Antibiotics 101 for Laboratory Professionals: Part Two

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OUTLINE

I. Trying to understand the choice

II. Selected classes of antimicrobials

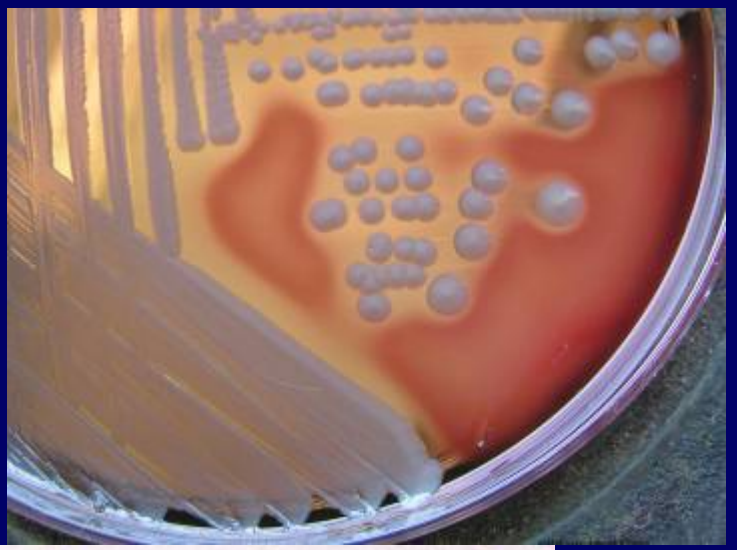
III. Bacterium-specific examples of resistance

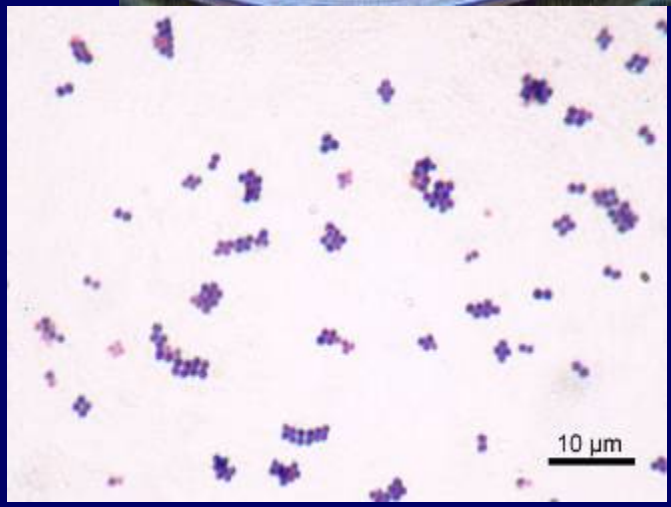
- A. *Streptococcus pneumoniae*
- B. *Staphylococcus aureus*
- C. *Klebsiella pneumoniae*

"D#*%it, Jim,
I'm not a physician."

Staphylococcus aureus

- Skin and soft tissue infections
- Necrotizing pneumonia
- Otitis media
- Bacteremia
- Osteomyelitis
- Endocarditis





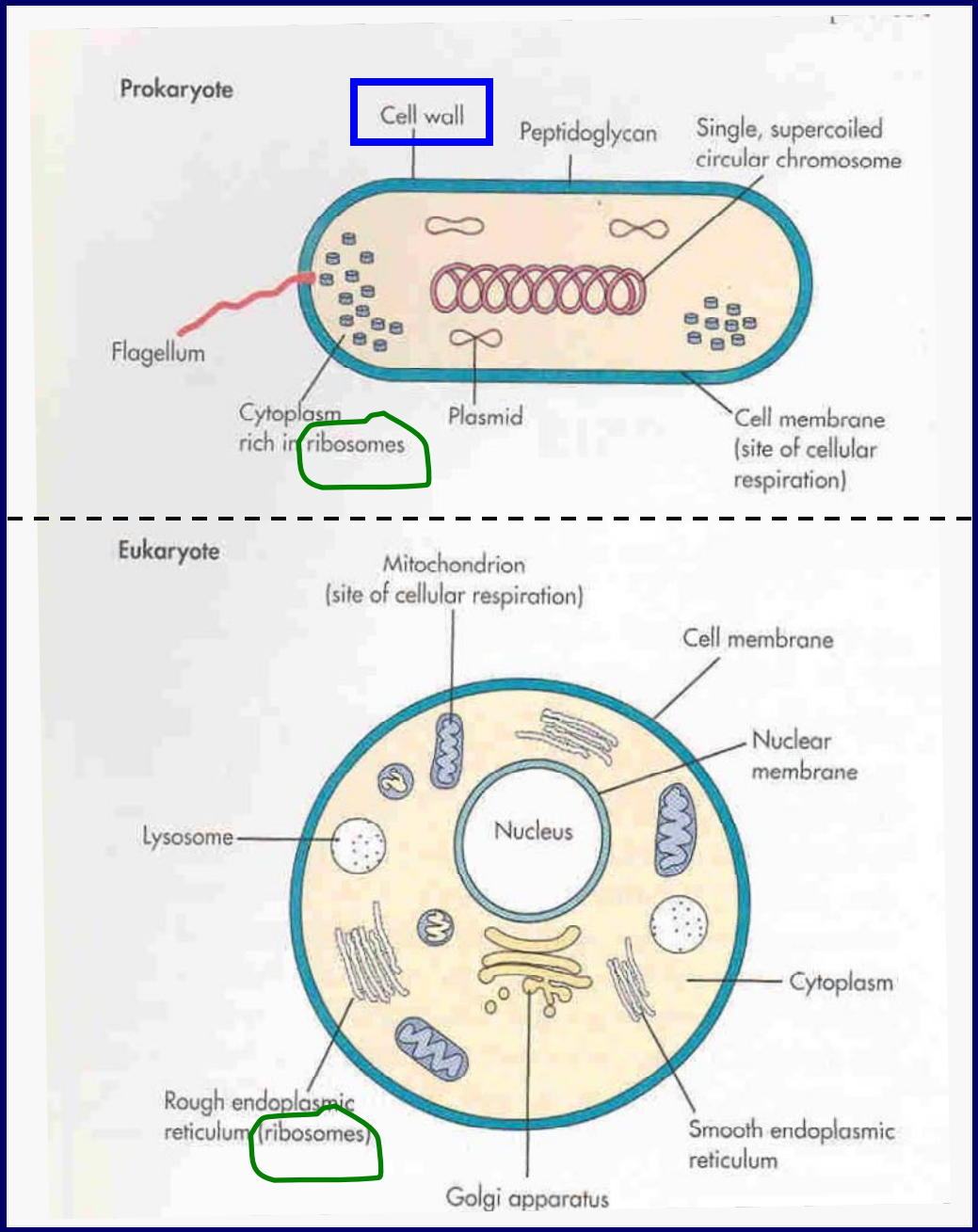
TWO BASIC SUBDIVISIONS

- β-lactam

Penicillins	**Cell wall synthesis**

- Non-β-lactam

Glycopeptides	**Cell wall synthesis**
Lincosamides	**Protein synthesis**
Streptogramins	
Oxazolidinones	


Prokaryote
Cell wall
Peptidoglycan
Single, supercoiled circular chromosome
Flagellum
Cytoplasm rich in ribosomes
Plasmid
Cell membrane (site of cellular respiration)
Eukaryote
Mitochondrion (site of cellular respiration)
Cell membrane
Nuclear membrane
Lysosome
Nucleus
Cytoplasm
Rough endoplasmic reticulum (ribosomes)
Smooth endoplasmic reticulum
Golgi apparatus

PENICILLIN CLASS

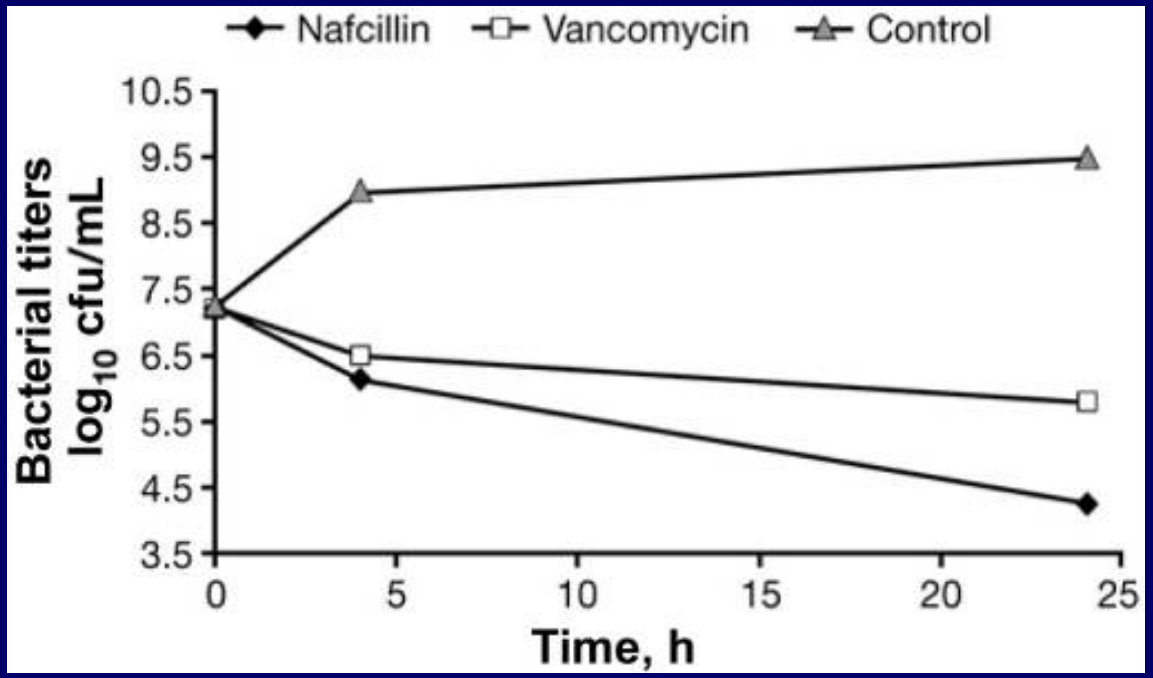
Subclass (if appropriate)	Agent(s)
penicillin	penicillin
aminopenicillin	amoxicillin
	ampicillin
carboxypenicillin	carbenicillin
	ticarcillin
ureidopenicillin	piperacillin
penicillinase-stable penicillins	dicloxacillin
	methicillin
	nafcillin
	oxacillin

