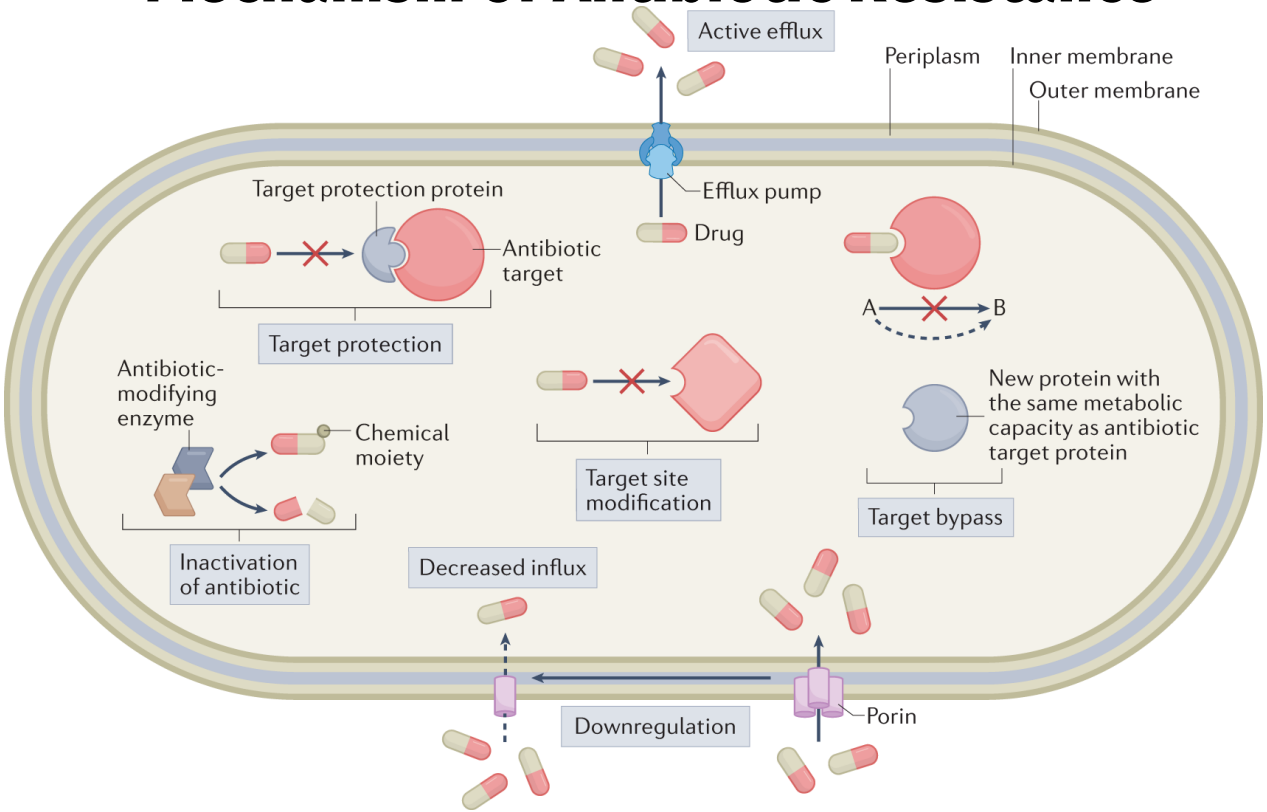
Antibiotic Resistance



Definitions

Multidrug-resistant	• Isolate is nonsusceptible to at least one agent in three or more antibiotic groups (ie, third- or fourth-generation cephalosporins, fluoroquinolones, aminoglycosides, carbapenems, piperacillin-tazobactam, ampicillin-sulbactam).
Extensively drug-resistant	• Isolate is nonsusceptible to at least one agent in all but two or fewer antibiotic classes.
Carbapenem-resistant	• Isolate is nonsusceptible to at least one antipseudomonal carbapenem.
Pandrug-resistant	• Isolate is nonsusceptible to all agents.

Mechanism of Antibiotic Resistance



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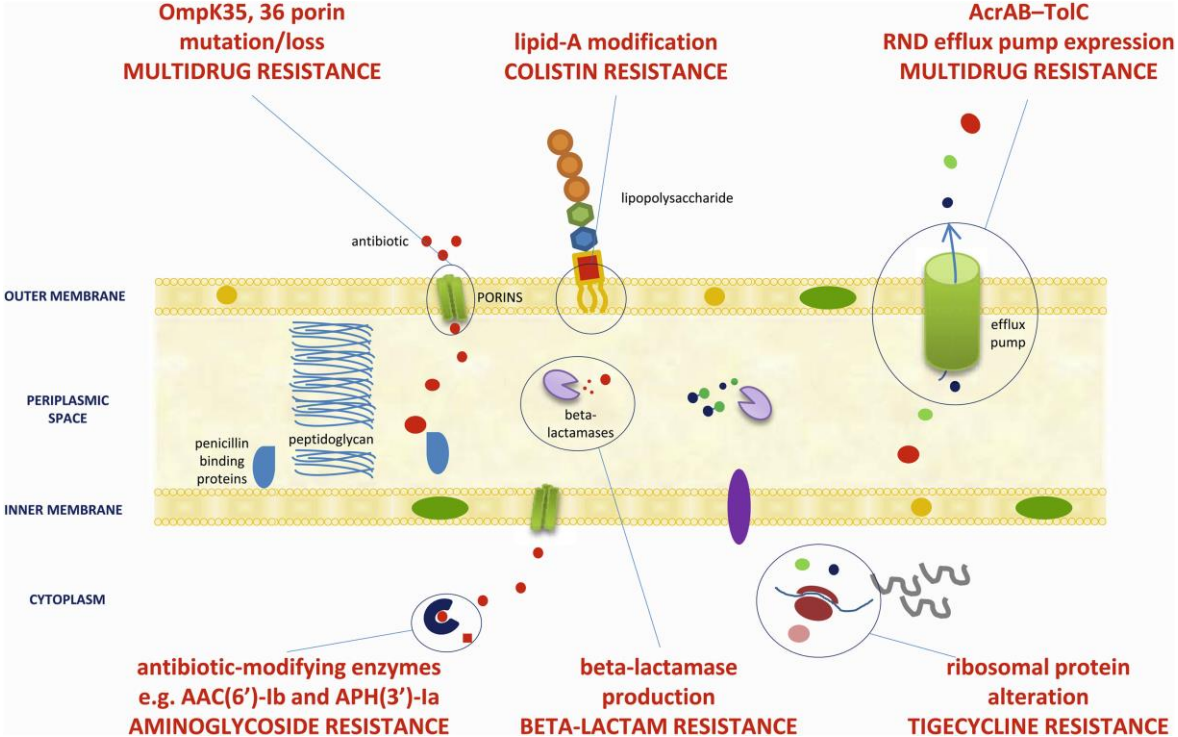
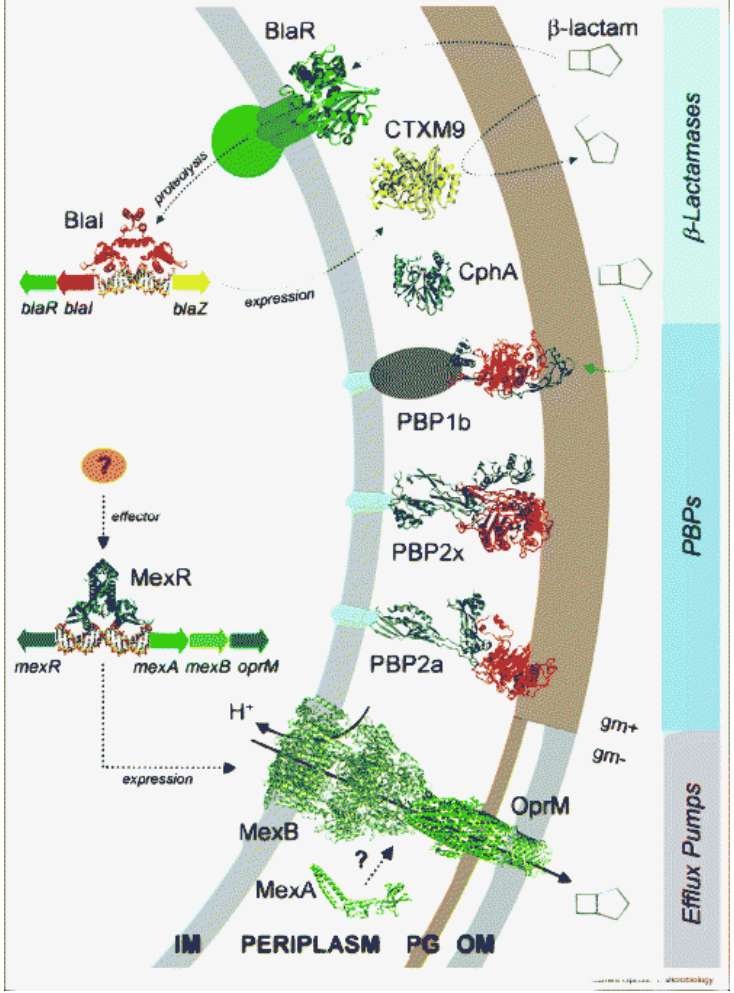
Major Mechanisms of Antimicrobial Resistance

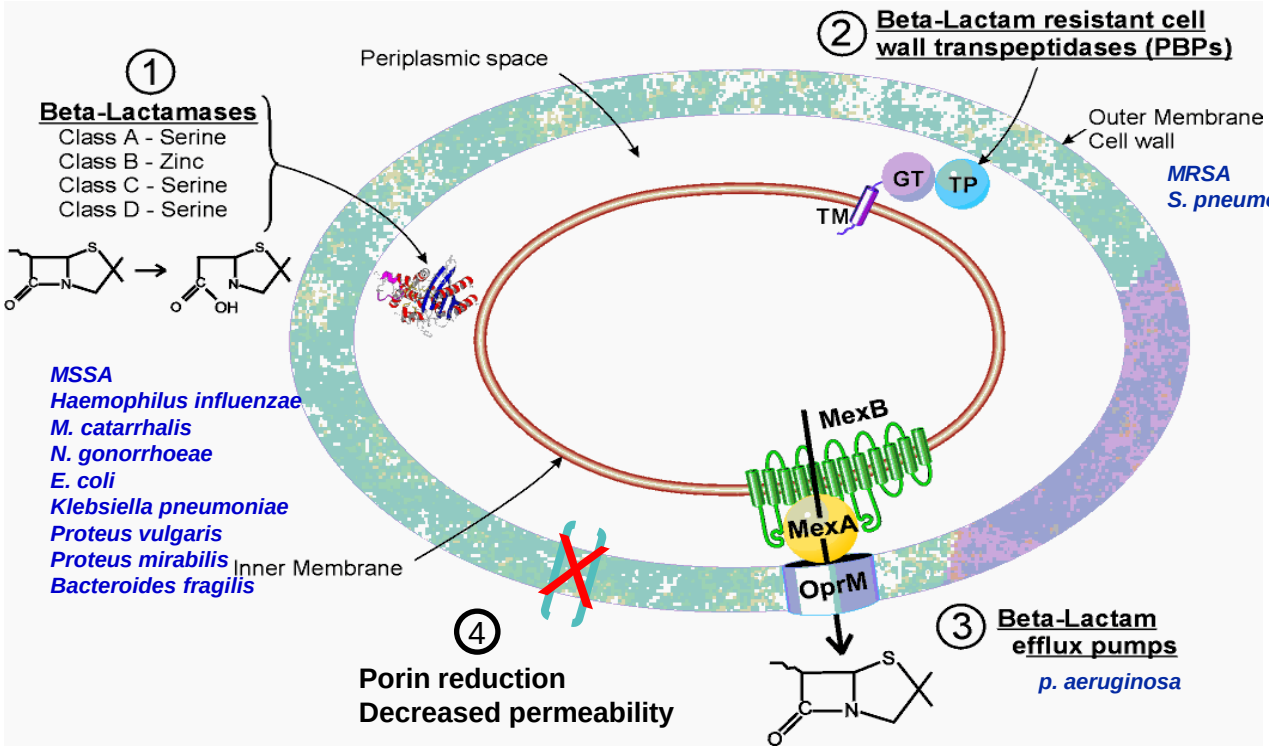


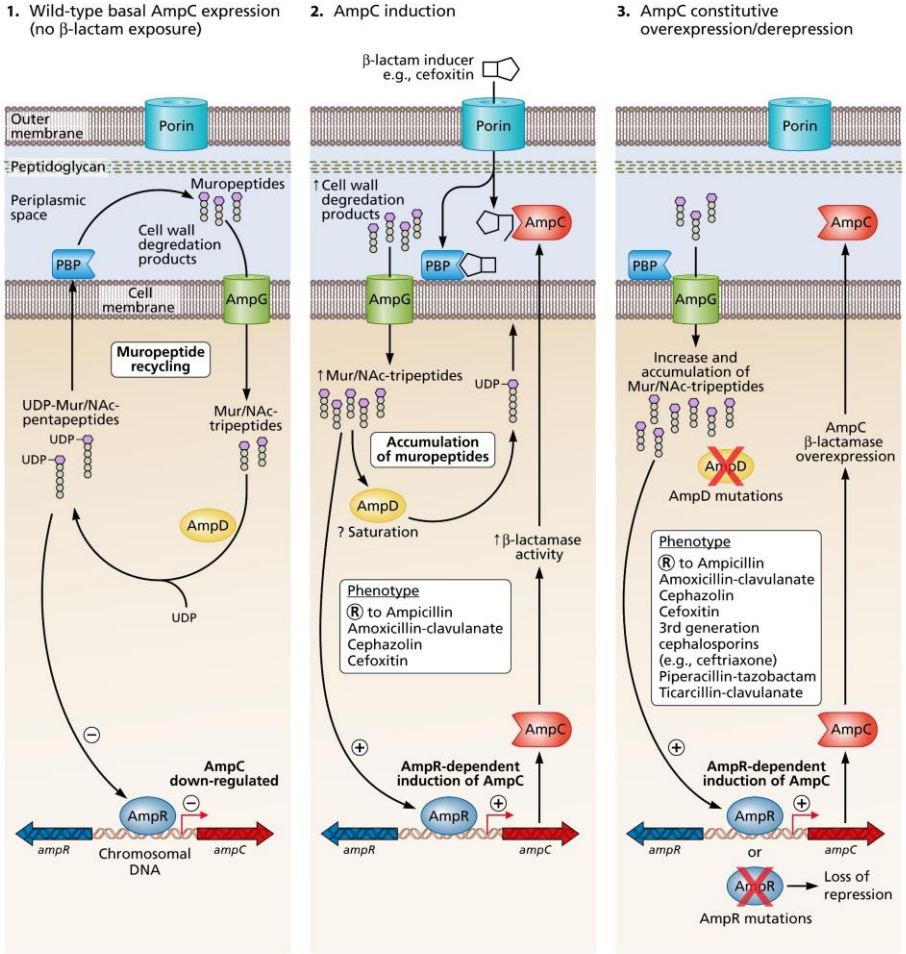
E. Durante-Mangoni, R. Andini, R. Zampino, Management of carbapenem-resistant Enterobacteriaceae infections, Clinical Microbiology and Infection, Volume 25, Issue 8, 2019, Pages 943-950,



Mark S Wilke, Andrew L Lovering, Natalie CJ Strynadka, β-Lactam antibiotic resistance: a current structural perspective, Current Opinion in Microbiology, Volume 8, Issue 5, 2005, Pages 525-533,

Major Bacterial Beta-Lactam Resistance Mechanisms





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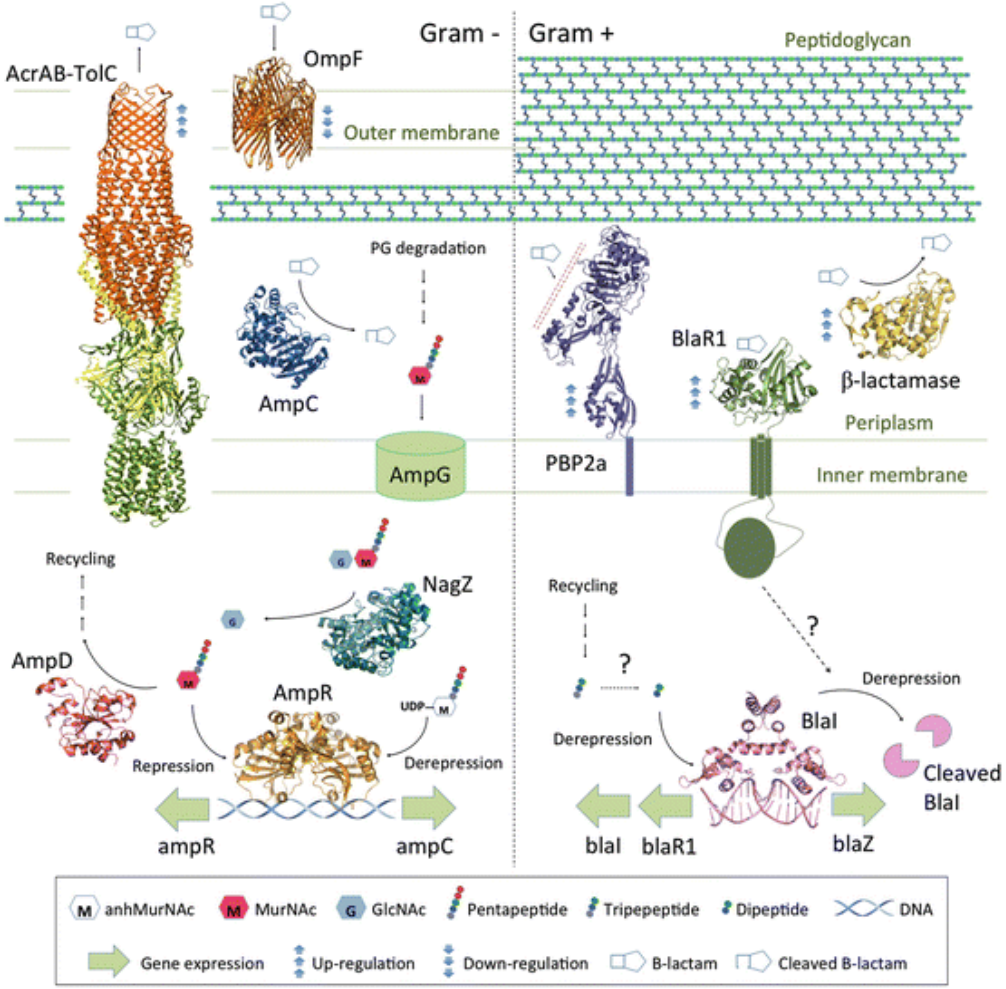
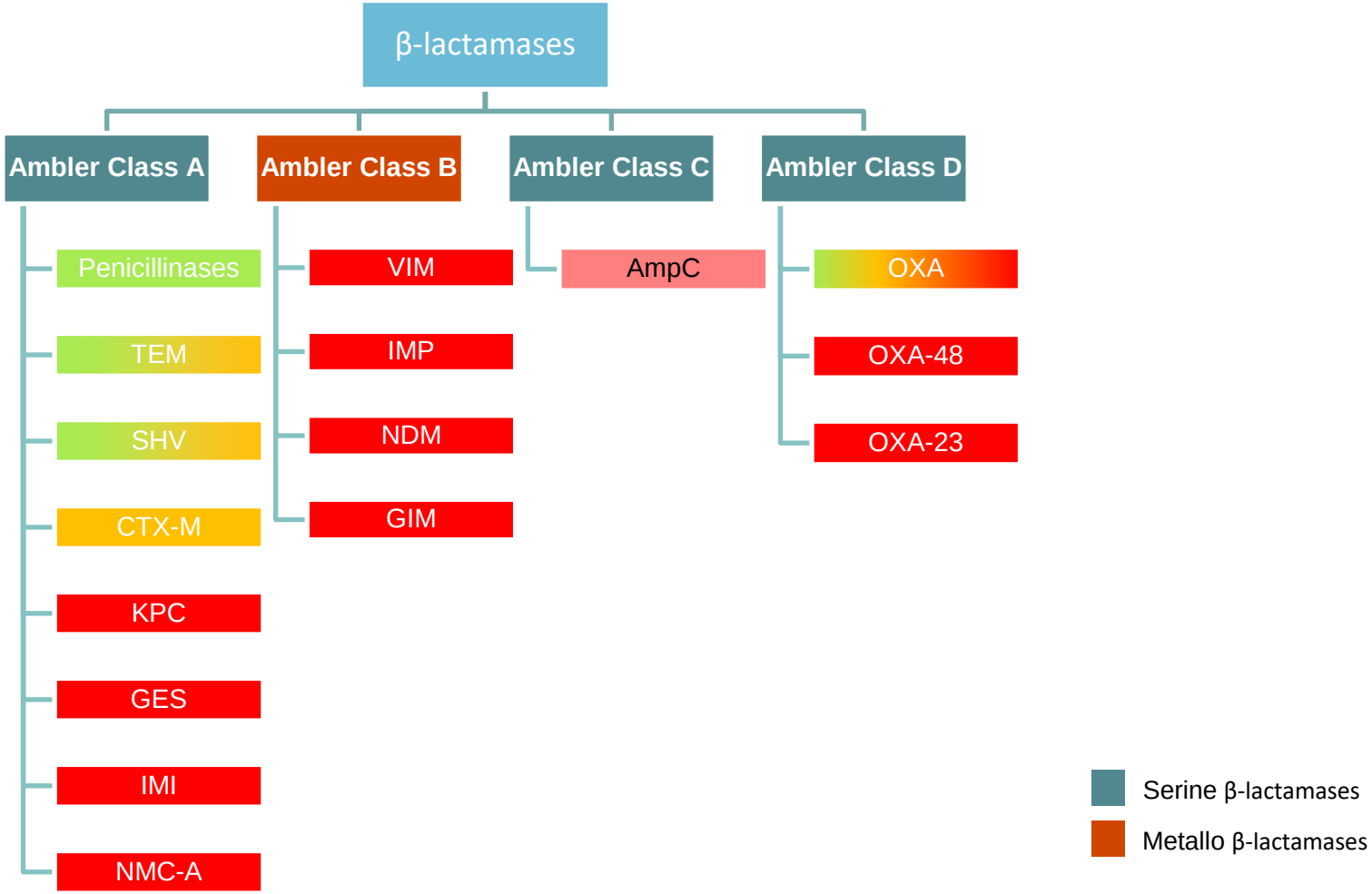
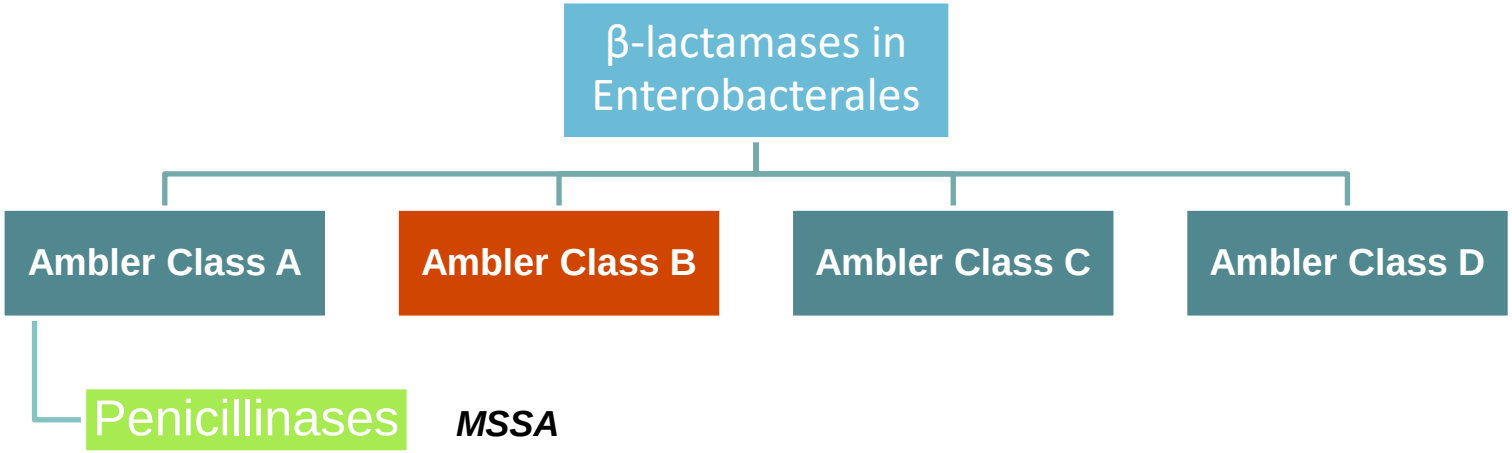


King, D.T., Sobhanifar, S., Strynadka, N.C.J. (2014). The Mechanisms of Resistance to β-Lactam Antibiotics. In: Gotte, M., Berghuis, A., Matlashewski, G., Wainberg, M., Sheppard, D. (eds) Handbook of Antimicrobial Resistance. Springer, New York, NY. https://doi.org/10.1007/978-1-4939-0667-3_10-1

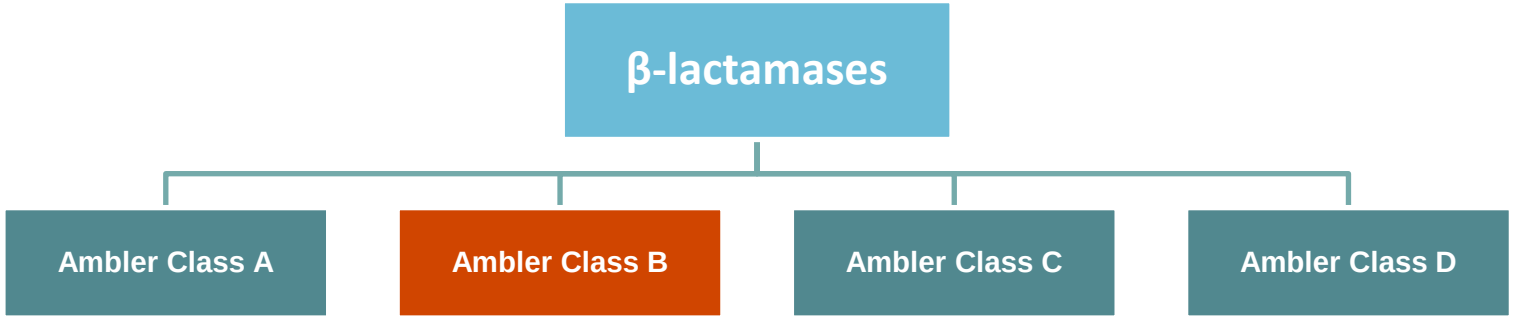
Ambler Classification of Beta-lactamases


β-lactamases
Ambler Class A
Ambler Class B
Ambler Class C
Ambler Class D
Penicillinases
TEM
SHV
CTX-M
KPC
GES
IMI
NMC-A
VIM
IMP
NDM
GIM
AmpC
OXA
OXA-48
OXA-23
Serine β-lactamases
Metallo β-lactamases



Substrates								
Penicillin	1st Gen. Ceph.	2nd Gen. Ceph.	Cefoxitin	3rd Gen. Ceph.	4th Gen. Ceph.	β-lactamase Inhibitors	Aztreonam	Carbapenems

Narrow-spectrum ESBL Broad-spectrum Carbapenemase



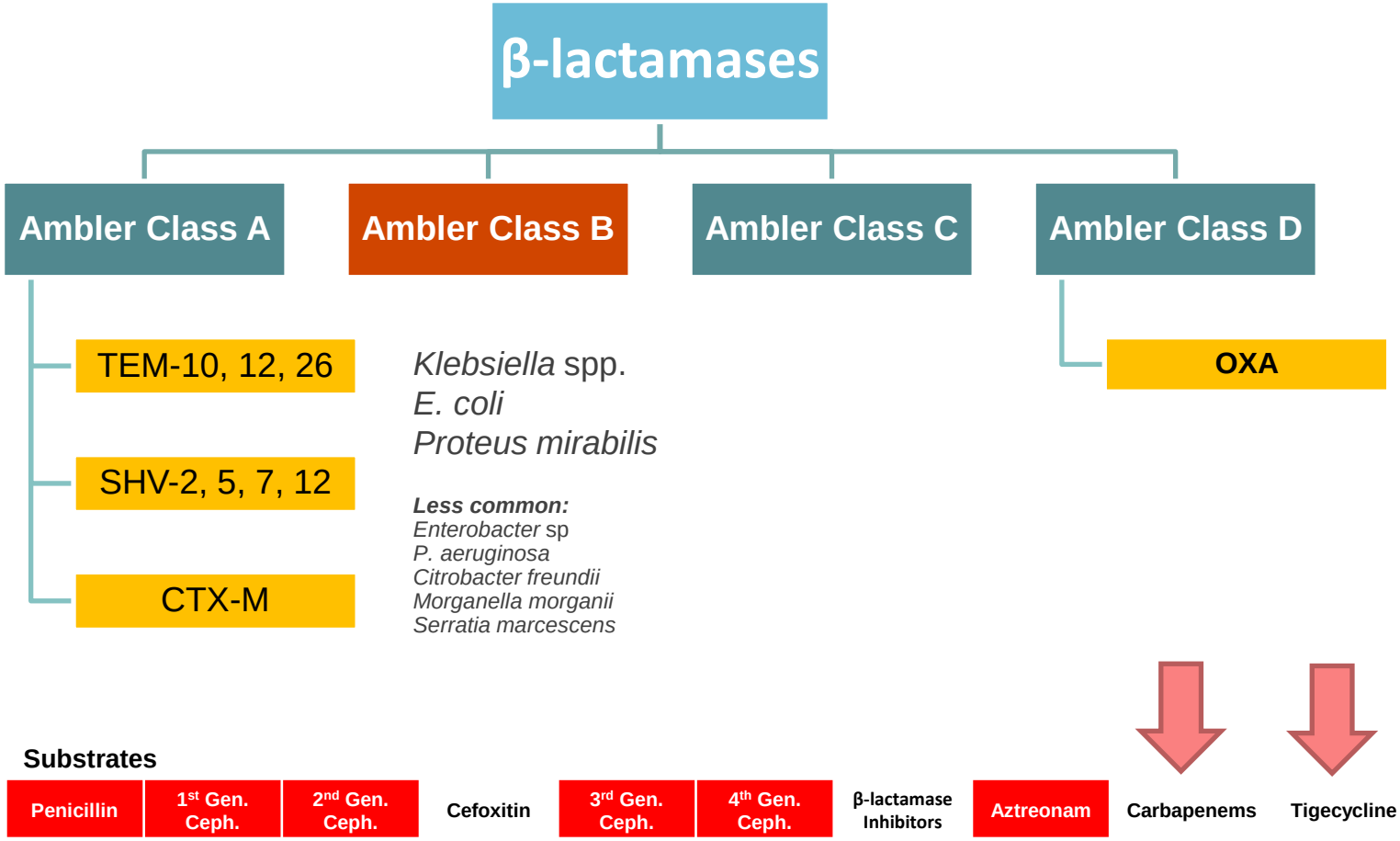
- TEM-1, 2
- SHV-1

MSSA
Haemophilus influenzae
M. catarrhalis
N. gonorrhoeae
E. coli
Klebsiella pneumoniae
Proteus vulgaris
Proteus mirabilis
Bacteroides fragilis

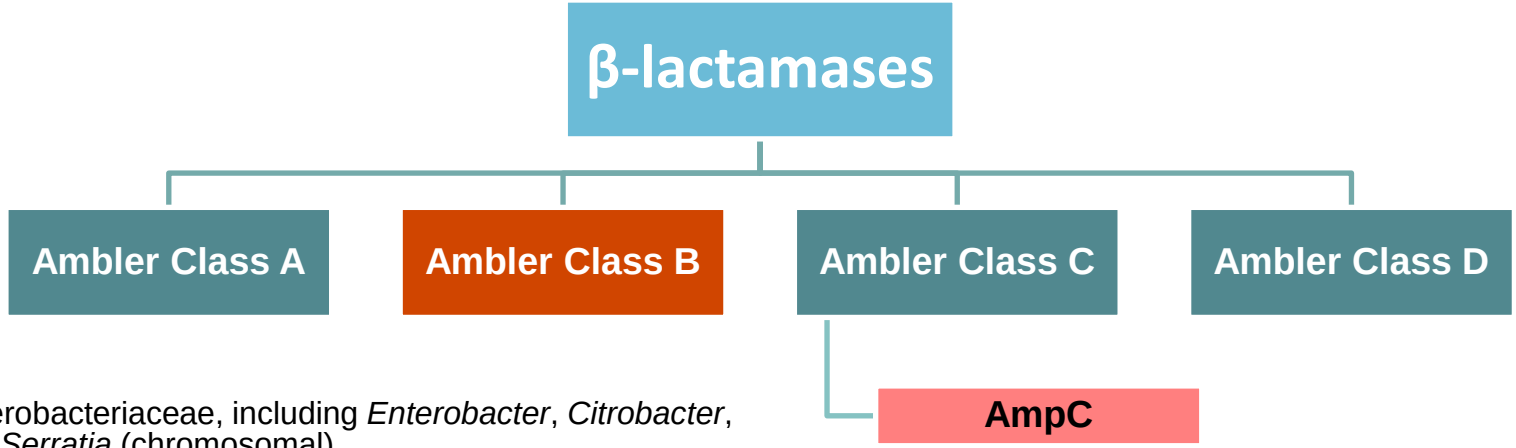
Substrates

Penicillin	1st Gen. Ceph.	2nd Gen. Ceph.	Cefoxitin	3rd Gen. Ceph.	4th Gen. Ceph.	β-lactamase Inhibitors	Aztreonam	Carbapenems

Narrow-spectrum ESBL Broad-spectrum Carbapenemase



Narrow-spectrum ESBL Broad-spectrum Carbapenemase



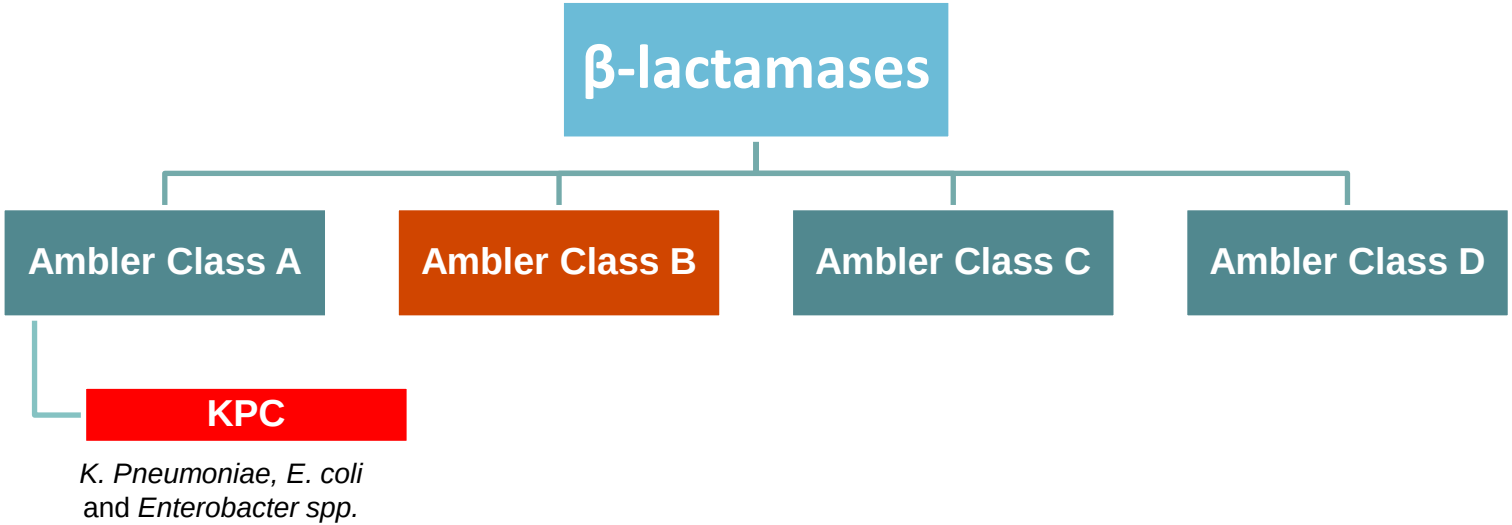
Enterobacteriaceae, including *Enterobacter*, *Citrobacter*, and *Serratia* (chromosomal)

Plasmid-mediated AmpC b-lactamases (Salmonella spp., E. coli)

Substrates

Penicillin	1st Gen. Ceph.	2nd Gen. Ceph.	Cefoxitin	3rd Gen. Ceph.	4th Gen. Ceph.	β-lactamase Inhibitors	Aztreonam	Carbapenems

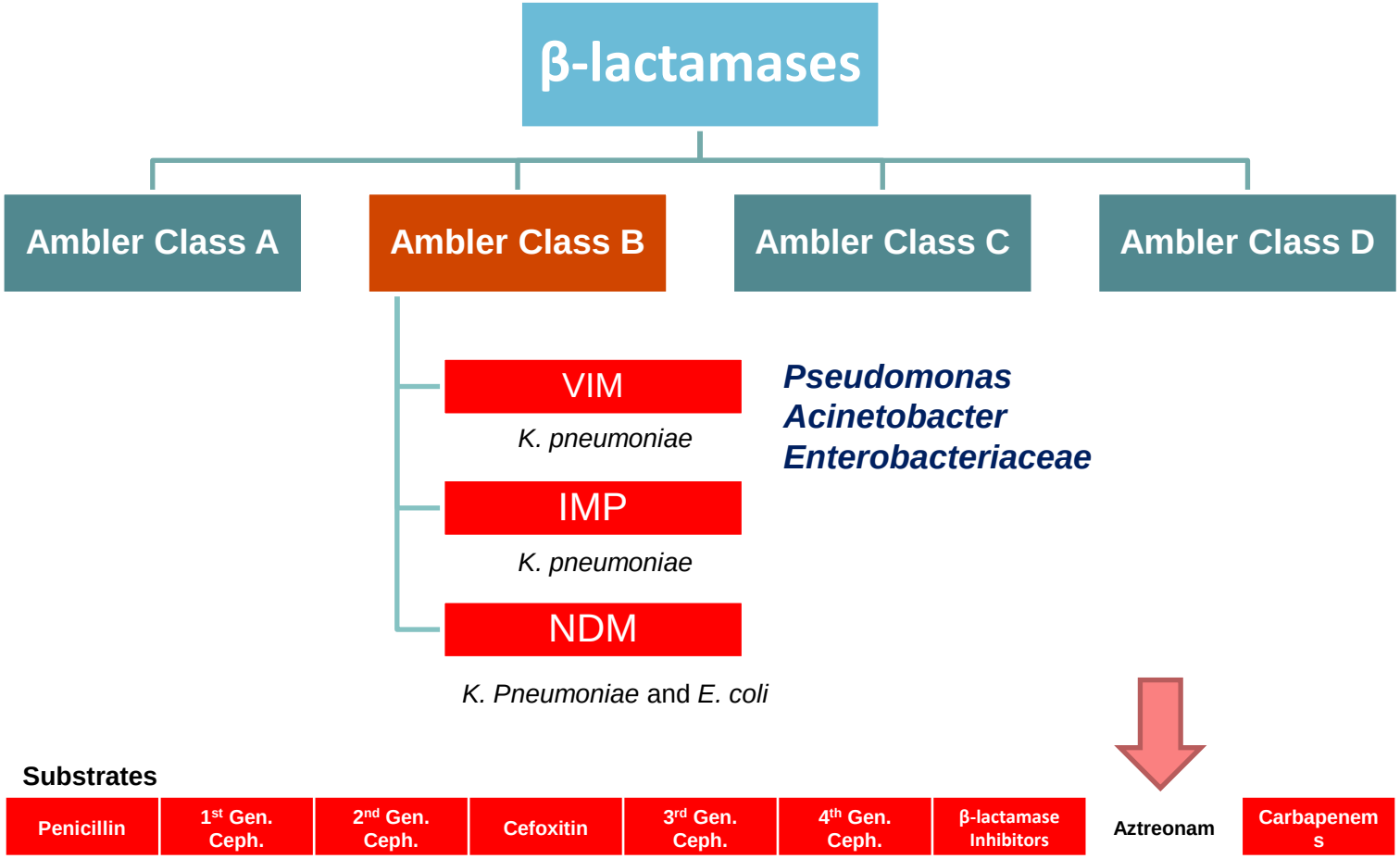
Narrow-spectrum ESBL Broad-spectrum Carbapenemase