PENICILLIN CLASS

Parameter	Description
Spectrum of activity	Penicillins: streptococci, anaerobes, *Neisseria*, agent of syphilis Aminopenicillins: (similar to penicillin PLUS) *Listeria*, enterococci, *Haemophilus*, some enteric GNR Carboxypenicillins: better enteric GNR coverage, some *Pseudomonas aeruginosa*, anaerobes Ureidopenicillins: even better enteric GNR coverage, better *Pseudomonas aeruginosa*, anaerobes Penicillinase-stable penicillins: Staph w/o *mecA*
Interesting stuff	Despite “narrow” spectrum of activity, nafcillin with greater potency than broad spectrum vancomycin

CONSERVATIVE EMPIRICAL RX??

Higher treatment failure/mortality rates in MSSA bacteremic patients treated with vancomycin than in those treated with nafcillin



Clin. Infect. Dis. **42(suppl 1):** S51-S57; 2006

GLYCOPEPTIDE CLASS

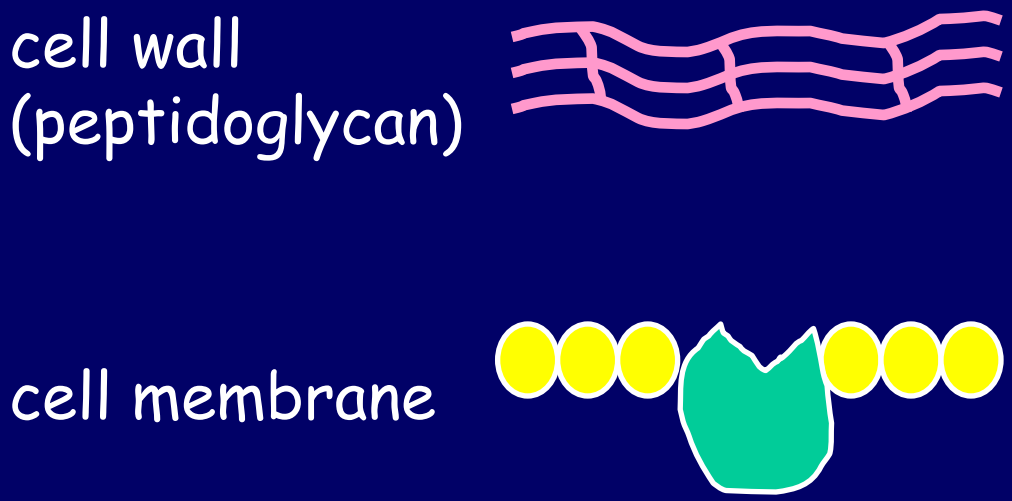
Subclass (if appropriate)	Agent(s)
glycopeptide	vancomycin
lipoglycopeptide	teicoplanin

GLYCOPEPTIDE MECHANISM

Complexes with D-alanine-D-alanine residues on cell wall precursor

↓

Inhibit peptidoglycan synthesis



GLYCOPEPTIDE CLASS

Parameter	Description
Mechanism of action	Inhibits peptidoglycan synthesis by complexing with D-alanine-D-alanine residues
Activity rendered	Cidal
Route of administration	IV (PO for *C. difficile*)
Distribution	Well; CNS penetration at high doses
Half-life	4-6 hours → q12h
Excretion	Renal and biliary
Adverse effects	Fever, chills, phlebitis at infusion site; red man syndrome with rapid/bolus infusion; kidneys (with AG)

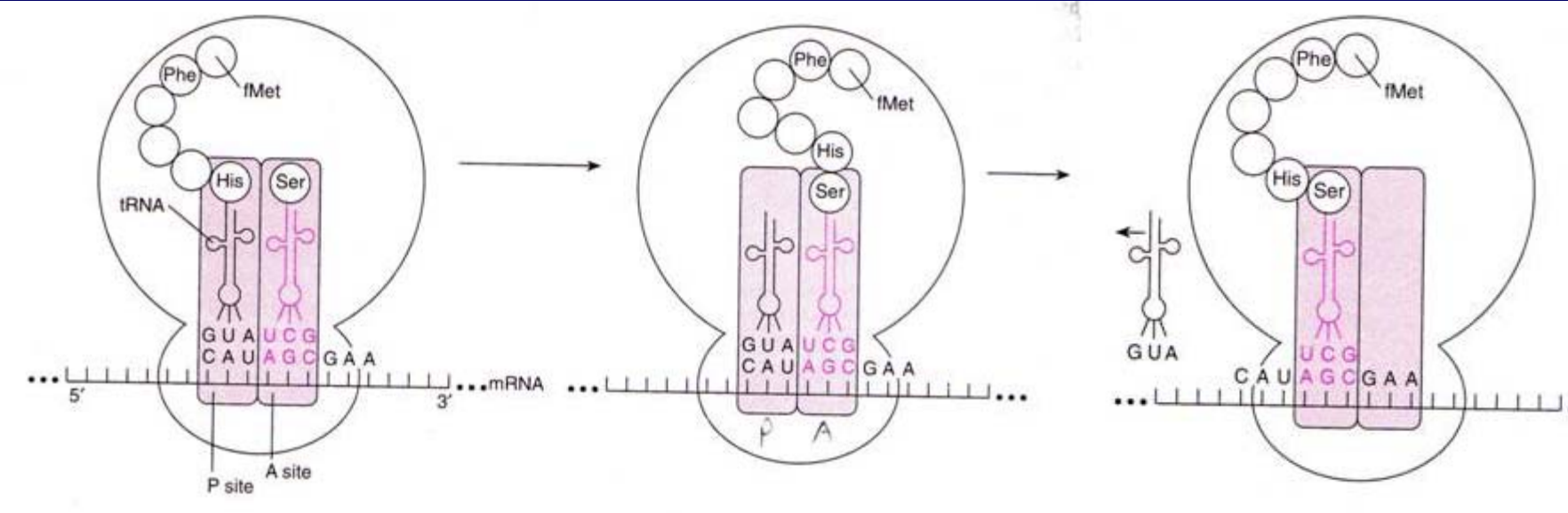
GLYCOPEPTIDE CLASS

Parameter	Description
Spectrum of activity	Broad spectrum (Gram positive anaerobes, facultatives) MRSA *Clostridium difficile* *Corynebacterium jeikeium* Penicillin- or cephalosporin-allergic patients Empiric therapy for sepsis Aminoglycoside synergy
Interesting stuff	Activity against just one Gram negative organism (*Flavobacterium meningosepticum*)

LINCOSAMIDE CLASS

Subclass (if appropriate)	Agent(s)
NONE	clindamycin

LINCOSAMIDE CLASS



- Reversible binding to 50S ribosomal subunit
- Blocks translocation reaction of peptide elongation (no A to P)

LINCOSAMIDE CLASS

Parameter	Description
Mechanism of action	Bind reversibly to 50S ribosomal subunits, blocking the translocation reaction of polypeptide chain elongation
Activity rendered	Static; can be cidal
Route of administration	PO or IV
Distribution	Well (including bone, placenta, intracellular); no CNS
Half-life	2.4 hours → q6h or q8h
Excretion	Renal and biliary
Adverse effects	Diarrhea in 20% of patients; association with *Clostridium difficile*; rash and fever

LINCOSAMIDE CLASS

Parameter	Description
Spectrum of activity	Gram positive facultative: Option for MRSA Not *Enterococcus* spp. *S. pneumoniae* (not CSF) Anaerobes: Good for actinomycosis 10-15% resistance in *Bacteroides* 10-20% resistance in *C. perfringens* *Babesia*, *Plasmodium*, *Toxoplasma*, *Pneumocystis*
Interesting stuff	~40% resistance rate in β-hemolytic streptococci; emerging problem in penicillin-allergic patients

STREPTOGRAMIN CLASS

Subclass (if appropriate)	Agent(s)
NONE	quinupristin-dalfopristin

STREPTOGRAMIN CLASS

- Combination of two structurally-unrelated compounds (group A and group B streptogramins) acting in synergy