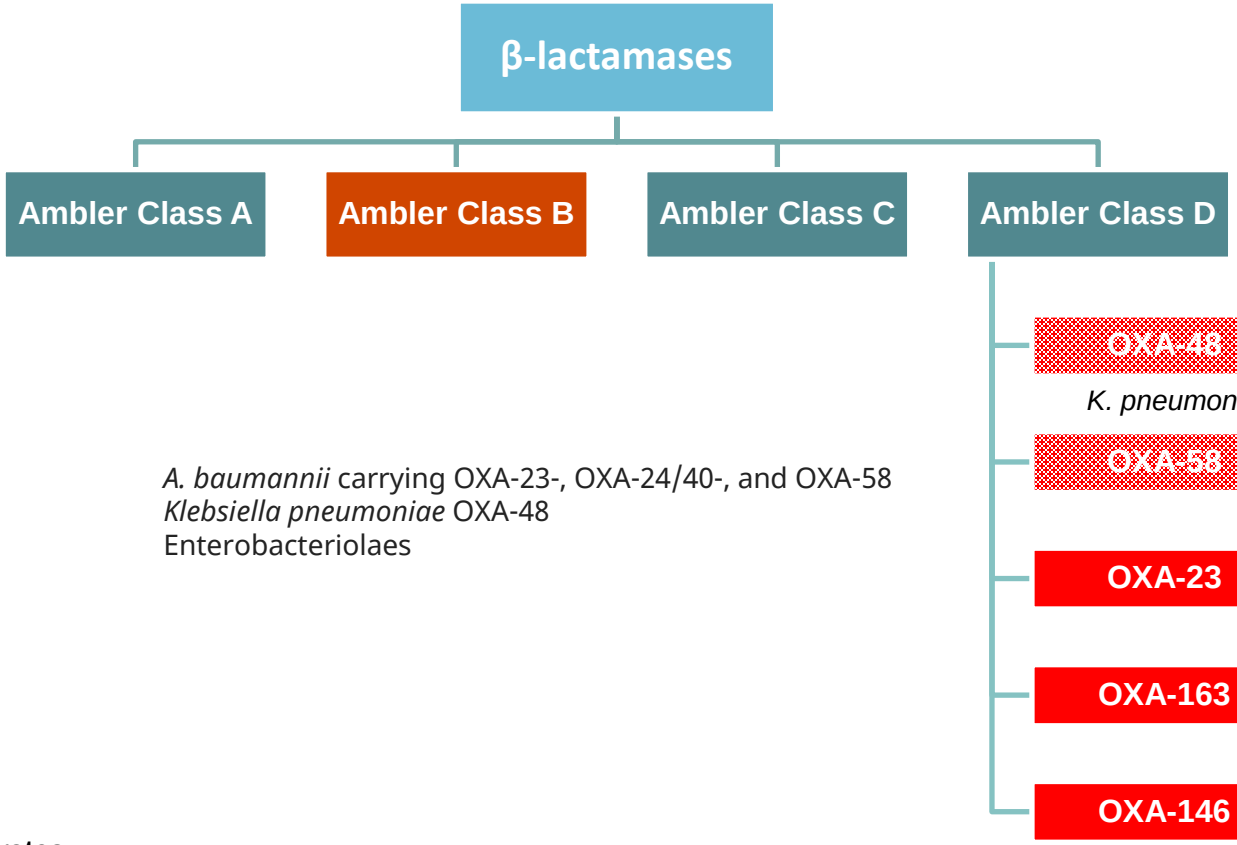


Substrates

Penicillin	1st Gen. Ceph.	2nd Gen. Ceph.	Cefoxitin	3rd Gen. Ceph.	4th Gen. Ceph.	β-lactamase Inhibitors	Aztreonam	Carbapenems

Narrow-spectrum ESBL Broad-spectrum Carbapenemase


β-lactamases
Ambler Class A
Ambler Class B
Ambler Class C
Ambler Class D
VIM
K. pneumoniae
IMP
K. pneumoniae
NDM
K. Pneumoniae and E. coli
Pseudomonas
Acinetobacter
Enterobacteriaceae
Substrates
Penicillin
1st Gen. Ceph.
2nd Gen. Ceph.
Cefoxitin
3rd Gen. Ceph.
4th Gen. Ceph.
β-lactamase Inhibitors
Aztreonam
Carbapenems
Narrow-spectrum
ESBL
Broad-spectrum
Carbapenemase

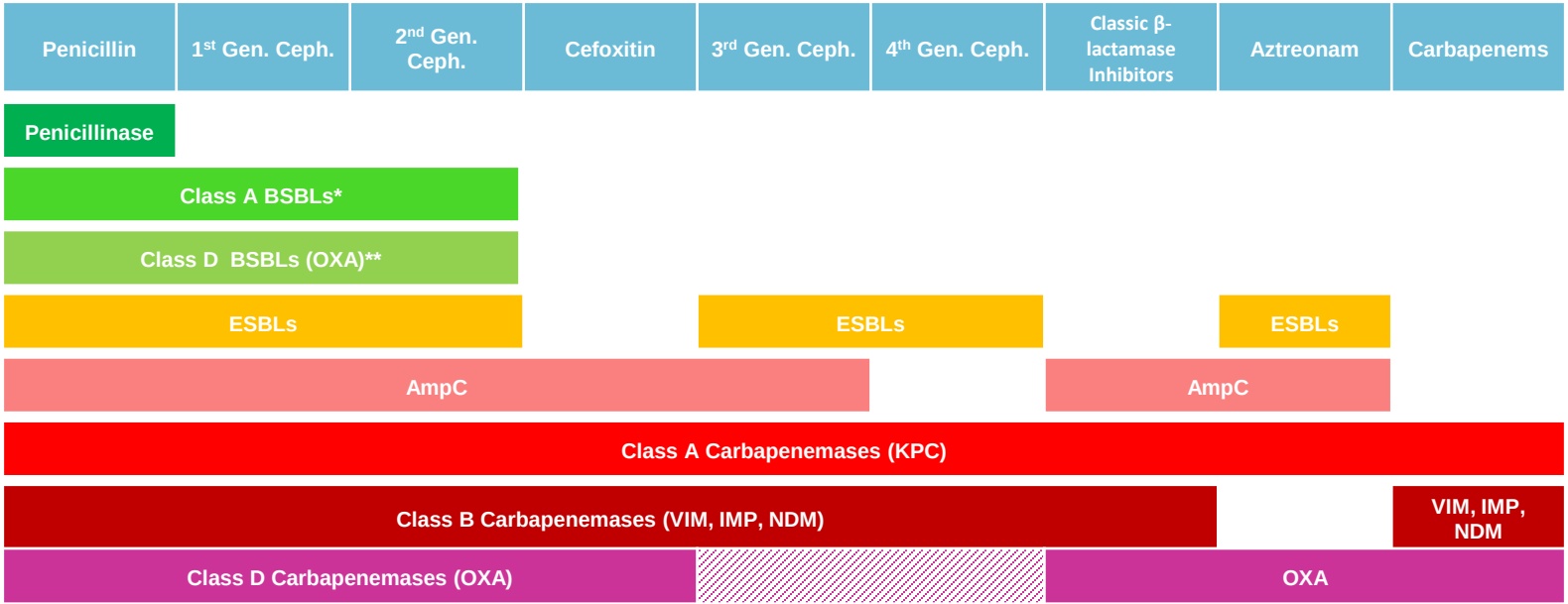


Substrates

Penicillin	1st Gen. Ceph.	2nd Gen. Ceph.	Cefoxitin	3rd Gen. Ceph.	4th Gen. Ceph.	β-lactamase Inhibitors	Aztreonam	Carbapenems

Narrow-spectrum ESBL Broad-spectrum Carbapenemase

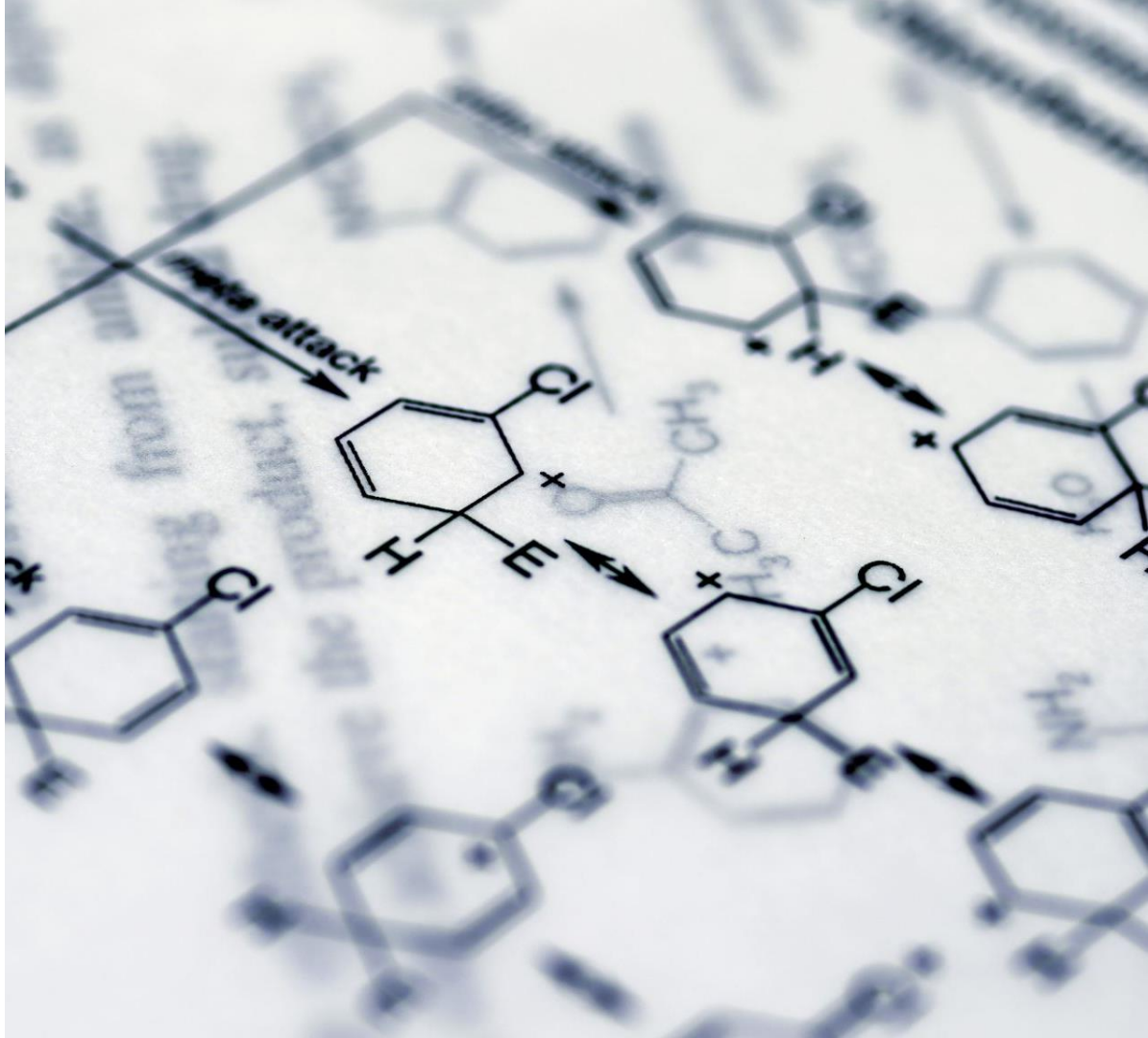
The degradation pattern for each type of β-lactamase



*including benzylpenicillins, aminopenicillins, carboxypenicillins, ureidopenicillin, narrow spectrum cephalosporins (cefazolin and cefuroxime and others)

**BSBL substrates plus oxacillin, nafcillin, and dicloxacillin

Beta-lactamases Inhibitors



Activity Spectrum of Beta-lactamases

	Class A			Class B	Class C	Class D
	Narrow spectrum	**ESBL**	**Carbapenemases (KPC)**	**MBL**	**AmpC**	**OXA-48**
Clavulanic acid[1]						
Sulbactam[2]						
Tazobactam[3]						
Avibactam[4]						
Relebactam[5]						
Vaborbactam[6]						

1. Amoxicillin, ticarcillin
2. Ampicillin, piperacillin, cefoperazone
3. Piperacillin, ceftolozane
4. Ceftaroline, ceftazidime, aztreonam
5. Imipenem
6. Biapenem, meropenem

Classification and characteristics of major carbapenemases in Enterobacteriaceae

Carbapenemase	KPC	MBLs (NDM, VIM, IMP)	OXA-48
Ambler molecular class	A	B	D
Substrates of hydrolysis	All β-lactams	All β-lactams except for aztreonam	Penicillins and carbapenems
Inhibited by classic β-lactamase inhibitors	Minimally	No	No
Inhibited by avibactam	Yes	No	Yes
Inhibited by vaborbactam	Yes	No	No
Inhibited by relebactam	Yes	No	No
Common species in *Enterobacteriaceae*	*K. pneumoniae, E. coli, Enterobacter* spp.	NDM: *K. pneumoniae, E. coli* VIM: *K. pneumoniae* IMP: *K. pneumoniae*	*K. pneumoniae*

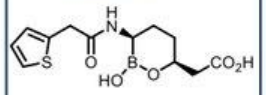
KPC, Klebsiella pneumoniae carbapenemase; MBL, metallo-β-lactamase; NDM, New Delhi metallo-β-lactamase; VIM, Verona integrin-encoded metallo-β-lactamase; IMP, imipenemase; OXA, oxacillinase.

Sheu, Chau-Chyun & Chang, Ya-Ting & Lin, Shang-Yi & Chen, Yen-Hsu & Hsueh, Po-Ren. (2019). Infections Caused by Carbapenem-Resistant Enterobacteriaceae: An Update on Therapeutic Options. Frontiers in Microbiology. 10. 80. 10.3389/fmicb.2019.00080.

Boronic Acid β-lactamase Inhibitors

Evolution of Boronic Acid Beta-Lactamase Inhibitors
Discovery of QPX7728

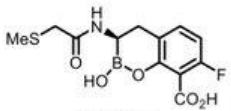
Class I



Vaborbactam

- KPC-only
- Oral bioavailability (prodrug)
- FDA-approved 2017

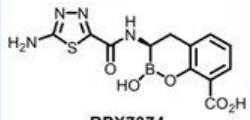
Class IIa



RPX7323

- Bicyclic amide
- **Serine enzymes, ESBL and class C**
- Oral bioavailability (prodrug)

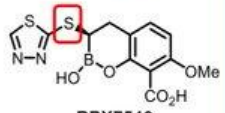
Class IIb



RPX7374

- Bicyclic amide
- Serine enzymes (ESBL and class C)
- **Some MBL activity (no IMP)**

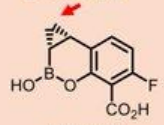
Class III



RPX7546

- Bicyclic thioether
- Serine enzymes (ESBL and class C)
- **Broader MBL activity**
- Oral bioavailability (prodrug)

Class IV

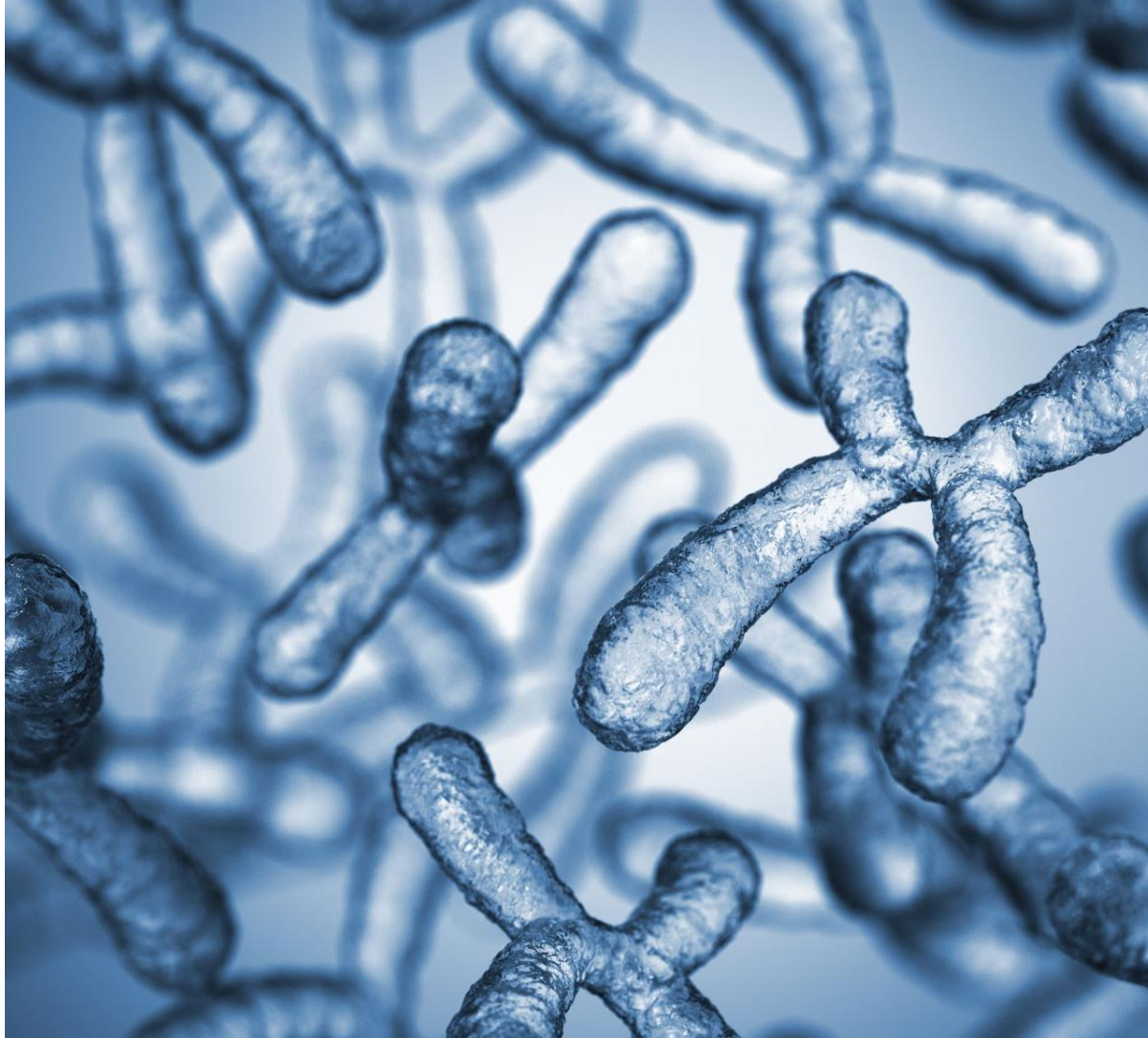


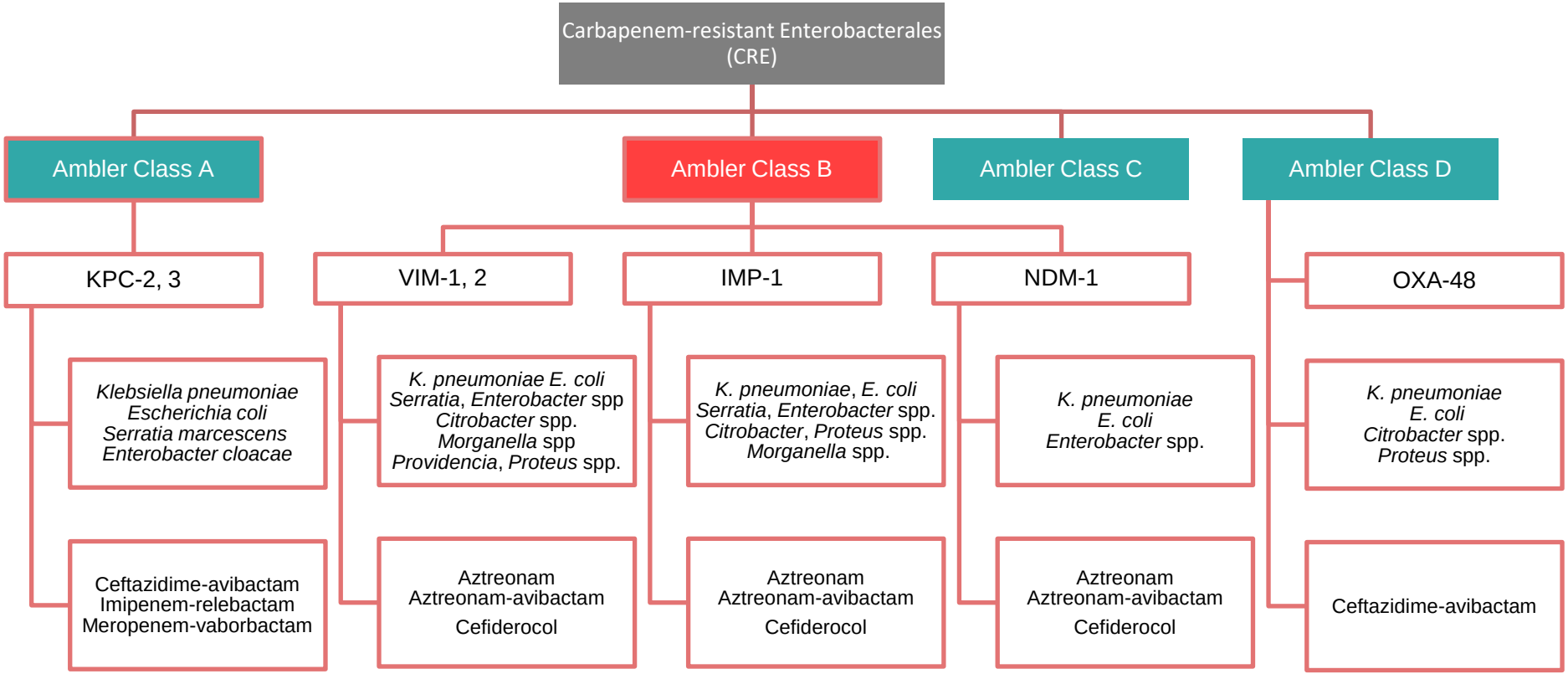
QPX7728

- **Bicyclic unsubstituted**
- **Ultra-broad spectrum (MBL and SBL including OXA from Acinetobacter)**
- **Reduced effects of MDR mechanisms**
- **Orally bioavailable in rats**

S. J. Hecker, et al., "Discovery of QPX7728, an Ultra-broad-spectrum Inhibitor of Serine and Metallo Beta-lactamases." J Medicinal Chemistry 2020;63:7491-7507

Carbapenem Resistant *Enterobacteriaceae*





Narrow-spectrum ESBL Broad-spectrum Carbapenemase

mbler Class	Acronym	Hydrolysing mechanism	Most common variants	Involved species	Carbapenem resistance extent	*In vitro* active molecules/therapeutic options
A	KPC	serine-based	KPC-2 KPC-3	*Klebsiella pneumoniae*, *Escherichia coli*, *Serratia marcescens*, *Enterobacter cloacae*	+++	ceftazidime-avibactam imipenem-relebactam meropenem-vaborbactam
B	NDM	zinc-based	NDM-1	*K. pneumoniae*, *E. coli*, *Enterobacter* spp.	+++	aztreonam aztreonam-avibactam
B	IMP	zinc-based	IMP-1	*K. pneumoniae*, *E. coli*, *Serratia* spp., *Enterobacter* spp., *Citrobacter* spp., *Proteus* spp., *Morganella* spp.	+	aztreonam aztreonam-avibactam
B	VIM	zinc-based	VIM-1 VIM-2	*K. pneumoniae*, *E. coli*, *Serratia* spp., *Enterobacter* spp., *Citrobacter* spp., *Morganella* spp., *Providencia* spp., *Proteus* spp.	+	aztreonam aztreonam-avibactam
D	OXA	serine-based	OXA-48	*K. pneumoniae*, *E. coli*, *Citrobacter* spp., *Proteus* spp.	++	ceftazidime-avibactam

Resistant *Pseudomonas*

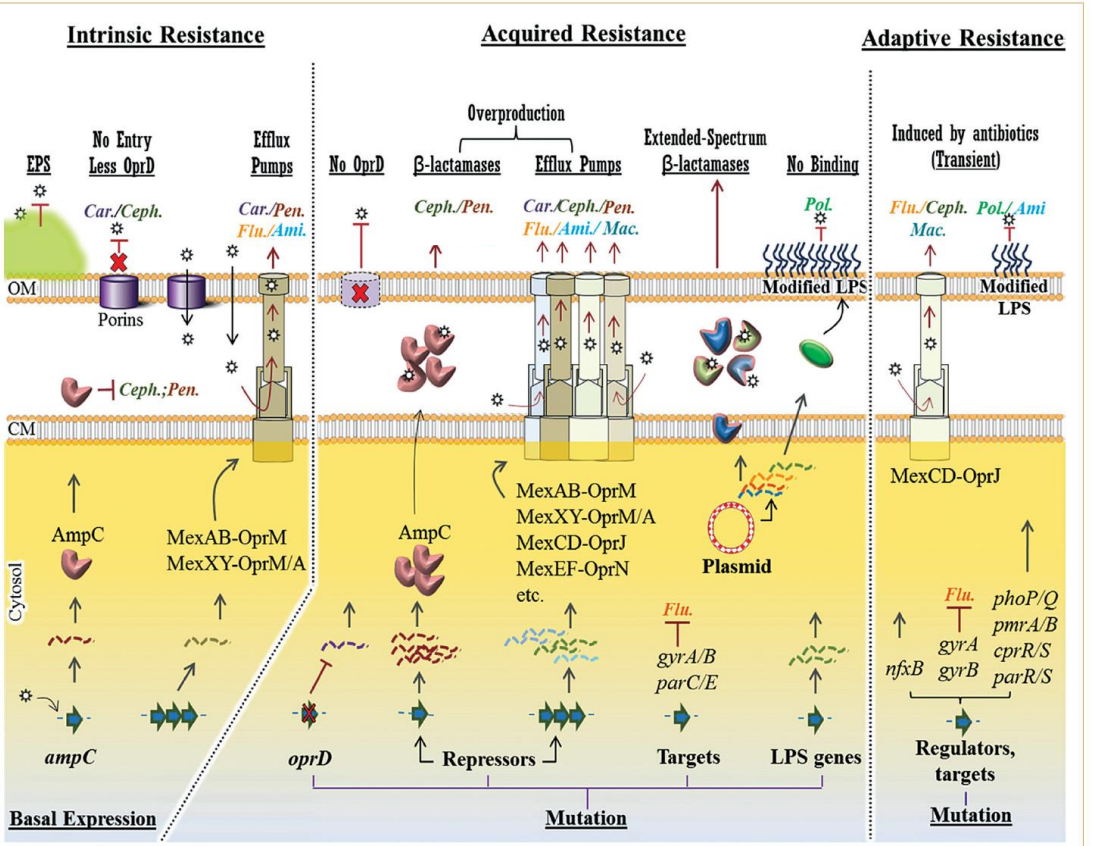


Figure 1. Intrinsic, acquired, and adaptive mechanisms confer antibiotic resistance in *P. aeruginosa*.

Car = carbapenems; Ceph = cephalosporins; Pen = penicillins; Ami = aminoglycosides; Flu = fluoroquinolones; Mac = macrolides and Pol = polymyxins

CM = cytoplasmic membrane; LPS = lipopolysaccharide; OM = outer membrane

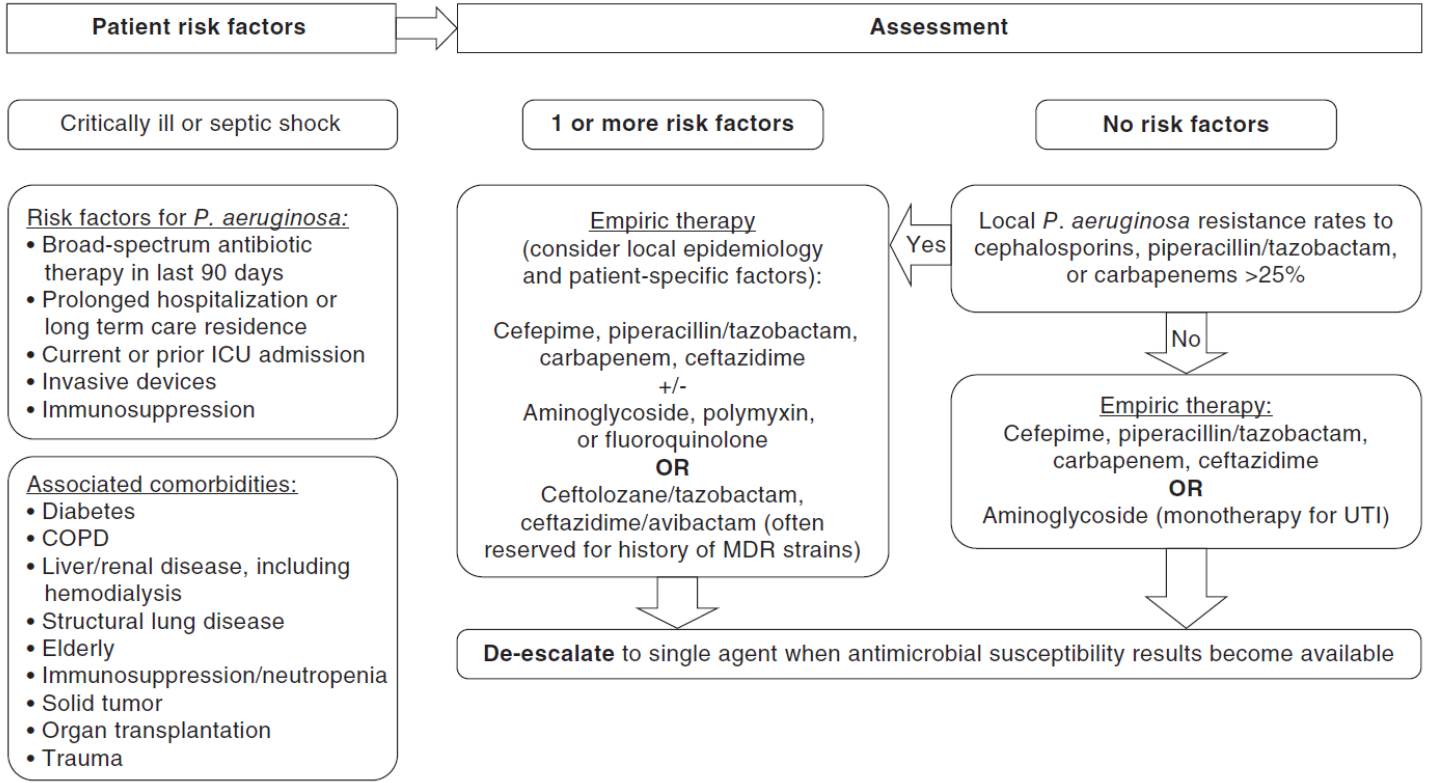


Figure 2. Clinical approach to the patient with *P. aeruginosa* infection.

Information from: Mensa J, Barberan J, Soriano A, et al. Antibiotic selection in the treatment of acute invasive infections by *Pseudomonas aeruginosa*: guidelines by the Spanish Society of Chemotherapy. Rev Esp Quimioter 2018;31:78-100.

Pseudomonas aeruginosa Resistance to Beta-lactams

SIDP SOCIETY OF INFECTIOUS DISEASES PHARMACISTS

Note: Chart is meant as a general teaching tool for common and advanced mechanisms of antimicrobial resistance (AMR).
Resistance in *P. aeruginosa* is complex and various mechanisms may be simultaneously present, impacting *in vitro* activity of each agent.

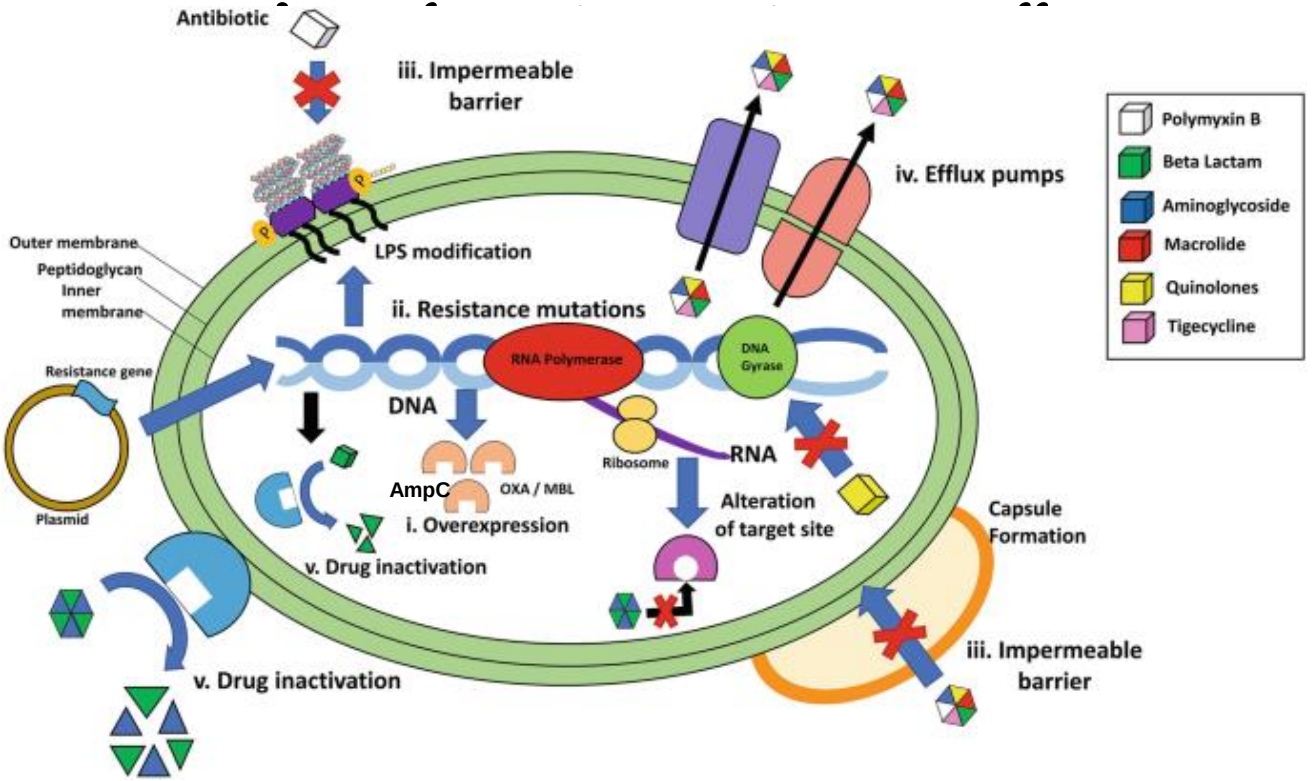
✓ Minimally impacted by AMR mechanism
✗ Heavily impacted by AMR mechanism **R**=Resistant
⚠ Some AMR impact
± Possible association

		Porin Channels	Efflux Pumps	AmpC	Carbapenemases Minor AMR contributor
Standard Agents	Ceftazidime	± ↑ MIC Loss of OprF	⚠ ↑ MIC or R Upregulated MexAB-OprM	✗	✗
	Cefepime	± ↑ MIC Loss of OprF	⚠ ↑ MIC or R Upregulated MexAB-OprM, MexXY-OprM, MexCD-OprJ	⚠ ↑ MIC or R Overexpression	✗
	Piperacillin-Tazobactam	± ↑ MIC Loss of OprF	⚠ ↑ MIC or R Upregulated MexAB-OprM	✗	✗
	Imipenem	✗ R Loss of OprD	✓	⚠ ↑ MIC Overexpression	✗
	Meropenem	⚠ ↑ MIC Loss of OprD	⚠ ↑ MIC or R Upregulated MexAB-OprM & MexXY-OprM	✓	✗
MDR Agents	Ceftazidime-Avibactam	± ↑ MIC Loss of OprF	⚠ ↑ MIC or R Upregulated MexAB-OprM	⚠ ↑ MIC or R AmpC mutants	⚠ Inhibits some carbapenemases rarely found in PsA, does not inhibit MBL
	Ceftolozane-Tazobactam	✓	✓	⚠ ↑ MIC or R AmpC mutants	✗
	Imipenem-Relebactam	✓	⚠ ↑ MIC or R (Relebactam only) Upregulated MexAB-OprM & MexEF-OprN	✓	⚠ Inhibits some carbapenemases rarely found in PsA, does not inhibit MBL
	Meropenem-Vaborbactam	⚠ ↑ MIC Loss of OprD	⚠ ↑ MIC or R Upregulated MexAB-OprM & MexXY-OprM	✓	⚠ Inhibits some carbapenemases rarely found in PsA, does not inhibit MBL
	Cefiderocol	⚠ ↑ MIC Mutation of Iron Transport system	✓	⚠ ↑ MIC or R AmpC mutants	Active vs KPC, MBL, GES ⚠ ↑ MIC for NDM

SIDP Breakpoints Podcast Episode #59 Resistance in *P. aeruginosa*: Pearls & Perils - Hosted by Dr. Erin McCreary, featuring Drs. Maggie Monogue and Antonio Oliver

Resistant *Acinetobacter*

Antibiotic Resistance Mechanisms and Their Transmission



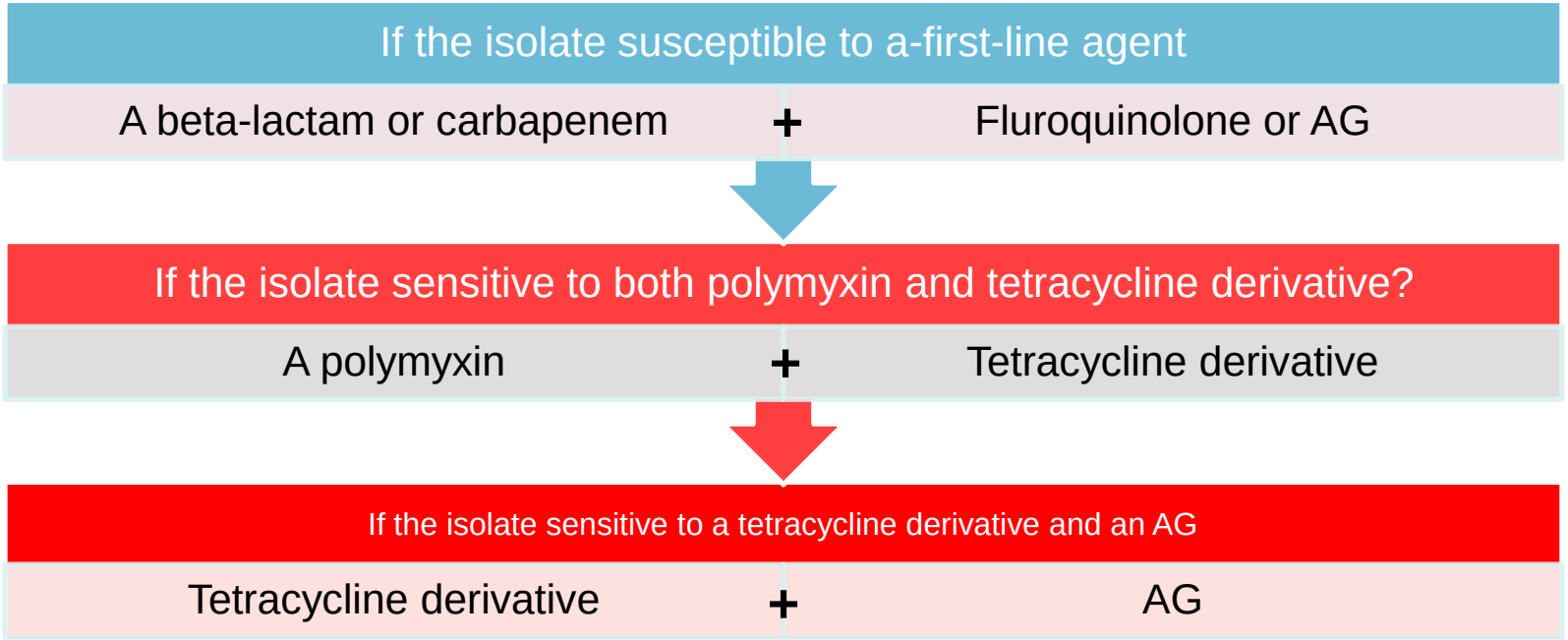
First-line Agents for Acinetobacter

Agents	
Ceftazidime	2 g intravenously every 8 hours (infuse each dose over 3 to 4 hours)*
Cefepime	2 g intravenously every 8 hours (infuse each dose over 3 to 4 hours)*
Piperacillin-tazobactam	4.5 g intravenously every 8 hours (infuse each dose over 4 hours)*
Ampicillin-sulbactam¶	Mild carbapenem-susceptible infections: 3 g intravenously every 6 hours Mild carbapenem-resistant infections: 3 g intravenously every 4 hours Moderate to severe infections: 9 g intravenously every 8 hours (infuse each dose over 4 hours)*, **or** 27 g intravenously every 24 hours as a continuous infusion*
Meropenem	Cystitis: 1 g intravenously every 8 hours (infuse each dose over 30 minutes) Infections other than cystitis: 2 g intravenously every 8 hours (infuse each dose over 3 hours)*
Imipenem-cilastatin	Cystitis: 500 mg intravenously every 6 hours (infuse each dose over 30 minutes) Infections other than cystitis: 500 mg intravenously every 6 hours, or 1 g intravenously every 6 to 8 hours (infuse each dose over 3 hours)*
Ciprofloxacin$^{\Delta}$	400 mg intravenously every 8 hours, or 750 mg orally every 12 hours
Levofloxacin$^{\Delta}$	750 mg intravenously or orally once daily
Trimethoprim-sulfamethoxazole$^{\lozenge}$	Cystitis: 1 double-strength tablet (trimethoprim 160 mg and sulfamethoxazole 800 mg) orally twice daily

Second-line Agents for Acinetobacter

Agents	
Colistin (colistimethate)[§]	**Intravenous dose:** Loading dose of 300 mg CBA (equivalent to approximately 9 million units colistimethate sodium), followed by a daily maintenance dose of 300 to 360 mg CBA (approximately 9 to 11 million units colistimethate sodium) divided into 2 doses infused over 1 hour **Inhaled dose:** 75 to 150 mg CBA (2.25 to 4.5 million units) every 12 hours
Polymyxin B	Loading dose of 2 to 2.5 mg/kg (20,000 to 25,000 units/kg), followed by 1.25 to 1.5 mg/kg (12,500 to 15,000 units/kg) every 12 hours; doses should be based on total body weight
Tigecycline[¥]	Mild infections and carbapenem-susceptible infections: 100 mg loading dose, followed by 50 mg intravenously every 12 hours Moderate to severe carbapenem-resistant infections: 200 mg loading dose, followed by 100 mg intravenously every 12 hours
Cefiderocol	2 g intravenously every 8 hours (infuse each dose over 3 hours); in patients with creatinine clearance ≥120 mL/minute, administer 2 g intravenously every 6 hours (infuse each dose over 3 hours)