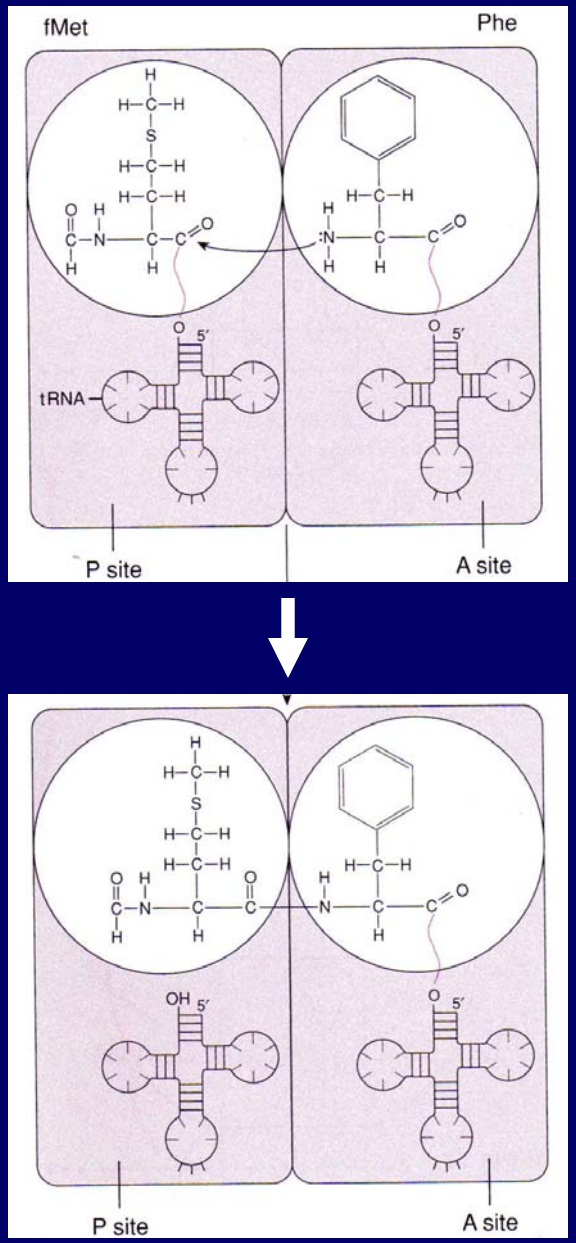
- Synercid: 30% quinupristin
  70% dalfopristin

STREPTOGRAMIN CLASS

Group A streptogramin binds to 50S subunit of ribosome

↓

Prevent peptide bond formation during chain elongation step



STREPTOGRAMIN CLASS

Conformation change of ribosome (group A) increases affinity for group B streptogramins

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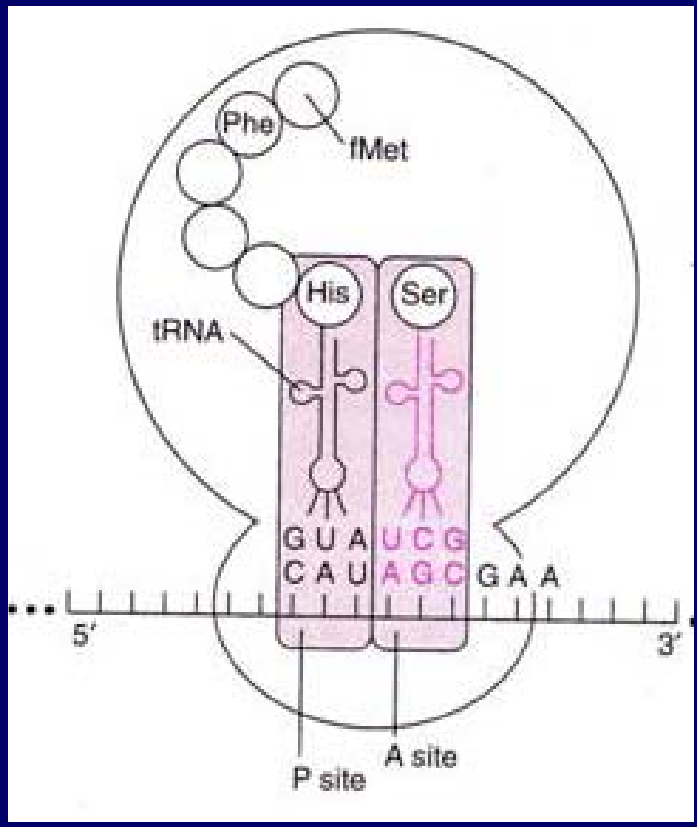
Release of incomplete peptides from 50S subunit of ribosome



STREPTOGRAMIN CLASS

Parameter	Description
Mechanism of action	streptogramin A: block translocation function of polypeptide chain elongation streptogramin B: release of incomplete chain from ribosome
Activity rendered	Cidal
Route of administration	IV
Distribution	Well; intracellular
Half-life	1 hour → q8h
Excretion	Biliary, renal
Adverse effects	Arthralgias, myalgias (reversible upon discontinuation); cutaneous reactions; GI

STREPTOGRAMIN CLASS

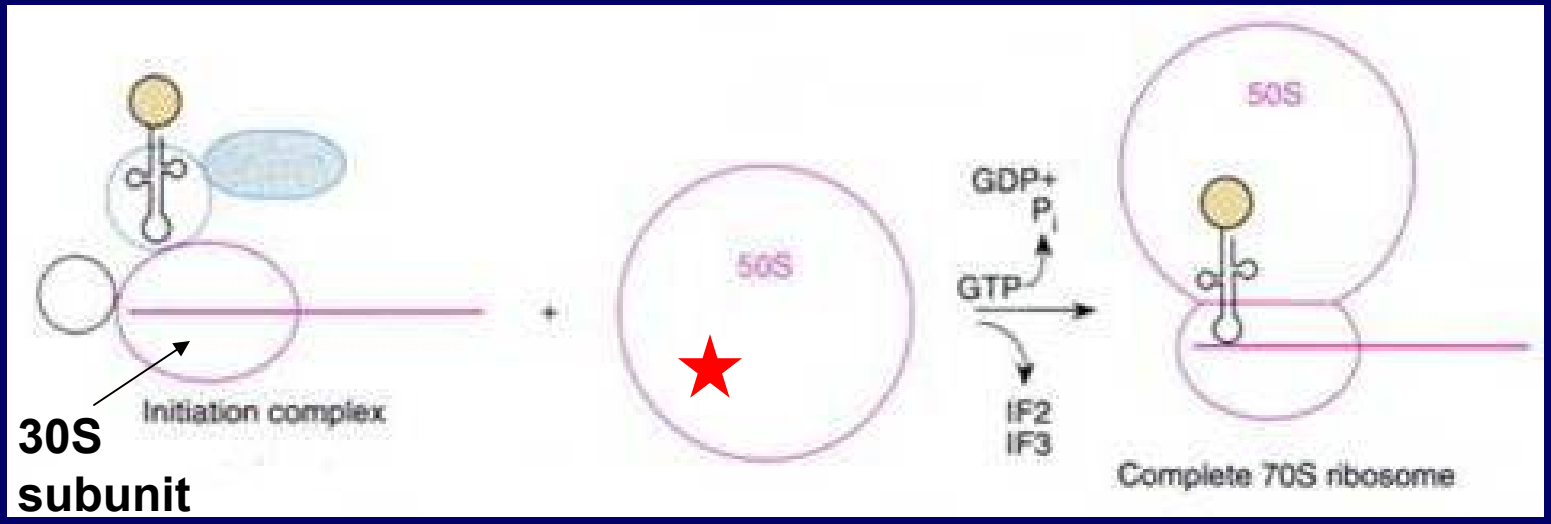
Parameter	Description
Spectrum of activity	Vancomycin-resistant *Enterococcus* (*E. faecium*) Staphylococci and streptococci (including species resistant to macrolides, β-lactams, fluoroquinolones) Agents of atypical pneumonia *Neisseria* spp. Most anaerobes
Interesting stuff	Losing battle versus enterococci (VRE)

OXAZOLIDINONE CLASS

Subclass (if appropriate)	Agent(s)
NONE	linezolid

OXAZOLIDINONE CLASS

Binds ribosomal RNA within 50S subunit (★), distorting binding site for first transfer RNA → Prevent formation of functional initiation complex



OXAZOLIDINONE CLASS

Parameter	Description
Mechanism of action	1. Prevents initiation of protein synthesis 2. No cross-resistance with other protein synthesis inhibitors
Activity rendered	Static
Route of administration	PO or IV
Distribution	Well; CNS penetration
Half-life	5 hours → q12h
Excretion	Renal
Adverse effects	Diarrhea, headache, nausea; prolonged use → neuropathy, myelosuppression (RBC, WBC, platelets)