Treatment Options for Acinetobacter



Case Study

Steps in Antibiotic Selection

Case Scenario

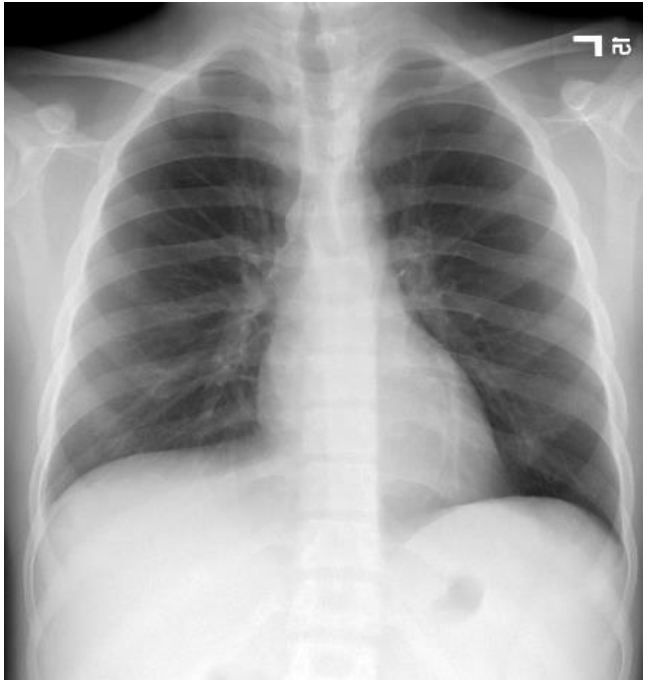
17-year-old male with PMH cycteinosis complicated with chronic renal failure requiring kidney transplantation X2 that failed and placed on chronic dialysis, patient acquired HBV

Admitted on January 17 with:

- Fulminant hepatitis secondary to HBV
- Acute liver failure
- Coagulopathy
- Hepatic encephalopathy

Management included ICU monitoring, hemodialysis, vitamin K, lactulose

Not candidate for liver transplantation



January 21, 2010: 4 Days Later

Respiratory distress

Fever

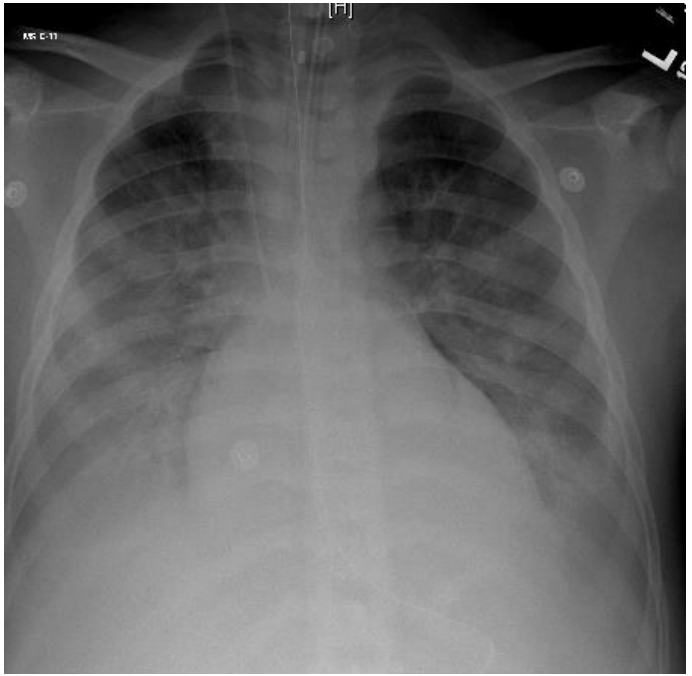
Developed bilateral pulmonary infiltrates

Intubated

FiO2 50%, pO_2: 65 mm Hg

Yellowish endotracheal aspirate

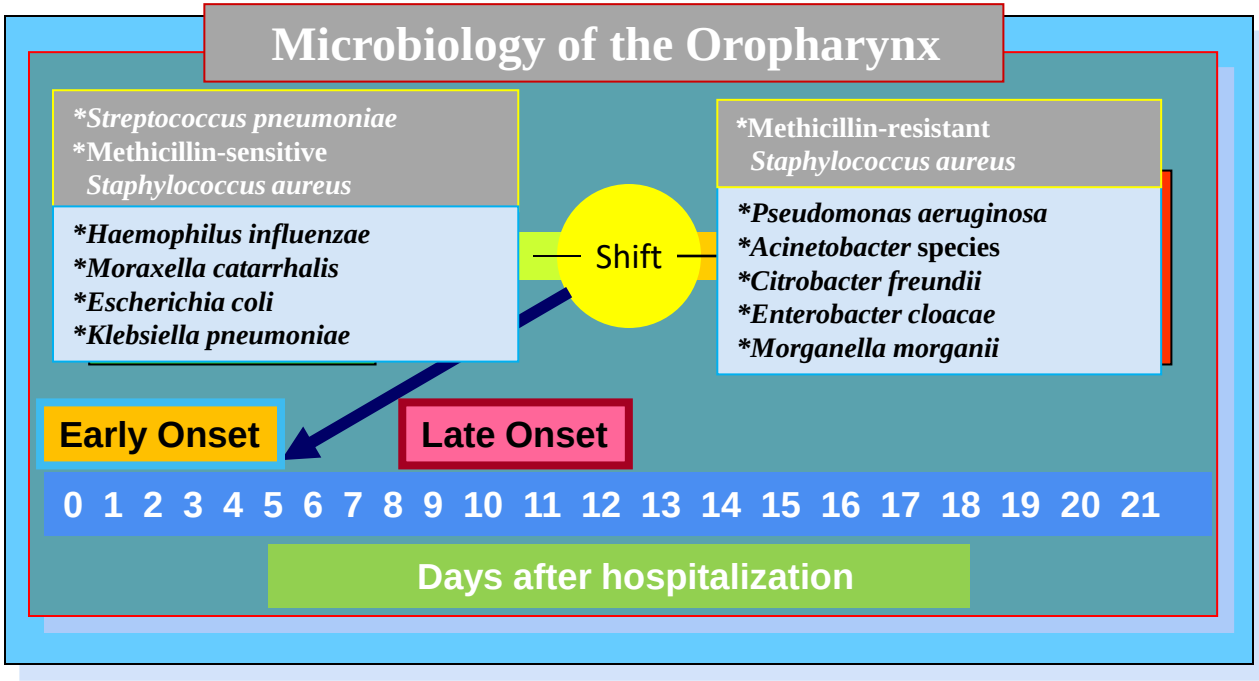
WBC: 12.400



What empiric antibiotics would you choose at this time?

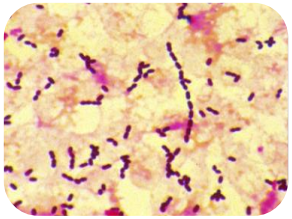
A. Ceftriaxone + clindamycin
B. Ceftriaxone
C. Piperacillin/tazobactam
D. Imipenem
E. Ciprofloxicin + metronidazole

HAP/VAP: Etiology



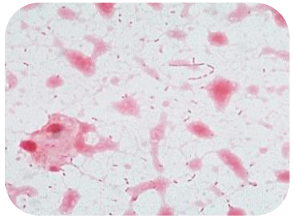
Early Hospital Acquired Aspiration Pneumonia:

Antibiotic Selection: Early with no risk of resistant organisms



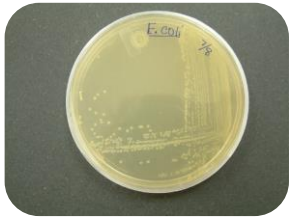
MSSA/Streptococcus pneumoniae

- Amp/Sulbactam
- Pip/Taz
- Ceftriaxone
- Levofloxain
- Tigecycline



Haemophilus influenzae* or *Moraxella catarrhalis

- Amp/Sulbactam
- Pip/Taz
- Ceftriaxone
- Levofloxain
- Tigecycline



Enterobacteriacae

- Amoxicillin/clavulanate
- Piperacillin/tazobactam
- Third- and fourth-generation cephalosporins
- Carbapenems
- Fluoroquinolones
- Tigecycline

Anaerobes

- Amoxicillin/clavulanate
- Piperacillin/tazobactam
- Cefoxitin
- Carbapenems
- Moxifloxacin
- Metronidazole
- Clindamycin
- Tigecycline

Penicillin/β-lactamase inhibitor: Ampicillin-sulbactam
Cephalosporins 3rd Generation: Cefpodoxime

Health Care Associated Aspiration Pneumonia:

Antibiotic Selection: Early with risk of Resistant Organisms

Pseudomonas aeruginosa

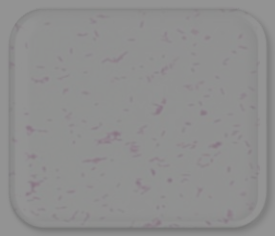
Piperacillin/Tazobactam
Ceftazidime
Cefepime
Ceftobiprole
Ceftolozane/tazobactam
Meropenem
Aztreonam
± Ciprofloxacin
± aminoglycoside

MRSA

- Vancomycin
- Ticoplanine
- Telavancin
- Daptomycin
- Linezolid
- Qiunupristin/Dalfopristin
- Tigecycline
- Clindamycin
- Ceftaroline

Enterobacteriacae

- Amoxicillin/clavulanate
- Piperacillin/tazobactam
- Ceftriaxone
- Cefepime
- Ertapenem
- Fluoroquinolones
- Tigecycline
- Ceftaroline

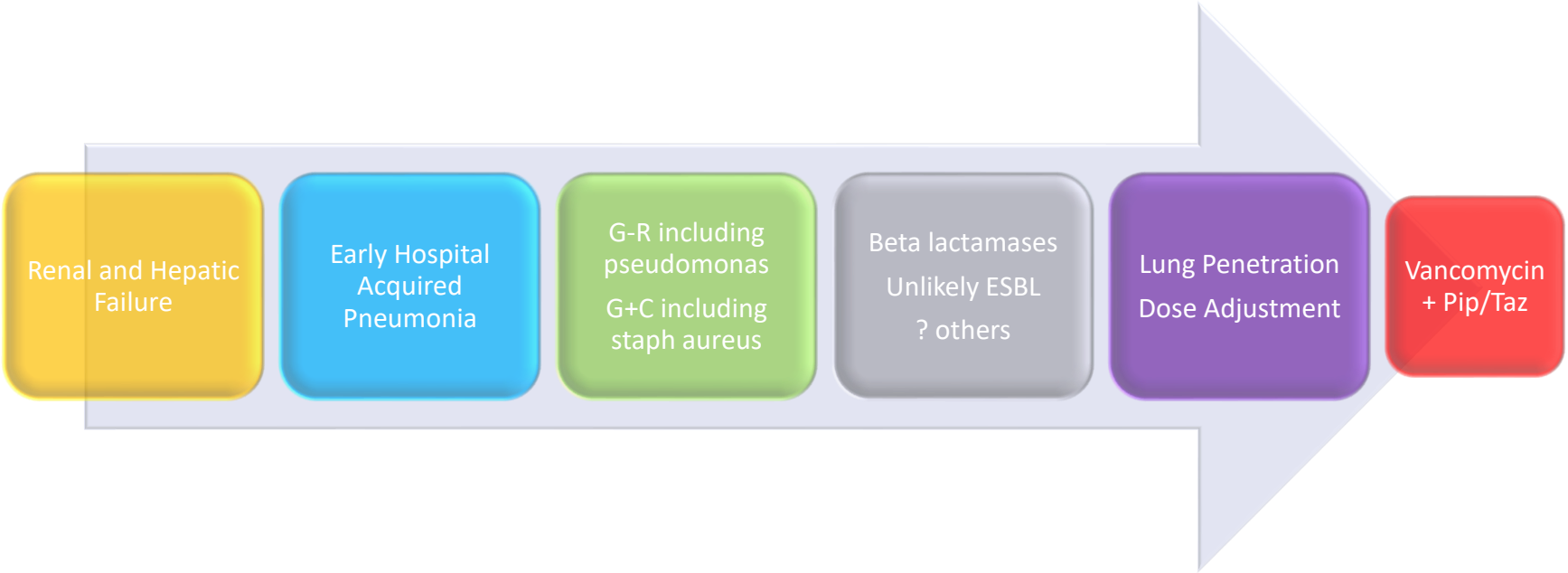


Anaerobes

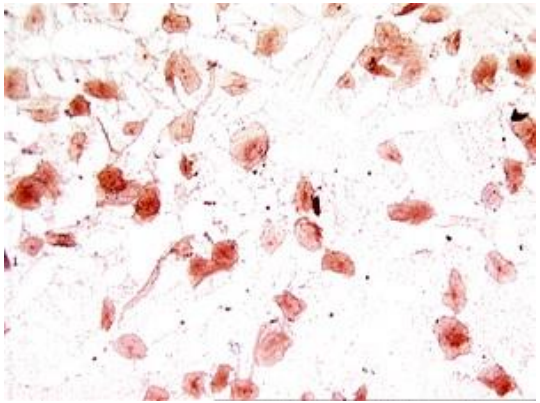
- Amoxicillin / clavulanate
- Piperacillin / tazobactam
- Cefoxitin
- Ceftolozam/Taz
- Carbapenems
- Metronidazole
- Clindamycin
- Moxifloxacin
- Tigecycline

Carbapenem (Imipenem, Meropenem, Ertapenem) Glycopeptide

Steps in Antibiotic Selection



Aspiration Pneumonia: BAL and Tx



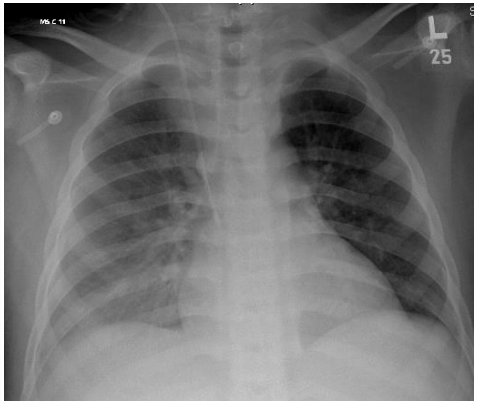
Broncho-alveolar Lavage

Microbiology Result Details - - 03

Respiratory Culture _Gram Stain - Accession: 0000020100230030

Micro Reports | Specimen | Action List

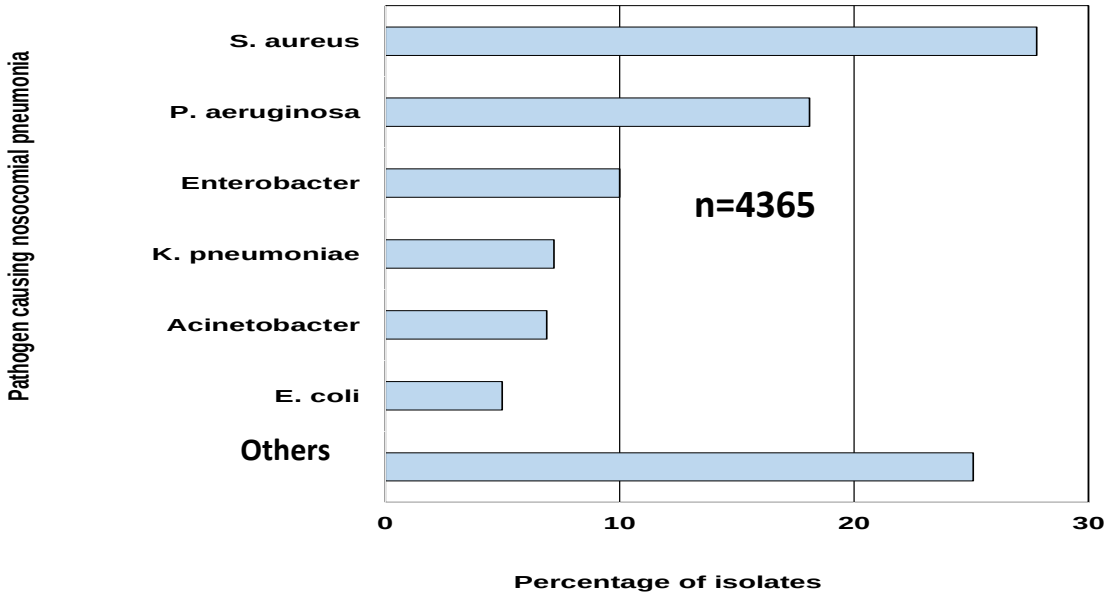
```
Final - 25 January, 2010 15:21 -
Scant Presumptive Candida albicans


Pre - 24 January, 2010 20:16 -
Scant Yeast
Further report to follow.


GS - 24 January, 2010 12:33 -
Epithelial cells 0
Polymorphonuclear leukocytes 3+
No organisms seen.
```



Broncho-alveolar Lavage

Vancomycin + Pip/Taz

Common HAP Pathogens in ICU Patients

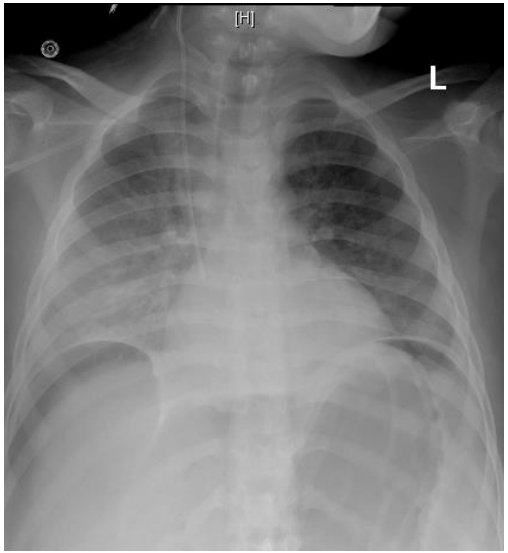


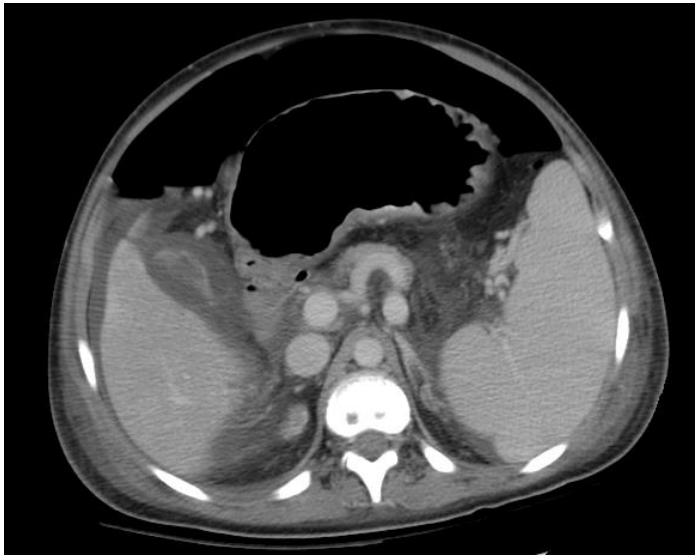
Data from the National Nosocomial Infections Surveillance (NNIS) system (1986–2003) for HAP. Gaynes et al. *CID* 2005;41:848– 54.

January 31: Perforated Viscus

Developed acute abdominal pain

Distended abdomen with tenderness and decreased bowel sounds





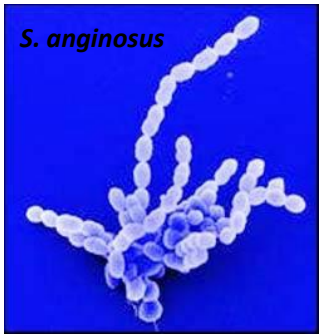
Managed conservatively secondary to high risk surgery

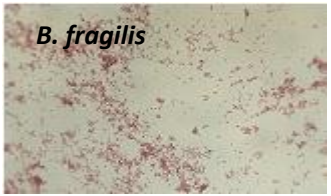
What empiric antibiotics would you choose at this time?

A. Ceftriaxone + metronidazole
B. Pipercillin/tazobactam
C. Imipenem
D. Tigecycline
E. Ciprofloxicin + metronidazole

Microbiology of Peritonitis

Primary (Monomicrobial)	Secondary (Polymicrobial)	Tertiary (Polymicrobial)
E. coli	*B. fragilis* group	*Enterococci*
Klebsiella spp.	*E. coli*	*Pseudomonas*
Streptococcus spp.	*Clostridium* spp.	*S. epidermidis*
Enterococcus spp.	*Klebsiella* spp.	*Candida*
Other gram-negative bacilli	*Streptococcus* spp.	
	Enterococcus spp.	
	Pseudomonas spp.	

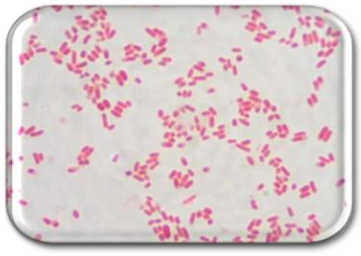




Barie PS. *J Chemother*. 1999;11:464-477.
LaRoche M, Harding G. *Eur J Clin Microbiol Infect Dis*. 1998;17:542-550.

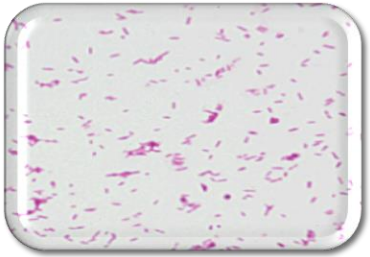
Secondary Peritonitis

(Antibiotic Selection)



Enterobacteriacea

- Amoxicillin/Clavulanate
- Piperacillin/Tazobactam
- Ceftriaxone
- Cefepime
- Ceftolozane/Tazobactam
- Ceftaroline
- Carbapenems
- Aztreonam
- Fluoroquinolones
- Tigecycline
- ± aminoglycoside

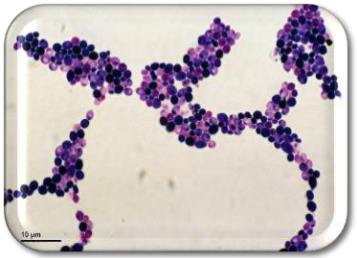


B. Fragilis Group

- Metronidazole
- Clindamycin
- Amoxicillin/Clavulanate
- Piperacillin/Tazobactam
- Cefoxitin
- Carbapenems
- Moxifloxacin
- Tigecycline

Enterococcus

- Ampicillin
- Vancomycin
- Ticoplanin
- Telavancin
- Daptomycin
- Linezolid
- Ceftaroline
- Quinupristin/Dalfopristin
- Tigecycline
- ±Aminoglycosides



Candida Albicans

- Fluconazole
- Micafungin
- Caspofungin
- Anidulafungin

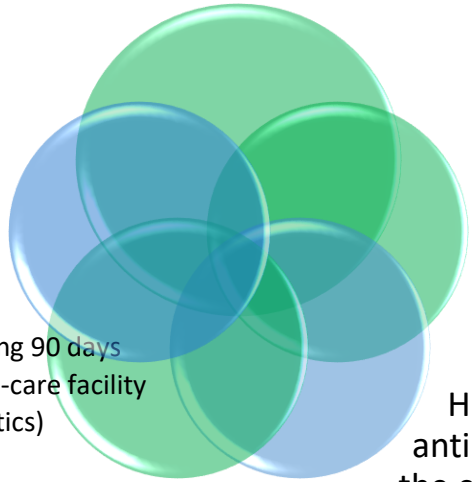
Risk factors for ESBL, AmpC or MDR?

Risk factors for MDR pathogens

Prior antimicrobial therapy in preceding 90 days

Immunosuppressive disease and/or therapy

Current hospitalization of >5 days

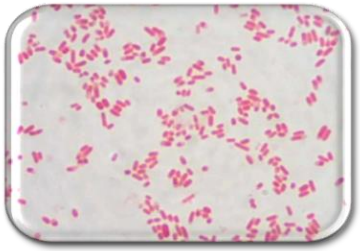


High frequency of antibiotic resistance in the community or in the specific hospital unit

Presence of other risk factors

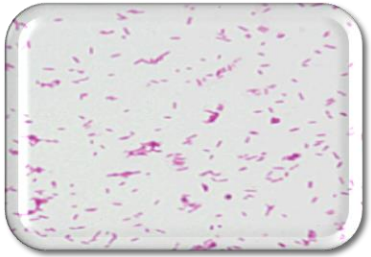
- Hospitalization for >2 days in the preceding 90 days
- Residence in a nursing home or extended-care facility
- Home infusion therapy (including antibiotics)
- Chronic dialysis within 30 days
- Home wound care
- Family member with MDR pathogen

Secondary Peritonitis
(Antibiotic Selection)



Enterobacteriacea

- Amoxicillin/Clavulanate
- Piperacillin/Tazobactam
- Ceftriaxone
- Cefepime
- Ceftolozane/tazobactam
- Ceftazidime/avibactam
- Ceftaroline
- Carbapenems
- Aztreonam
- Fluoroquinolones
- Tigecycline
- ± aminoglycoside



B. Fragilis Group

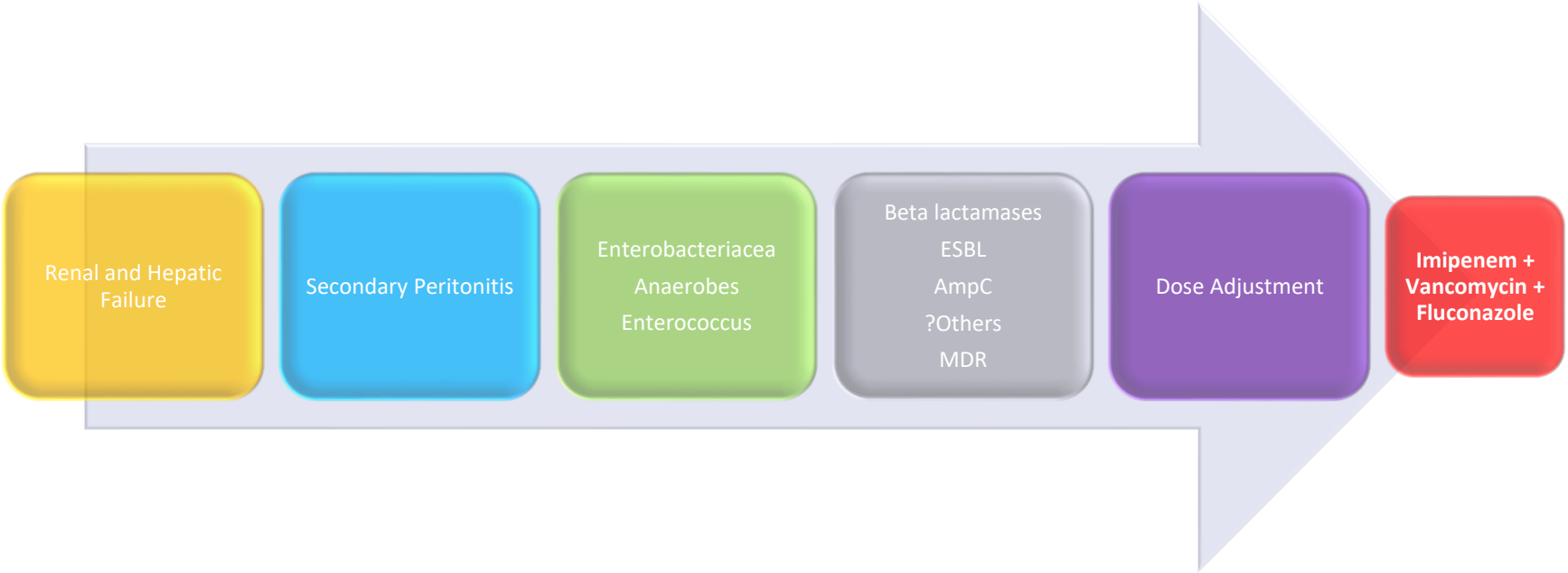
- Metronidazole
- Clindamycin
- Amoxicillin/Clavulanate
- Piperacillin/tazobactam
- Cefoxitin
- Carbapenems
- Moxifloxacin
- Tigecycline

Enterococcus

- Ampicillin
- Vancomycin
- Ticoplanin
- Telavancin
- Daptomycin
- Linezolid
- Ceftaroline
- Quinupristin/Dalfopristin
- Tigecycline
- ±Aminoglycosides

Risk factors for ESBL, AmpC or MDR?

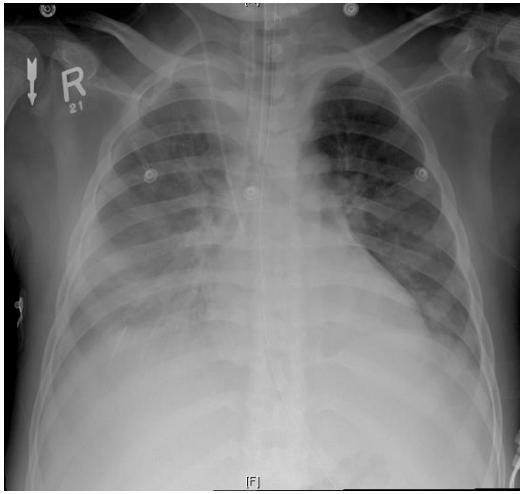
Steps in Antibiotic Selection

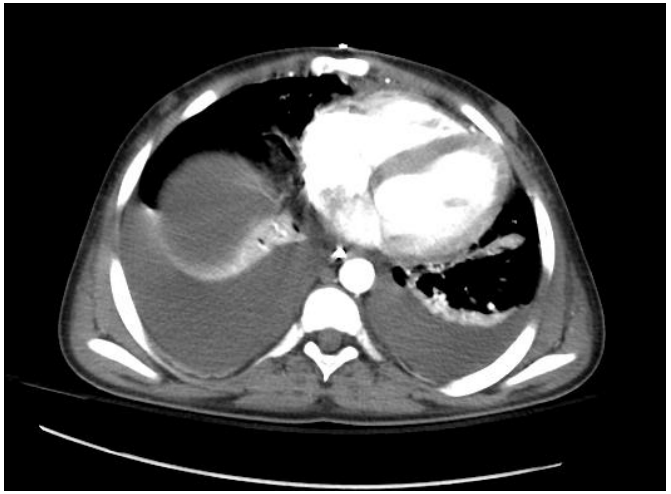


Feb 6, 2010

No improvement with conservative approach

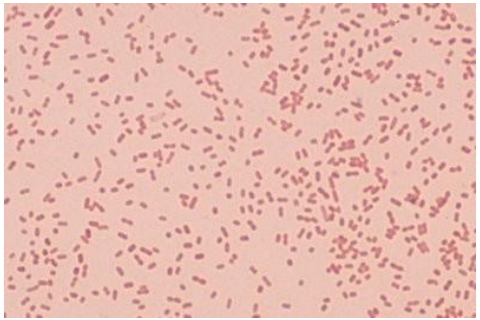
CT scan abdomen





Laporatomy revealed peritonitis, No clear perforation site, Washing and drains placed

Abdominal Drainage Feb 6



Drainage Fluid Culture - Accession: 000002010112001069

Micro Reports | Susceptibilities | Specimen | Action List

	A	B	C
1	Klebsiella pneumoniae		
2		MDIL	MINT
3	Ampicillin*	>=32	R
4	Amoxicillin/Clavulanate	16	I
5	Piperacillin/Tazobactam	>=128	R
6	Cephalothin*	>=64	R
7	Cefuroxime*	>=64	R
8	Cefoxitin	8	S
9	Ceftazidime*	16	R
10	Ceftriaxone*		R
11	Cefepime*	2	R
12	Ciprofloxacin	>=4	R
13	Gentamicin	>=16	R
14	Amikacin	<=2	S
15	Aztreonam*		R
16	Meropenem	<=0.25	S
17	Imipenem		S
18	Trimethoprim/Sulfamethoxazole	>=320	R
19	Extended Spectrum Beta-Lactamase*		Pos

Imipinem, + Vancomycin + Fluconazole

February 19

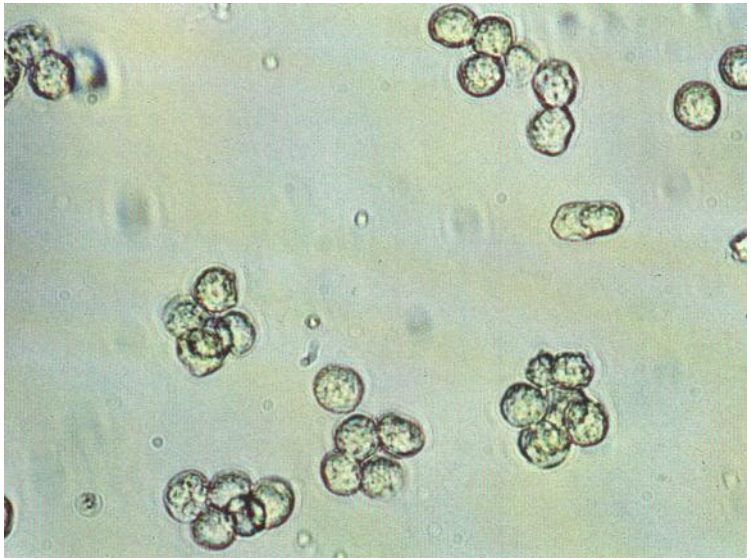
Patient improved and was transferred to the floor and now presented with:

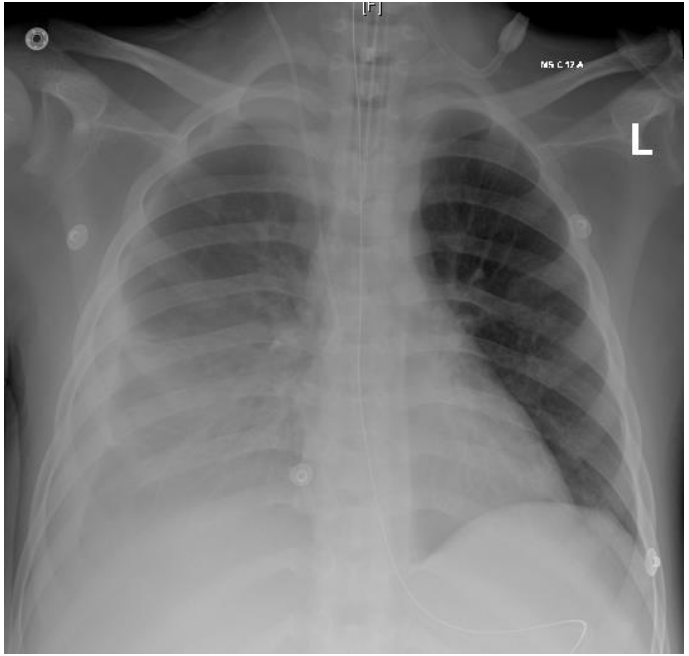
- Fever: T: 101.3
- Hypotension: SBP 70
- Tachypnea: RR 32
- Tachycardia: 130/min
- WBC: 28.4
- pO_2: 56 on FiO2 60%
- Thrombocytopenia: 87,000
- Anuric
- Lactic acid: 4.2

What is the likely source of sepsis?

A. Line infection?
B. Hospital-acquired pneumonia?
C. Further cIAI with or without abscesses?
D. Urinary catheter-related infection?
E. C-diff colitis
F. Any of the above

Investigations





What empiric antibiotics would you choose at this time?

A. Cefepime
B. Piperacillin/tazobactam
C. Imipenem
D. Tigecycline
E. Ciprofloxicin

CR-UTI
(Antibiotic Selection)

Pseudomonas

- Piperacillin / tazobactam
- Ceftazidime
- Cefepime
- Ceftobiprole
- Aztreonam
- Carbapenems (except ertapenem)
- Ciprofloxacin
- ± aminoglycoside

Candida

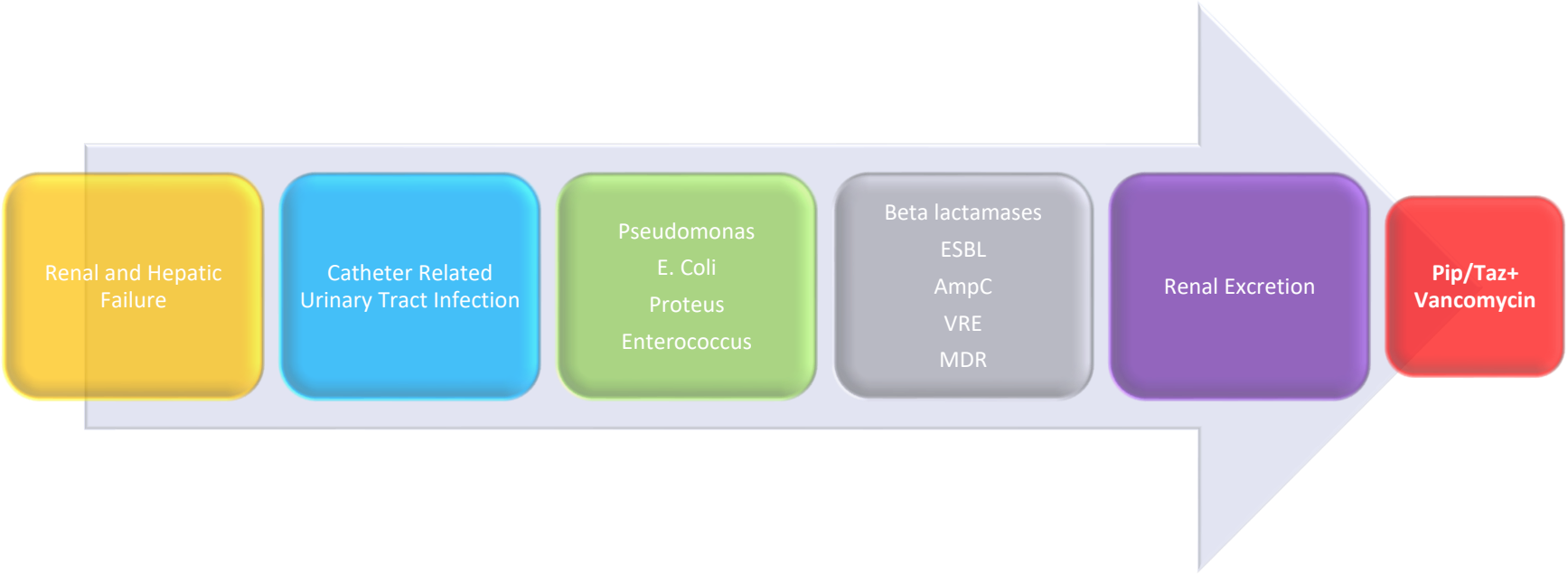
- Ampho B
- Azoles
- Echinocandins

Enterococcus

- Ampicillin
- Vancomycin
- Ticoplanin
- Telavancin
- ±Aminoglycosides
- Daptomycin
- Linezolid
- Quinupristin/Dalfopristin
- Tigecycline

Risk factors for ESBL, AmpC or MDR?

Steps in Antibiotic Selection



Microbiology: Blood and Urine Cx

Microbiology Result Details - [redacted] - 0323406

Blood Culture - Accession: 000002010050000396

Micro Reports | Susceptibilities | Specimen | Action List

	A	B	C
1	Pseudomonas aeruginosa		
2		MDIL	MINT
3	Piperacillin/Tazobactam	8	S
4	Ceftazidime	4	S
5	Cefepime	2	S
6	Gentamicin	<=1	S
7	Ciprofloxacin	<=0.25	S
8	Imipenem	<=1	S
9	Meropenem	<=0.25	S
10	Amikacin	<=2	S

Microbiology Result Details - [redacted]

Urine Culture - Accession: 000002010050000377

Micro Reports | Susceptibilities | Specimen | Action List

```
Final - 21 February, 2010 12:08 -
>100,000 cfu/ml Pseudomonas aeruginosa


Pre - 20 February, 2010 07:35 -
>100,000 cfu/ml Presumptive Pseudomonas species
Further report to follow.
```

Ceftazidime + Vancomycin

March 1

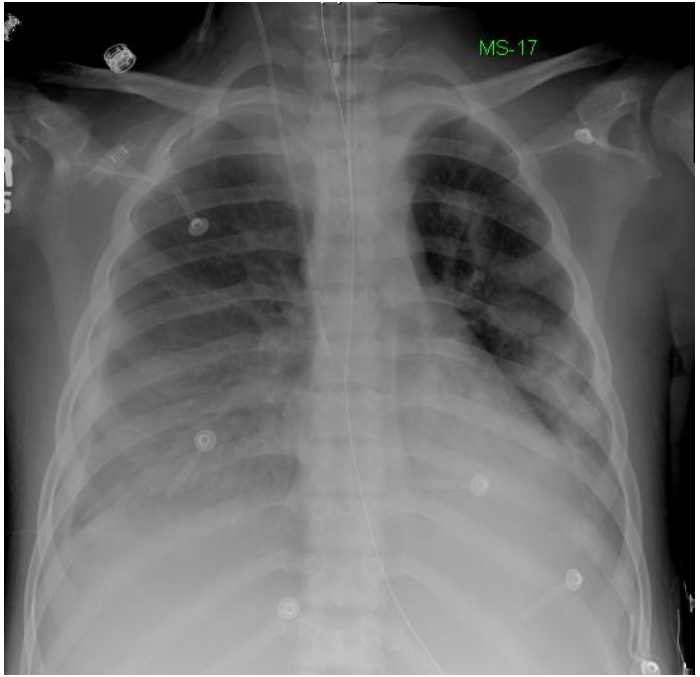
Distended abdomen

Decreased bowel sounds

Fever

WBC 2.5

Abdominal fluids: >1200 WBC, 85%PMN’s



What empiric antibiotics would you choose at this time?