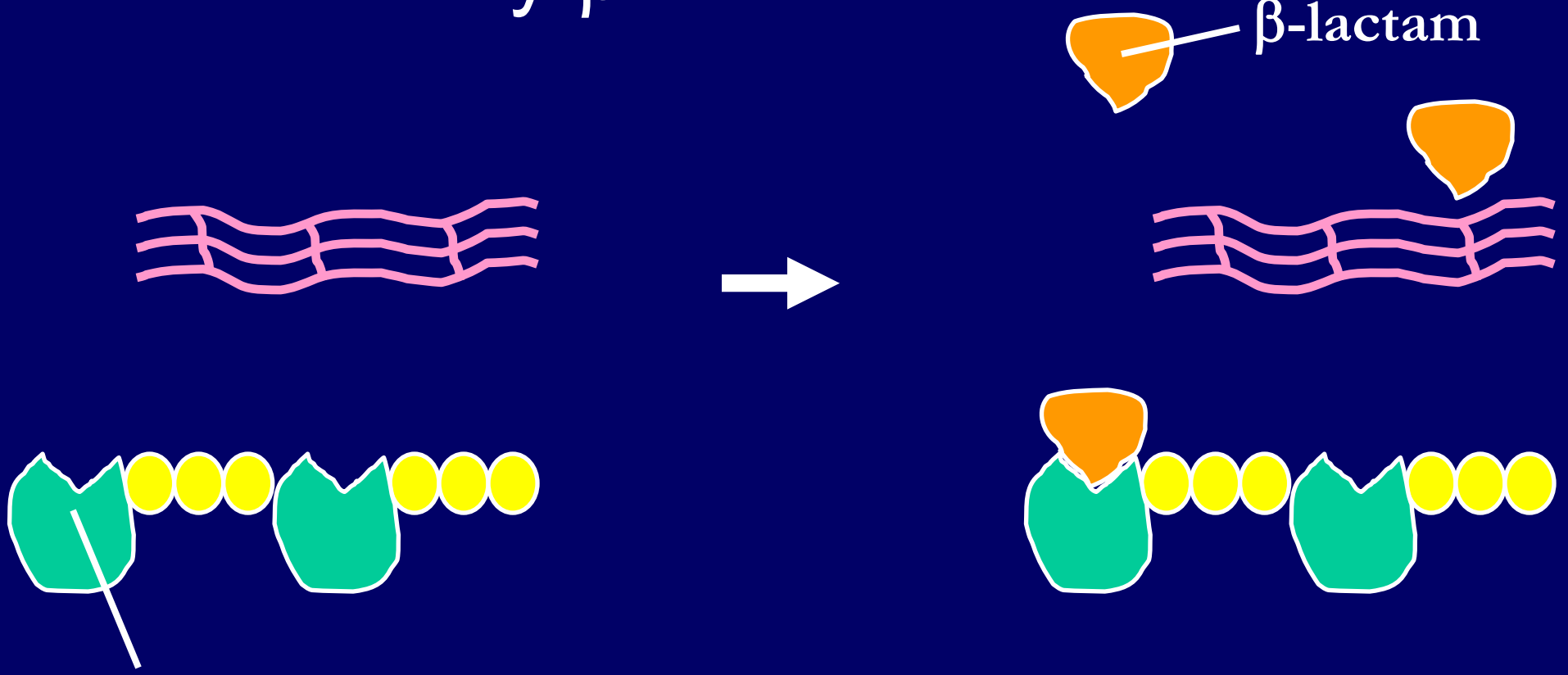
OXAZOLIDINONE CLASS

Parameter	Description
Spectrum of activity	Vancomycin-resistant *Enterococcus* spp. (VRE) Methicillin-resistant *Staphylococcus aureus* (MRSA) Gram positive facultatives and mycobacteria Gram positive anaerobes Skin and soft tissue infections Lower respiratory tract infections
Interesting stuff	"Do we want GI mad at us or do we want heme/onc mad at us?? (quinupristin-dalfopristin vs. linezolid)"

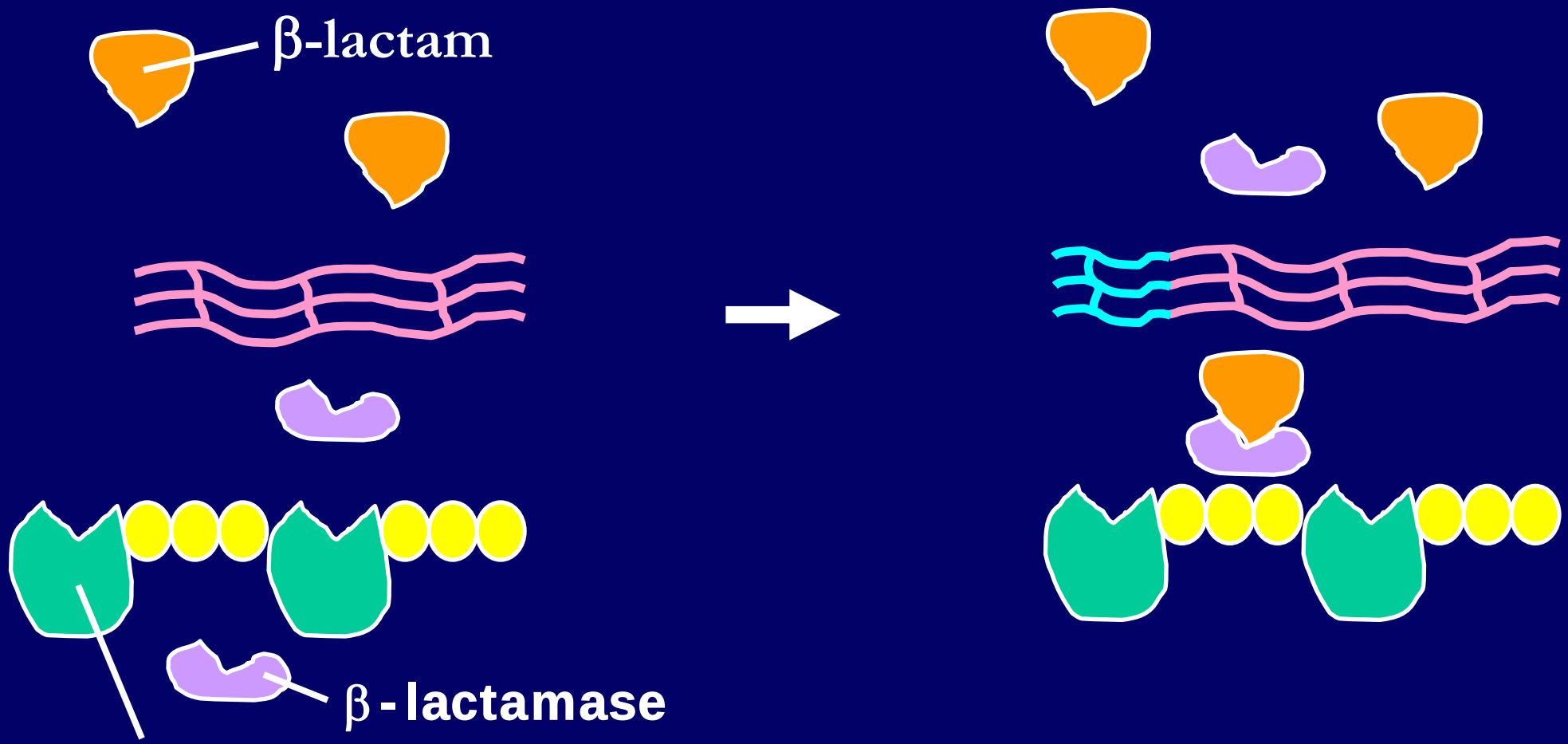
Mechanisms of Resistance

β-LACTAM RESISTANCE

- Mediated by β-lactamases



β-LACTAM RESISTANCE



β-LACTAMASE-POSITIVE STAPHYLOCOCCI

Predicts resistance to the following β-lactam agents:

penicillin
ampicillin
amoxicillin
carbenicillin
ticarcillin
piperacillin

Staphylococcus aureus THERAPY

- Penicillin

  > 90% resistance rate

- Nafcillin (tested by oxacillin)

β-LACTAM RESISTANCE

- Mediated by β-lactamases
- Mediated by penicillin-binding proteins

  mecA (origin likely *Staphylococcus sciuri*) transcribed, translated into PBP2a

  mecA influenced by several regulatory genes

  Constituent of SCC*mec* (staphylococcal cassette chormosome)

METHICILLIN-RESISTANCE INDUCTION

Organism	Increase in *mecA* Activity	
	Oxacillin (1 μg/mL)	Cefoxitin (1 μg/mL)
MRSA	**1.1-fold**	**9.7-fold**

J. Bacteriol. **183:** 6862-6868; 2001

DETECTION OF MRSA

Disk Diffusion Agent	Sensitivity	Specificity
Oxacillin	~81%	~70%
Cefoxitin	100%	100%

J. Clin. Microbiol. **43:** 3818-3825; 2005

CEFOXITIN-RESISTANT STAPHYLOCOCCI

Change categorical interpretation to "RESISTANT", regardless of MIC, for the following agents:

penicillins
cephems
monobactams
β-lactam/β-lactamase inhibitor combinations
carbapenems

Staphylococcus aureus THERAPY

- Penicillin

  > 90% resistance rate

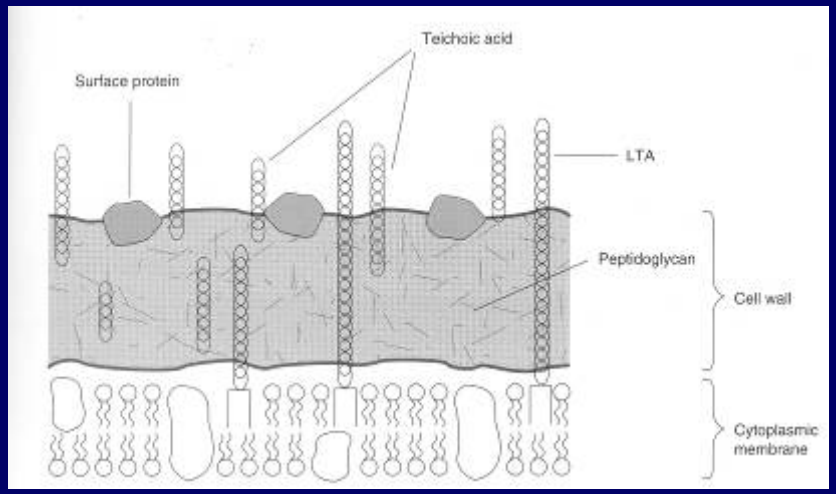
- Nafcillin (tested by cefoxitin)

  Variable resistance
  ~60% in Milwaukee (*mecA*)

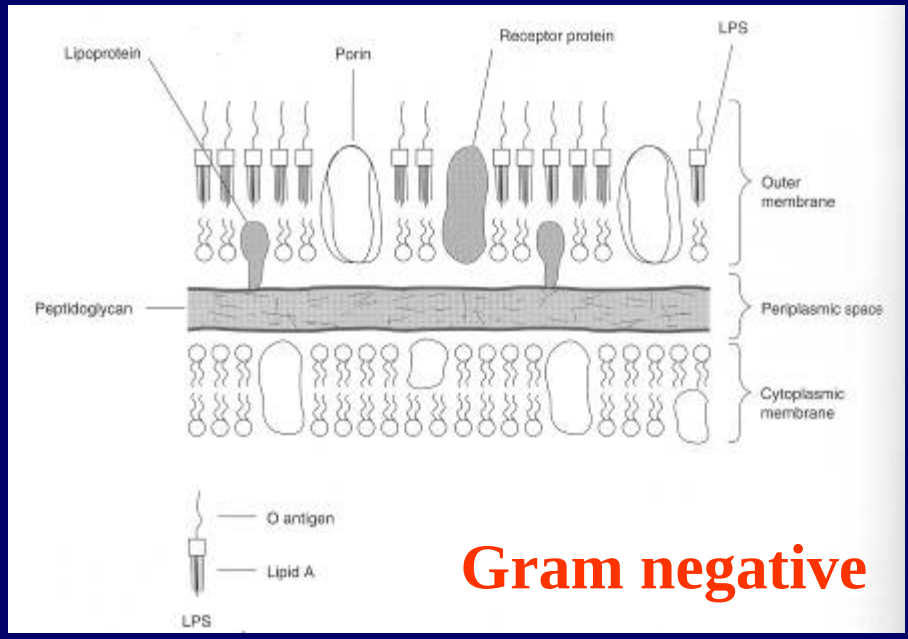
- Vancomycin (MRSA and MSSA)

GLYCOPEPTIDE RESISTANCE (INTRINSIC)

Large size limits ability to penetrate Gram negatives



Gram positive



Gram negative

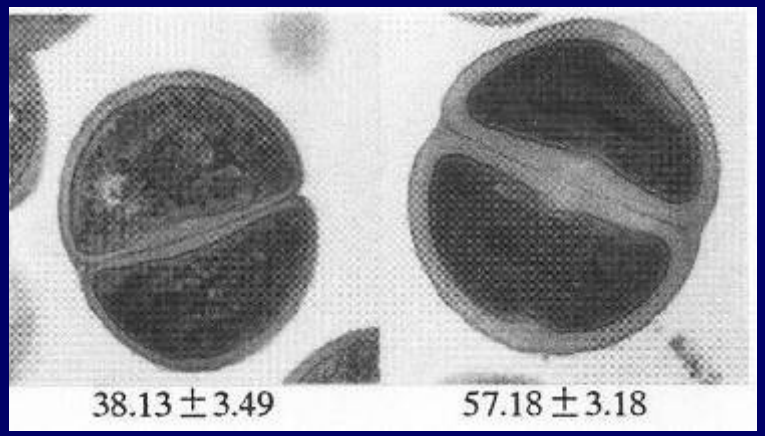
GLYCOPEPTIDE RESISTANCE (ACQUIRED)

- Mutational cell wall changes

  Characterized by reduced susceptibility, not resistance

  Characterized by thickened cell wall

Increased number of unlinked precursors
Abnormal septum formation



Antimicrobial Agents Chemother. **44:** 2276-2285; 2000

GLYCOPEPTIDE RESISTANCE (ACQUIRED)

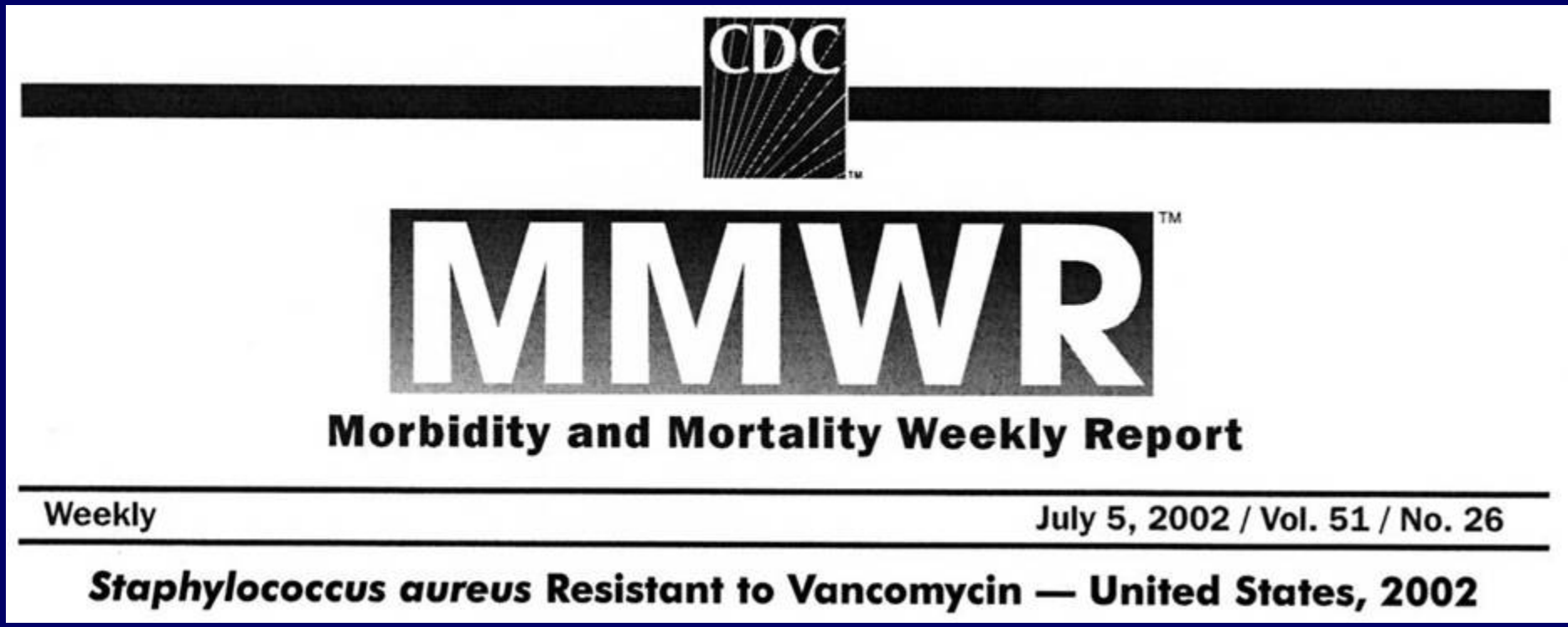
- Mutational cell wall changes
- Altered precursor formation

  Resistance genes promote change in terminus of peptidoglycan precursor to alanine~lactate

  1000-fold reduced affinity for vancomycin

vanA transposon (plasmid)
vanB transposon (plasmid)

vanC chromosomal
vanD chromosomal
vanE chromosomal
vanG chromosomal



CDC

MMWR™

Morbidity and Mortality Weekly Report

Weekly July 5, 2002 / Vol. 51 / No. 26

***Staphylococcus aureus* Resistant to Vancomycin — United States, 2002**

Vancomycin-resistant *Staphylococcus aureus* (VRSA)

VRSA IN MICHIGAN--2002

- Chronic renal failure; diabetic foot ulcers
- VRSA isolated from catheter exit site; VRE, VRSA, *Klebsiella* from ulcer
- *vanA* sequenced from VRSA

  Same as *vanA* from patient's VRE

  Same as *vanA* from VRE transposon

MMWR. **51:** 565-567; 2002

LINCOSAMIDE RESISTANCE

- Staphylococci and β-streptococci
- *msrA* → constitutive resistance (efflux)
- *erm* gene cassette → inducible resistance