A. Tigecycline + caspofungin
B. Colistin + caspofungin
C. Imipenem + caspofungin
D. Colistin+ Imipenem + caspofungin
E. Piperacillin/tazobactam + caspofungin

Tertiary Peritonitis
(Antibiotic Selection)

MDR Pseudomonas

- Meropenem
- Imipenem
- Cefepime
- Ceftolozane/Tazobactam
- Colistin
- Ceftobiprole
- Aztreonam
- Ciprofloxacin
- ± aminoglycoside

Candida

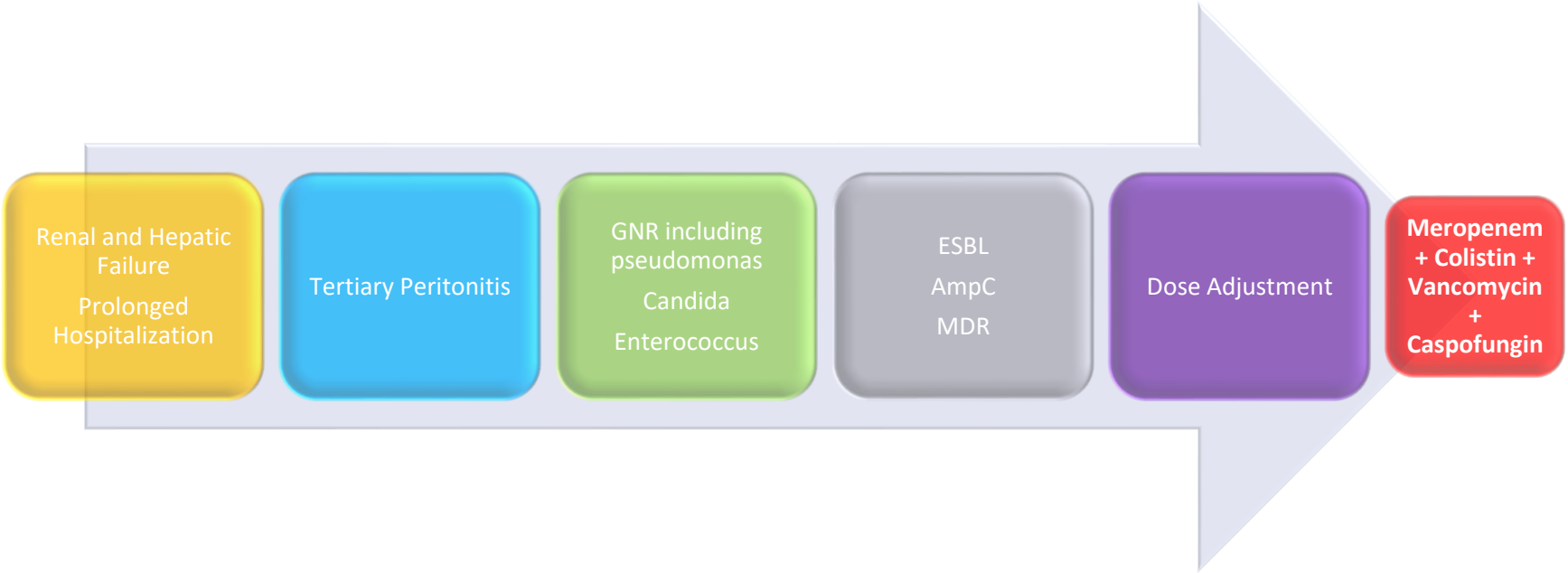
- Ampho B
- Anidulafungin
- Caspofungin
- Micafungin
- Fluconazole
- Voriconazole

Enterococcus

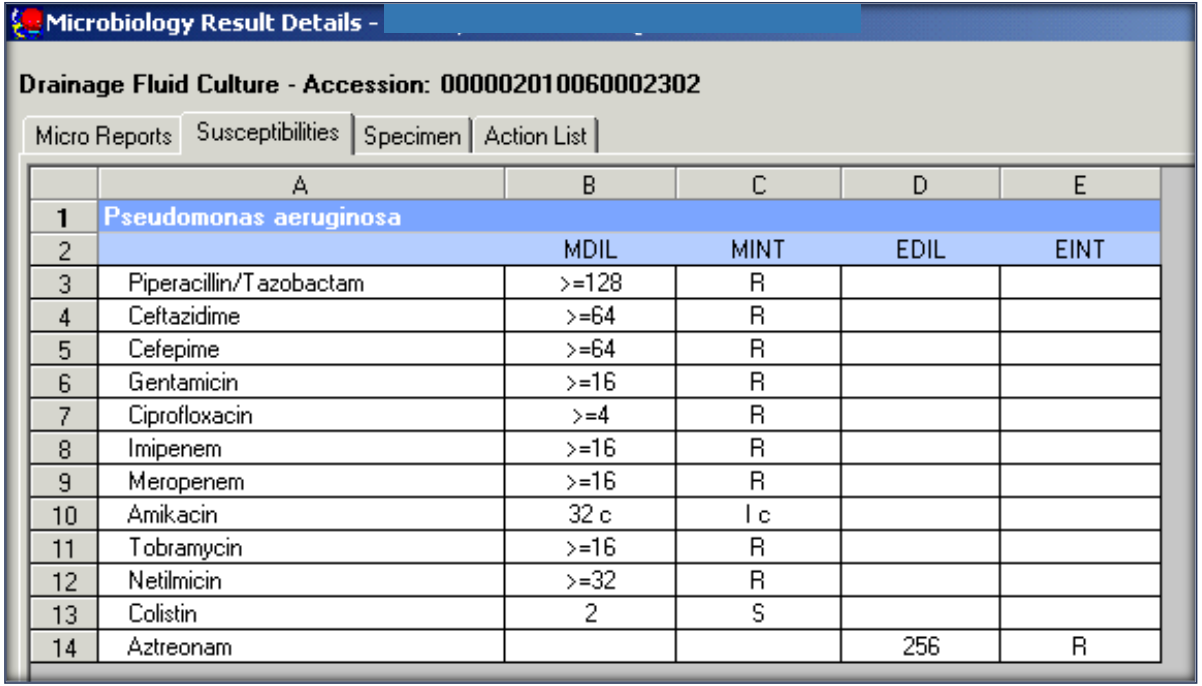
- Ampicillin
- Vancomycin
- Ticoplanin
- Telavancin
- ±Aminoglycosides
- Daptomycin
- Linezolid
- Quinupristin/Dalfopristin
- Tigecycline

Risk factors for ESBL, AmpC or MDR?

Steps in Antibiotic Selection



March 1, 2010



Microbiology Result Details -

Drainage Fluid Culture - Accession: 000002010060002302

Micro Reports | Susceptibilities | Specimen | Action List

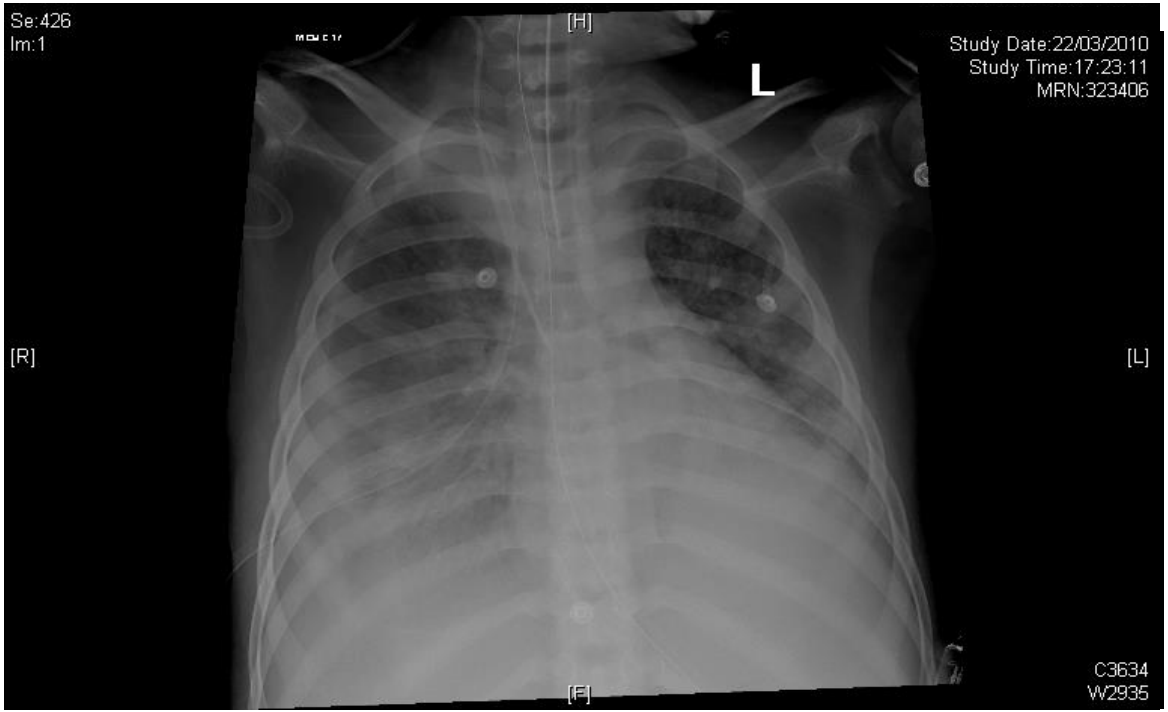
	A	B	C	D	E
1	**Pseudomonas aeruginosa**				
2		MDIL	MINT	EDIL	EINT
3	Piperacillin/Tazobactam	>=128	R		
4	Ceftazidime	>=64	R		
5	Cefepime	>=64	R		
6	Gentamicin	>=16	R		
7	Ciprofloxacin	>=4	R		
8	Imipenem	>=16	R		
9	Meropenem	>=16	R		
10	Amikacin	32 c	I c		
11	Tobramycin	>=16	R		
12	Netilmicin	>=32	R		
13	Colistin	2	S		
14	Aztreonam			256	R

Meropenem + Colistin + Vancomycin + Caspofungin

Antibiotic Course

Aspiration Pneumonia	Secondary Peritonitis	UTI	Tertiary Peritonitis
Jan 21	Feb 1	Feb 19	March 1
Candida sp	Klebsiella pneumoniae	Pseudomonas	
Pip/Taz	Imipenem	Pip/Taz then Ceftazidime	Meropenem
Vancomycin 2 days	Vancomycin 3 days	Vancomycin 3 days	Colistin
	Fluconazole		Caspofungin
			Vancomycin

March 21: Right pleural Effusion



Persistent Bacteremia

March 23-April 23

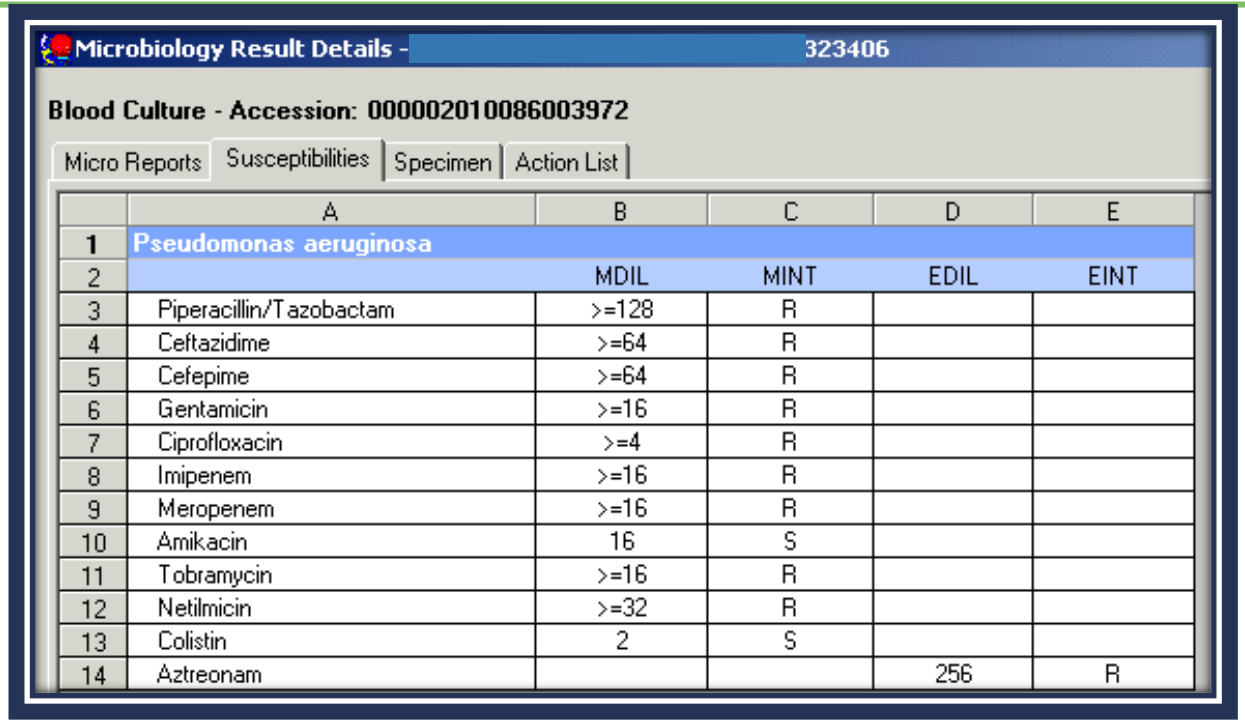
MRN:0323406 Age:17 years
Fin#:7165727 Gender:Male
Allergies: heparin Loc:MICU-C; 11; A Inpatient 17/Jan/2010 19:03 Active

Menu | Flowsheet | Print | 2 minutes ago

17 January, 2010 19:03 - 28 April, 2010 15:26 (Admit to Current Date)

Results								
23/03/2010 11:58			C POS					
23/03/2010 12:30			C POS					
23/03/2010 12:40						C POS		
23/03/2010 12:45						C POS		
27/03/2010 17:57			NEG					
27/03/2010 18:00			C POS					
03/04/2010 14:00			C POS					
03/04/2010 14:20			C POS					
03/04/2010 16:00			C POS					
04/04/2010 17:45					C POS			
05/04/2010 14:45			NEG					
07/04/2010 17:48			C POS					
07/04/2010 18:00			C POS					
17/04/2010 13:30			C POS	C (c) POS...				
17/04/2010 13:40			NEG					
17/04/2010 13:45			NEG					
17/04/2010 14:02						C POS		

MDR Pseudomonas



Microbiology Result Details - 323406

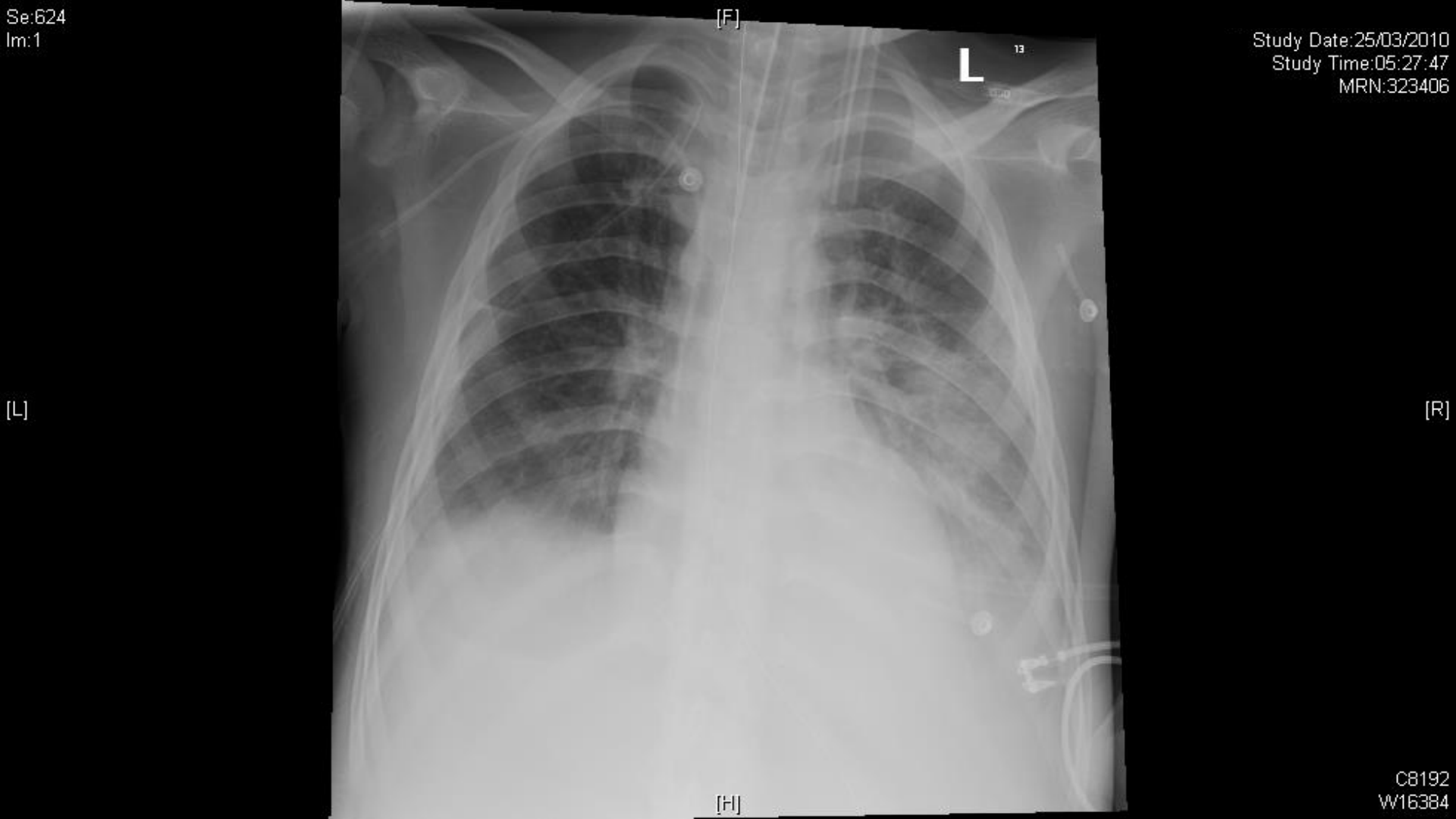
Blood Culture - Accession: 0000020100860039 72

Micro Reports | Susceptibilities | Specimen | Action List

	A	B	C	D	E
1	**Pseudomonas aeruginosa**				
2		MDIL	MINT	EDIL	EINT
3	Piperacillin/Tazobactam	>=128	R		
4	Ceftazidime	>=64	R		
5	Cefepime	>=64	R		
6	Gentamicin	>=16	R		
7	Ciprofloxacin	>=4	R		
8	Imipenem	>=16	R		
9	Meropenem	>=16	R		
10	Amikacin	16	S		
11	Tobramycin	>=16	R		
12	Netilmicin	>=32	R		
13	Colistin	2	S		
14	Aztreonam			256	R

What does persistent pseudomonas bacteremia indicate?