  a.k.a. MLS_B locus

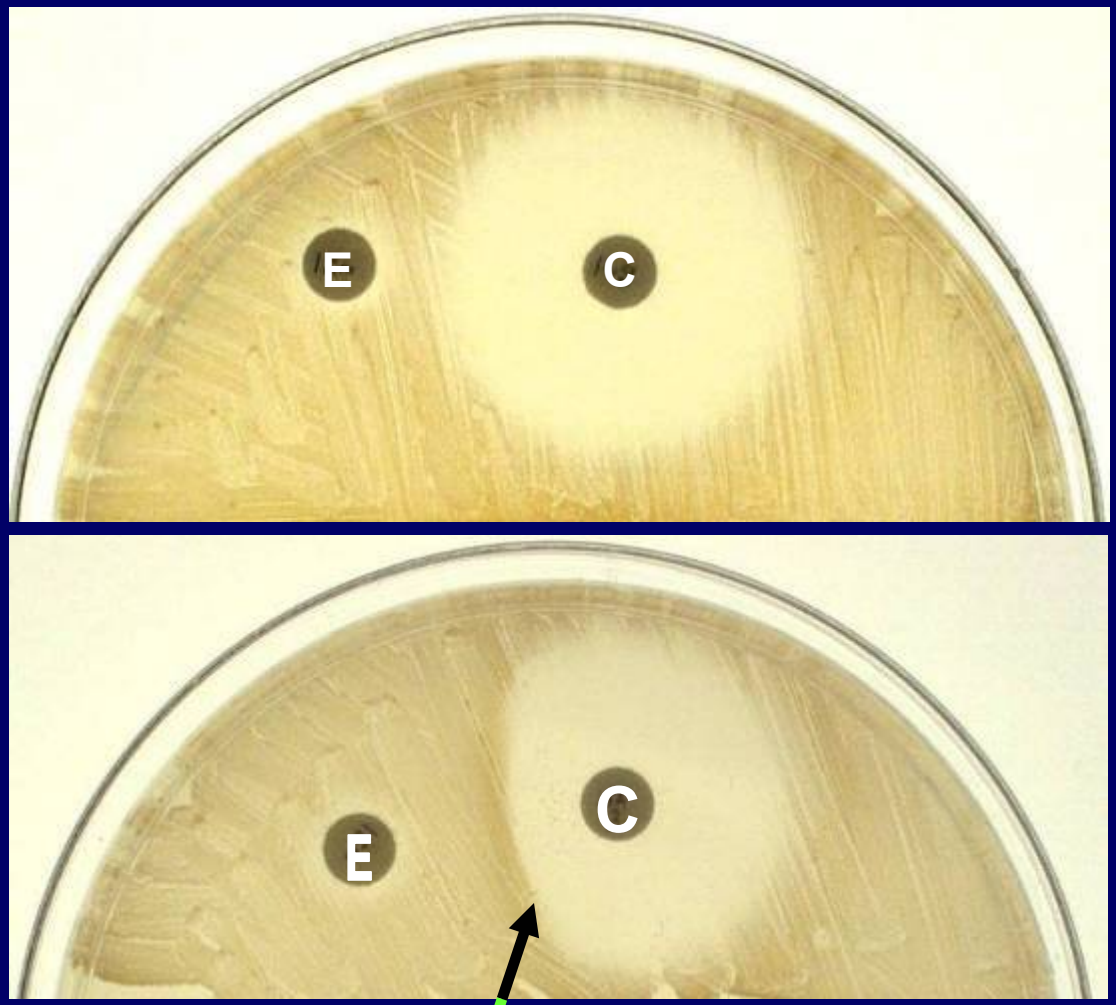
MACROLIDE
LINCOSAMIDE
STREPTOGRAMIN

Ribosome methylation

ERYTHROMYCIN/CLINDAMYCIN TESTING

msrA-mediated erythromycin resistance

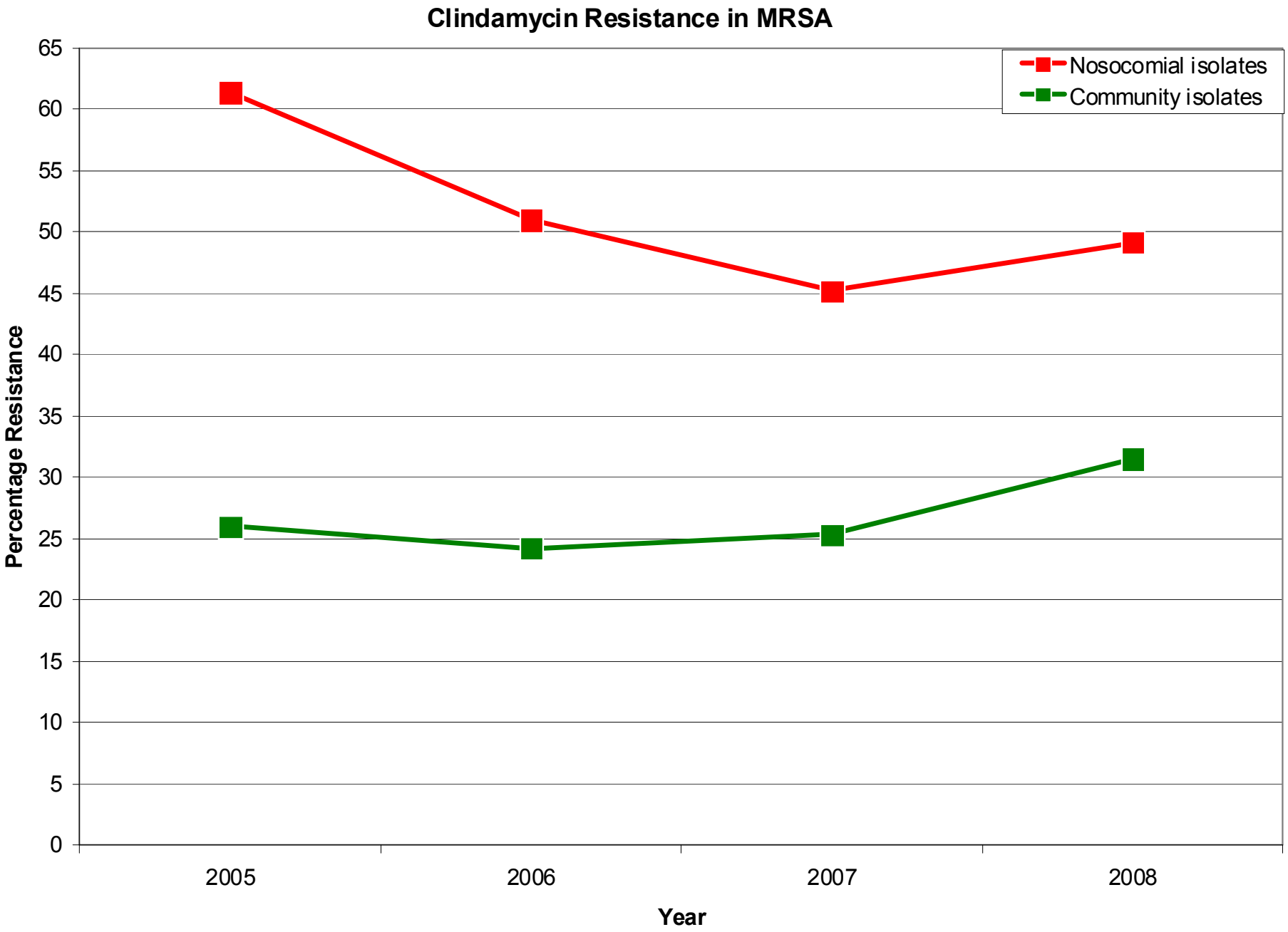
erm-mediated erythromycin resistance



Inducible clindamycin resistance

INDUCIBLE LINCOSAMIDE RESISTANCE

Organism Group	Percentage of Isolates with Inducible Clindamycin Resistance		
	Nosocomial	Outpatient	Total
Coagulase-negative staph	51.4	46.2	49.2
MRSA	31.3	26.2	27.3
MSSA	78.9	54.8	62.2


Clindamycin Resistance in MRSA
Nosocomial isolates
Community isolates
Percentage Resistance
65
60
55
50
45
40
35
30
25
20
15
10
5
0
2005
2006
2007
2008
Year

STREPTOGRAMIN RESISTANCE

- Streptogramin acetyltransferases

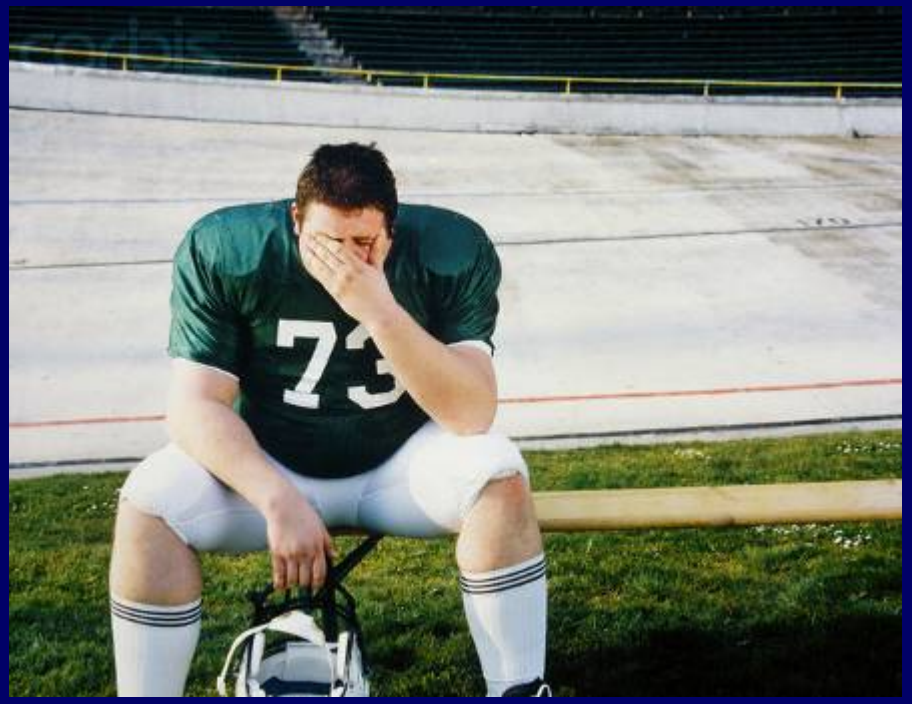
  (modification of streptogramin binding site)

- ATP-dependent efflux

- Several with unknown mechanism

OXAZOLIDINONE RESISTANCE

- Point mutation in gene that confers portion of 50S subunit
- Gene may have multiple copy number in some organisms → increased resistance
- First mutation promotes successive mutations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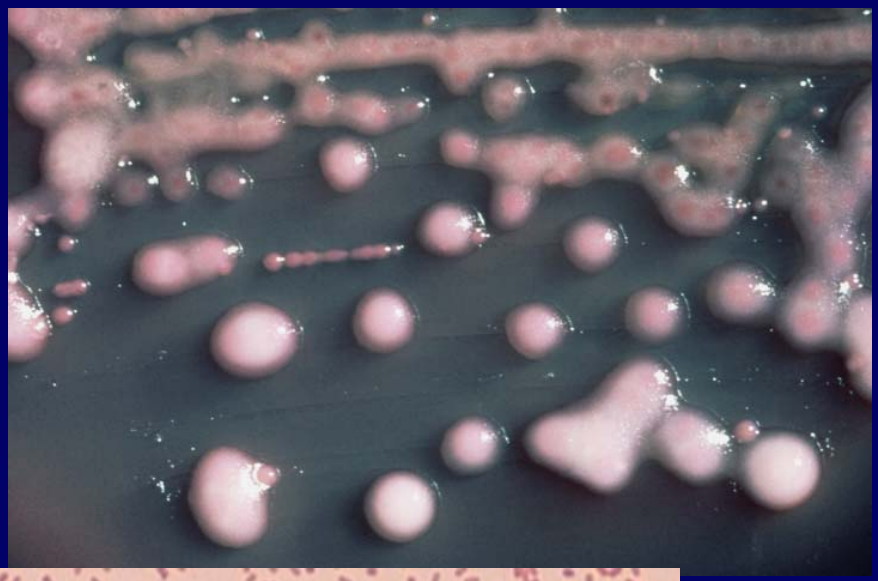
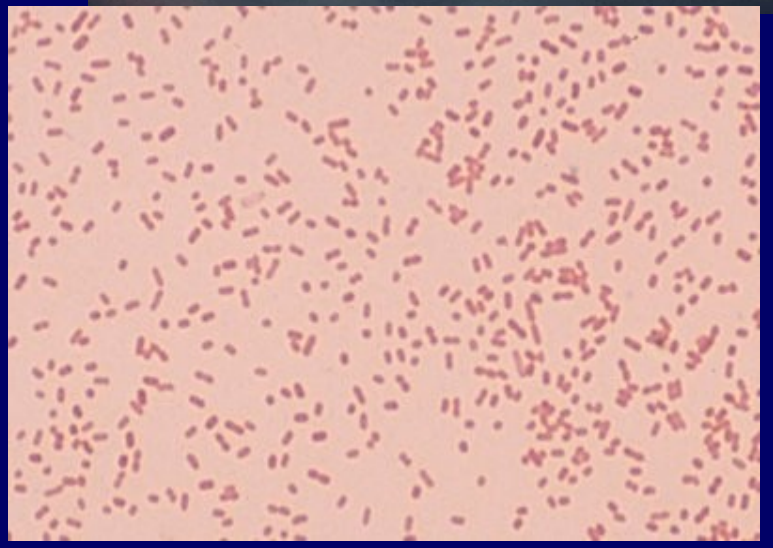
Klebsiella pneumoniae

- Pneumonia
- Peritonitis
- Urinary tract infection
- Bacteremia
- Skin and soft tissue
- Liver abscess





TWO BASIC SUBDIVISIONS

- β-lactam

  Cephems
  Monobactams
  Inhibitor combinations
  Penems

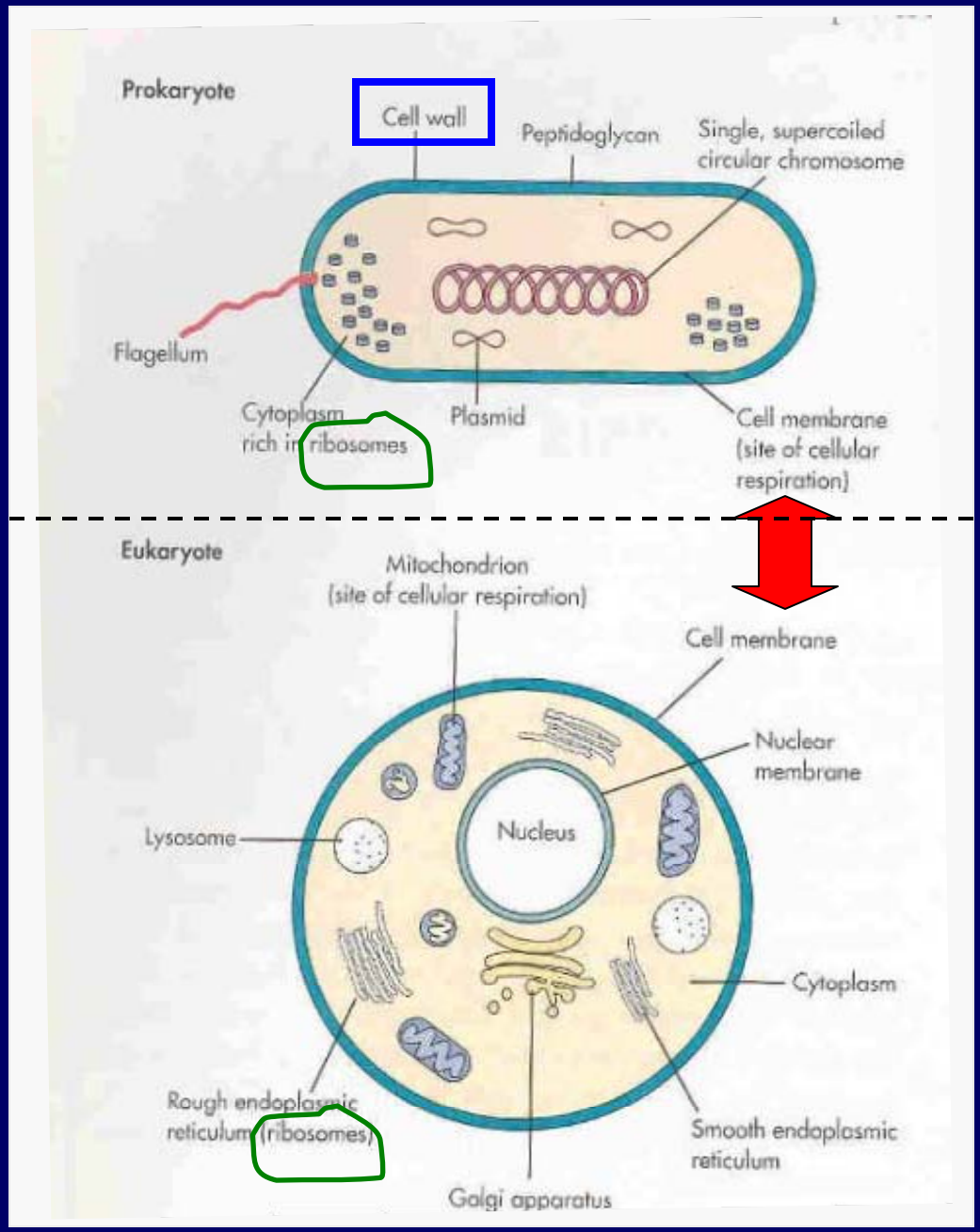
  Cell wall synthesis

- Non-β-lactam

  Aminoglycosides
  Lipopeptides

  Protein synthesis
  Cell membrane


Prokaryote
Cell wall
Peptidoglycan
Single, supercoiled circular chromosome
Flagellum
Cytoplasm rich in ribosomes
Plasmid
Cell membrane (site of cellular respiration)
Eukaryote
Mitochondrion (site of cellular respiration)
Cell membrane
Nuclear membrane
Lysosome
Nucleus
Cytoplasm
Rough endoplasmic reticulum (ribosomes)
Smooth endoplasmic reticulum
Golgi apparatus

ARBITRARY CLASSIFICATIONS

Activity	Generation
Narrow spectrum	First
Expanded spectrum	Second
Broad spectrum	Third
Extended spectrum	Fourth

GP

GN

OFFICIAL BREAKDOWN

Subclass (if appropriate)	Agent(s)
cephalosporin I	cefazolin
	cephalexin
cephalosporin II	cefuroxime
cephamycin (“cephalosporin II”)	cefoxitin
	cefotetan
cephalosporin III	ceftriaxone
	ceftazidime
	cefotaxime
	cefdinir
	cefoperazone
cephalosporin IV	cefepime
	ceftobiprole

CEPHEM CLASS

Parameter	Description
Mechanism of action	1. Bind to bacterial penicillin-binding proteins (PBP), interfering with cell wall synthesis 2. Can trigger membrane-associated autolytic enzymes that destroy cell wall
Activity rendered	Cidal
Route of administration	PO or IV; e.g., cephalexin vs. cefazolin
Distribution	Well; CNS penetration
Half-life	0.5 to 8 hours → q6h or q24h
Excretion	Mostly renal; cefoperazone with great biliary
Adverse effects	Allergic skin rash, drug fever, diarrhea; ↑creatinine, transaminases; leukopenia, thrombocytopenia

CEPHEM CLASS

Microbe(s)	I	II	Cephamycin	III	IV
Streptococcus spp.	+++	+++	+++	+++	++
MSSA	+++	+++	+++	+	+
MRSA	NO	NO	NO	NO	(NO)
Enterococcus spp.	NO	NO	NO	NO	NO
Haemophilus spp.	+	+++	+++	+++	+++
Enterics (basic)	+	++	++	+++	+++
Enterics (resistant)	NO	+	(++)	+++	+++
Pseudomonas spp.	NO	NO	NO	+++	+++
Anaerobes	++	++	+++	++	++
Bacteroides fragilis	NO	NO	+++	NO	NO