A. Persistent intra-abdominal infection
B. Persistent pneumonia
C. Catheter related blood stream infection
D. Enterovesicular fistula
E. Endocarditis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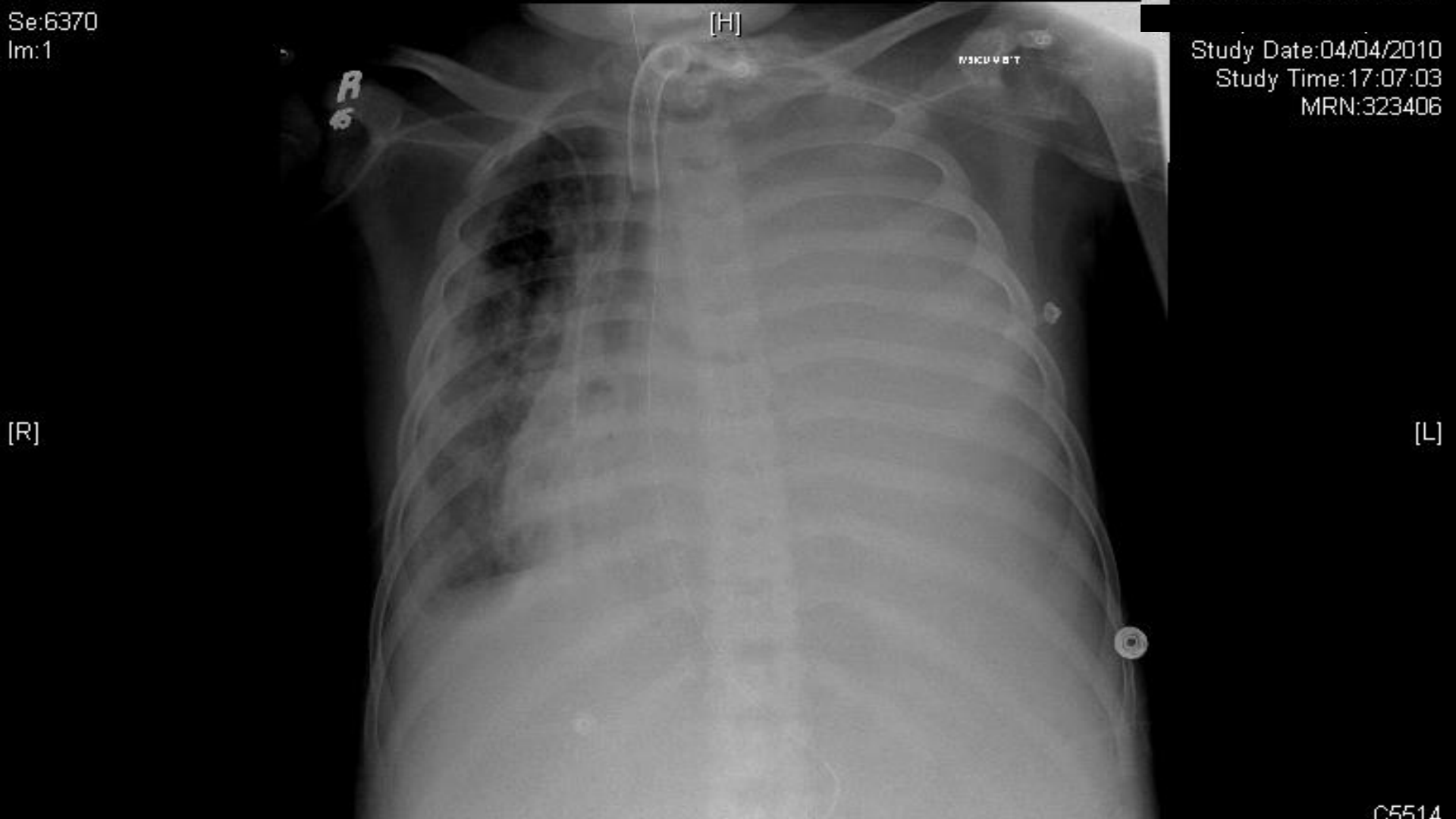
Study Time:05:27:47
MRN:323406
[L]
[R]
[H]
C8192
W16384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Study Time:17:07:03
MRN:323406
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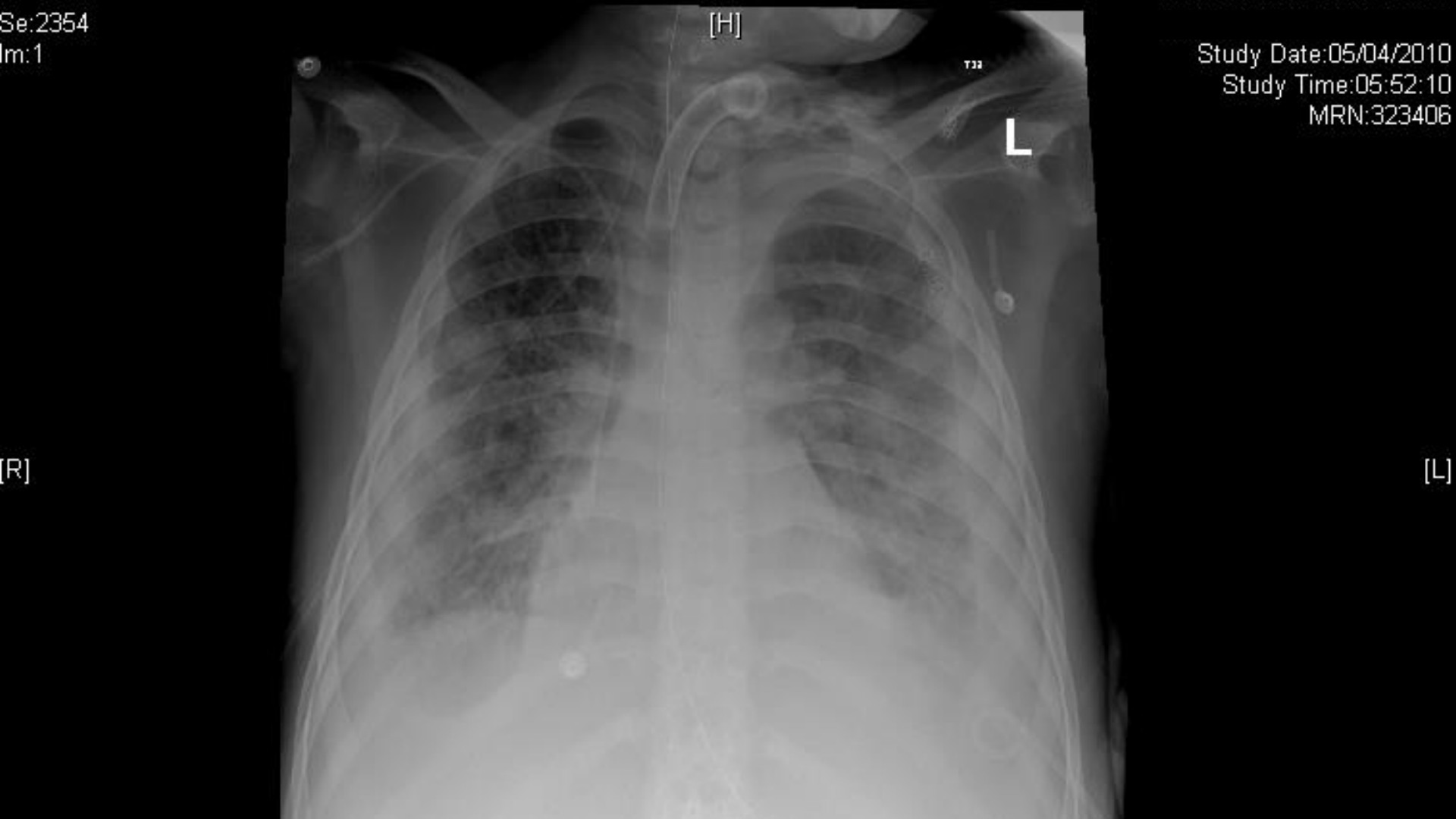
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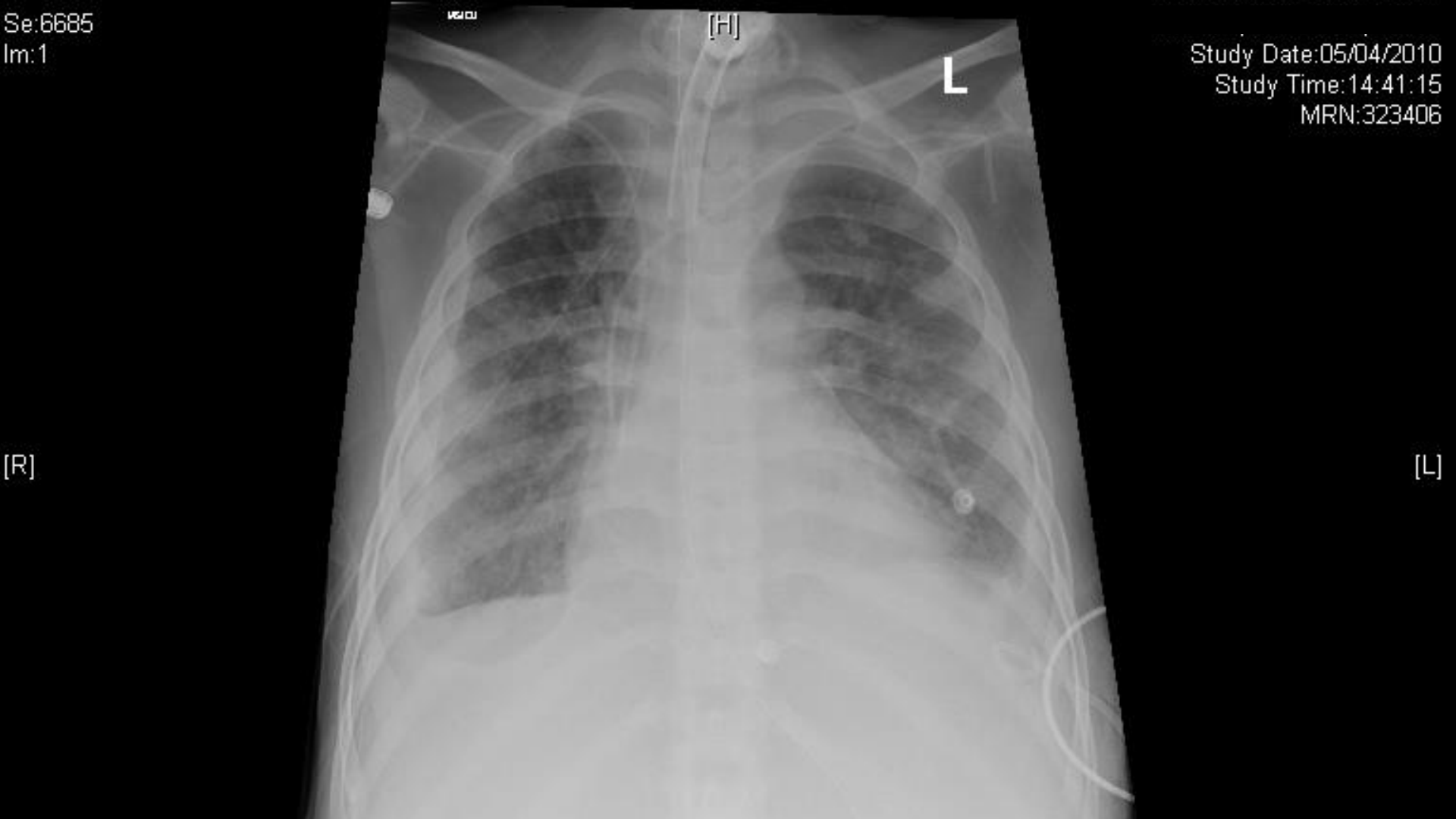
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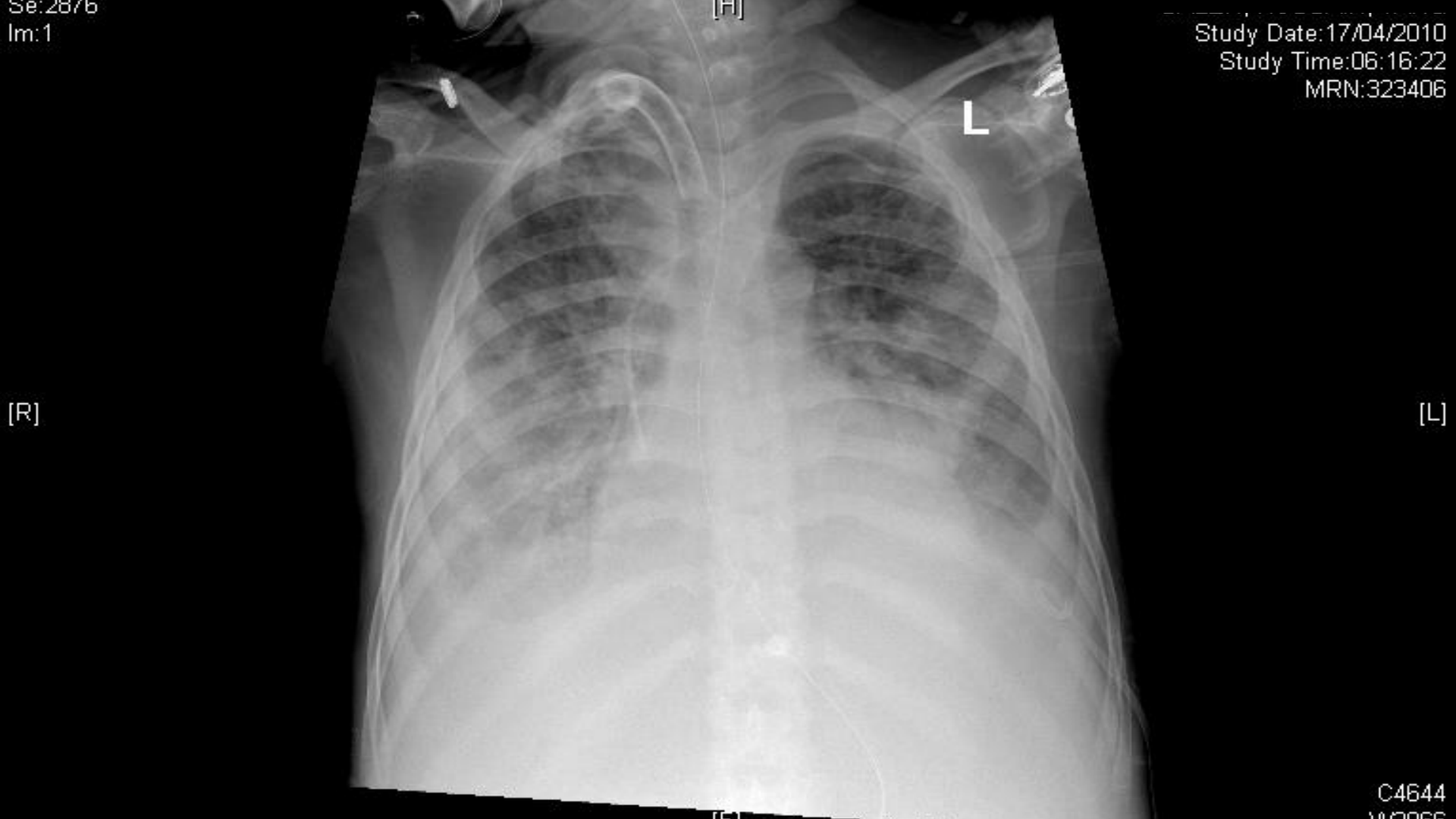
April 17

Fever

Increasing FiO2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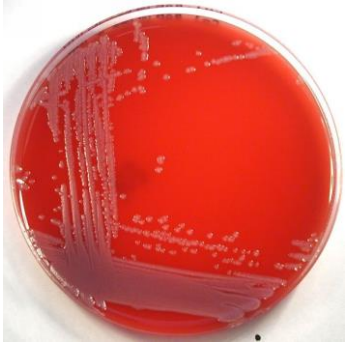
What Organisms?



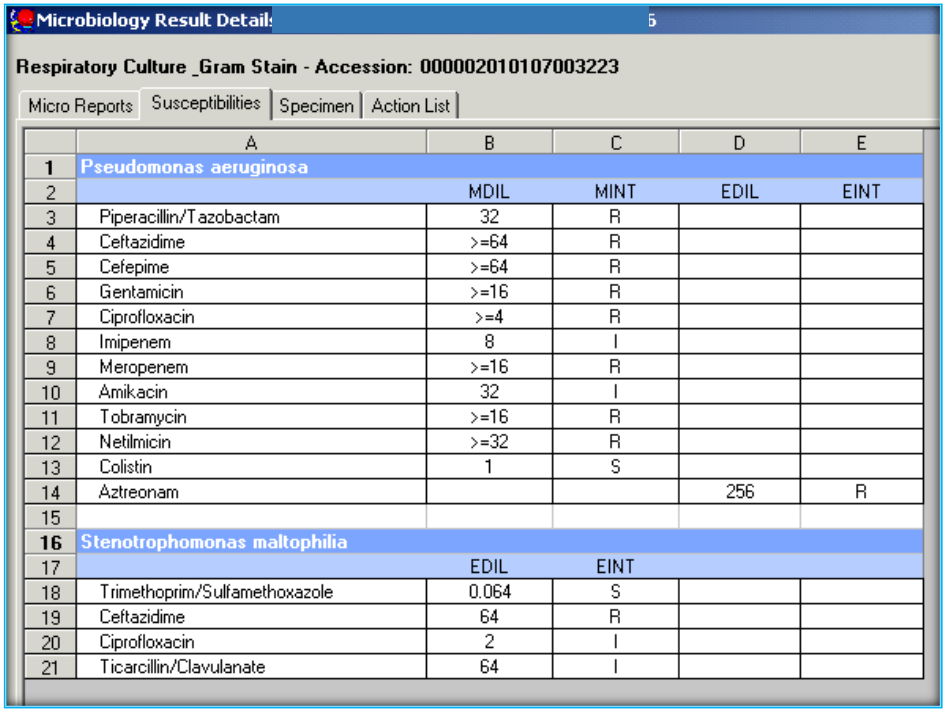
Stenotrophomonas maltophilia

Flavobacterium

MDR Pseudomonas aeruginosa

MDR Acinetobacter

April 17



Microbiology Result Details

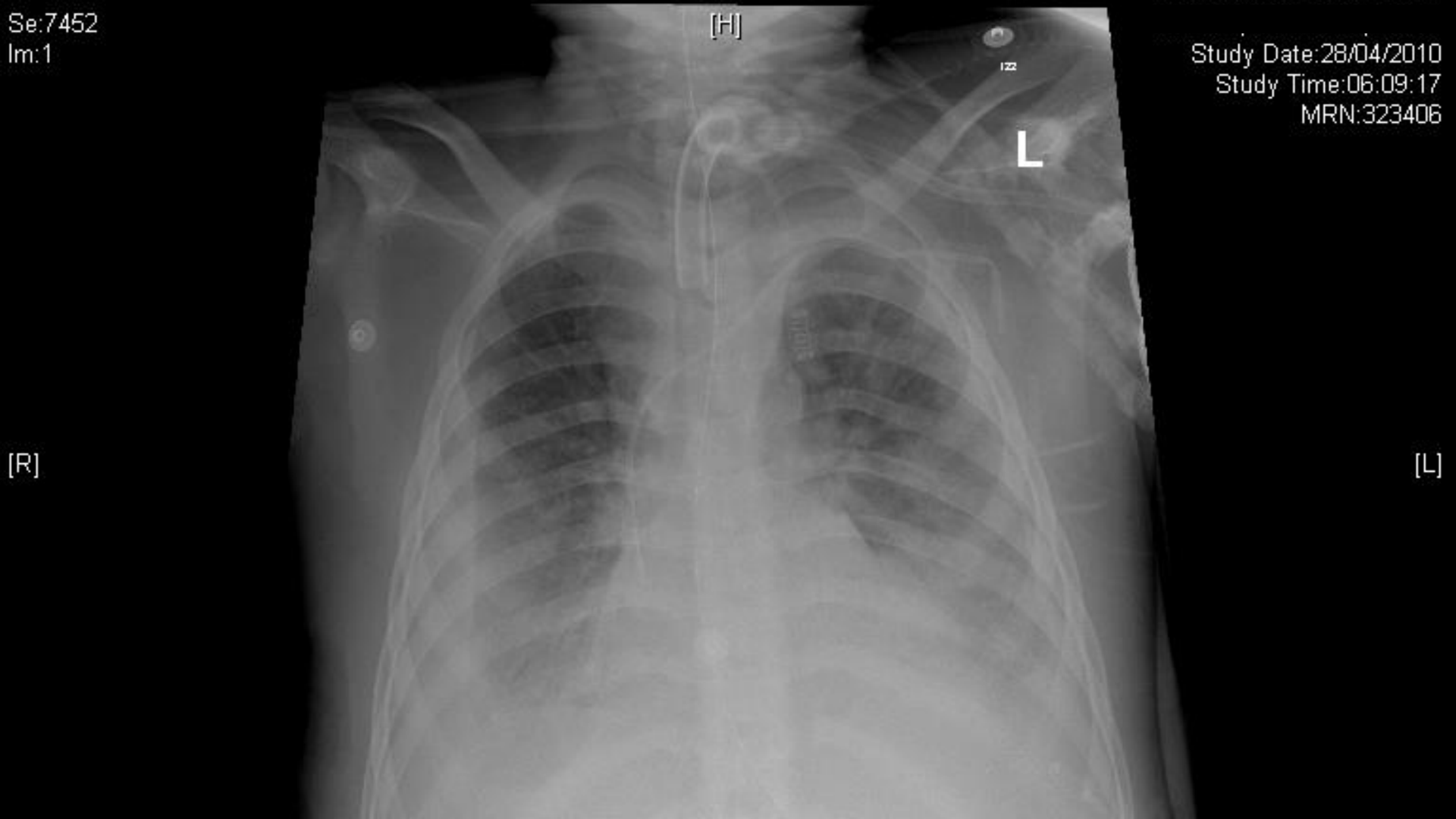
Respiratory Culture _Gram Stain - Accession: 000002010107003223

Micro Reports | Susceptibilities | Specimen | Action List

	A	B	C	D	E
1	**Pseudomonas aeruginosa**				
2		MDIL	MINT	EDIL	EINT
3	Piperacillin/Tazobactam	32	R		
4	Ceftazidime	>=64	R		
5	Cefepime	>=64	R		
6	Gentamicin	>=16	R		
7	Ciprofloxacin	>=4	R		
8	Imipenem	8	I		
9	Meropenem	>=16	R		
10	Amikacin	32	I		
11	Tobramycin	>=16	R		
12	Netilmicin	>=32	R		
13	Colistin	1	S		
14	Aztreonam			256	R
15					
16	**Stenotrophomonas maltophilia**				
17		EDIL	EINT		
18	Trimethoprim/Sulfamethoxazole	0.064	S		
19	Ceftazidime	64	R		
20	Ciprofloxacin	2	I		
21	Ticarcillin/Clavulanate	64	I		

What antibiotic would you add?

A. Bactrim
B. Doxyclycline
C. Tigecycline
D. Chloramphenicole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Steps in Antibiotic Selection

VAP

Patient has at least one any risk factor for MDR VAP

ceftazidime-avibactam, ceftolozane-tazobactam, cefiderocol, imipenem-cilastatin-relebactam, and meropenem-vaborbactam + Vancomycin or linezolid

No

Local resistance rate of gram-negative isolates to a monotherapy agent is >10% or unknown

ceftazidime-avibactam, ceftolozane-tazobactam, cefiderocol, imipenem-cilastatin-relebactam, and meropenem-vaborbactam

No

No risk factors for resistance and MDR prevalence is <10

Cefepime, pip/taz, levofloxacin, (meropenem, or imipenem)

Yes

MRSA prevalence is >10-20 percent or unknown

Vancomycin, linezolid, or telavancin

Newer Antibiotics with Activity Against Resistant Organisms

Agent	Enterobacteriaceae (e.g. E. coli, Klebsiella spp.)					Carbapenem-resistant *Pseudomonas aeruginosa*		*Acinetobacter baumannii*	*Stenotrophomonas maltophilia*
	ESBL	**KPC**	**AmpC**	**MBL**	**OXA-48**	***Efflux***	***AmpC***		
Aztreonam-avibactam									
Cefiderocol									
Ceftazidime-avibactam									
Ceftolozane-tazobactam									
Eravacycline									
Imipenem-relebactam									
Meropenem-vaborbactam									
Plazomicin									
Polymyxin B or Colistin									
Tigecycline									

Susceptibility >80% Susceptibility >30-80% Susceptibility <30%

Thank you
for your attentions