CEPHEM CLASS

Parameter	Description
Spectrum of activity	cefazolin: MSSA, streptococci cefuroxime: *Haemophilus*, *S. pneumoniae* cefoxitin/cefotetan: Anaerobes ceftriaxone: Resistant enterics, *N. gonorrhoeae* ceftazidime/cefepime: Resistant enterics, *Pseudo* ceftobiprole: MRSA (allegedly)
Interesting stuff	Cross-reaction in 3-7% of penicillin-allergic patients Hypoprothrombinemia and bleeding tendencies associated with cefotetan, cefoperazone

MONOBACTAM CLASS

Subclass (if appropriate)	Agent(s)
NONE	aztreonam

MONOBACTAM CLASS

Parameter	Description
Mechanism of action	Binds to penicillin-binding protein 3, interfering with cell wall synthesis
Activity rendered	Cidal
Route of administration	IV
Distribution	Well; CNS penetration
Half-life	1.7 hours → q8h
Excretion	Renal and biliary
Adverse effects	Nausea, diarrhea, rash, eosinophilia; mild/transient elevation of transaminases, creatinine

MONOBACTAM CLASS

Parameter	Description
Spectrum of activity	Aerobic Gram-negative bacteria Enterobacteriaceae (including resistant genera) *Haemophilus* spp. *Neisseria* spp. Aminoglycoside synergy No utility for: Anaerobes Gram-positive bacteria *Acinetobacter*, *Stenotrophomonas*
Interesting stuff	Alternative β-lactam agent for Gram-negative infections in penicillin- or cephem-allergic patients

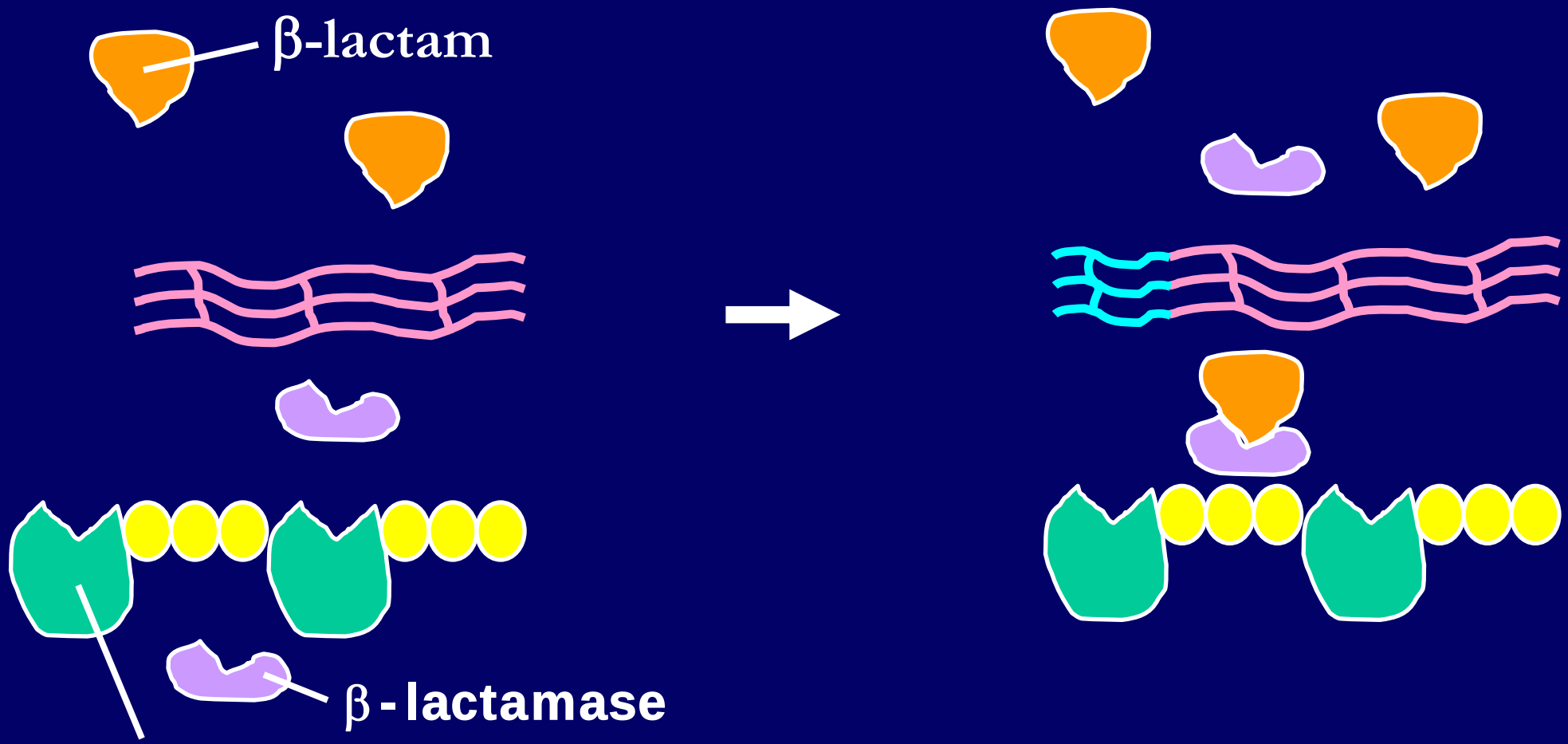
β-LACTAM/β-LACTAMASE INHIBITORS

Subclass (if appropriate)	Agent(s)
NONE	amoxicillin-clavulanic acid
	ampicillin-sulbactam
	piperacillin-tazobactam

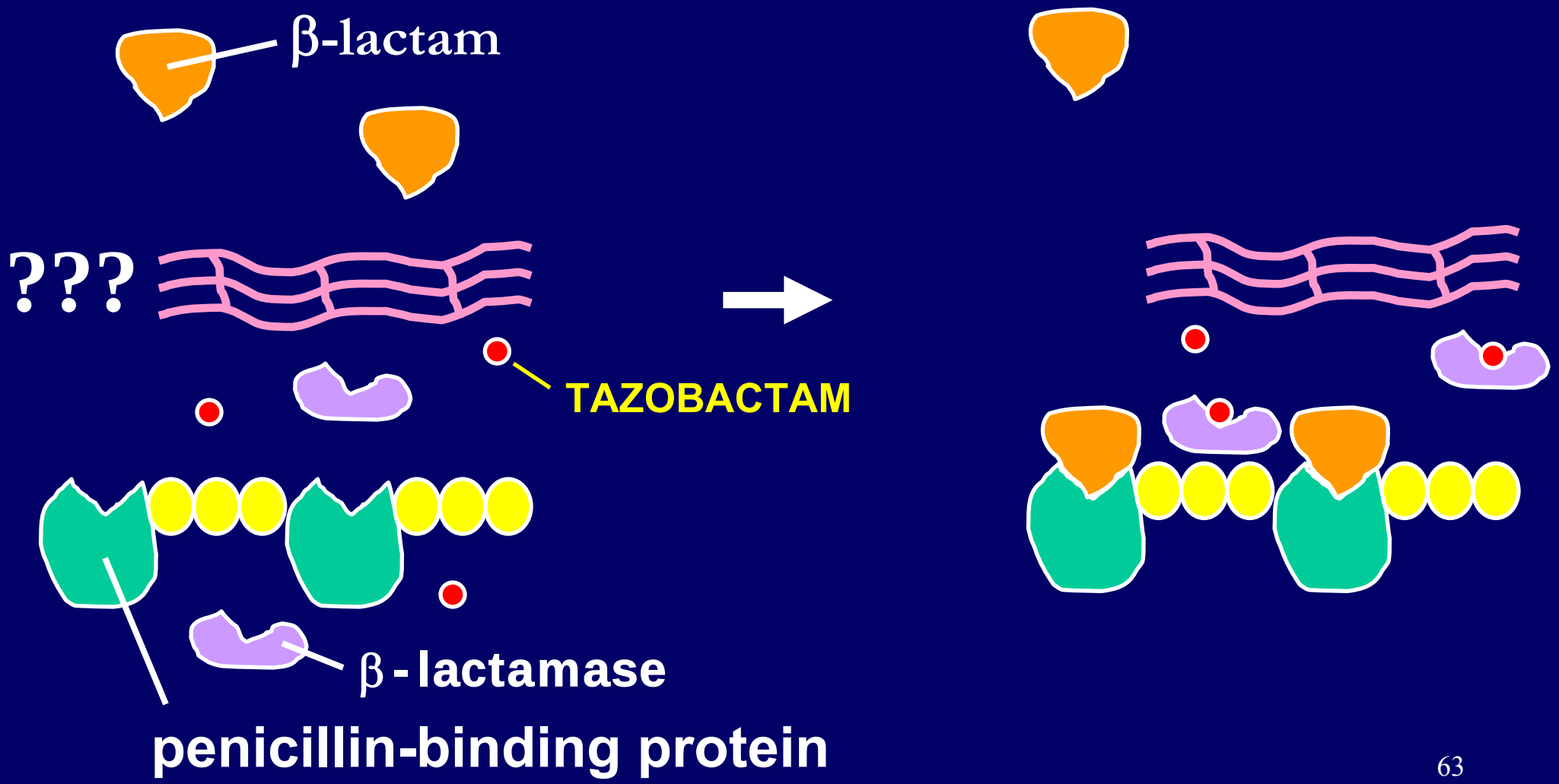
Clavulanic acid, sulbactam, tazobactam

1. Alone have poor intrinsic antibacterial activity
2. Irreversibly complex with β-lactamase → loss of enzyme activity
3. Can lower MIC up to 20-fold when combined with β-lactam agent

β-LACTAMASE



β-LACTAMASE INHIBITOR



AMOXICILLIN-CLAVULANIC ACID

Parameter	Description
Mechanism of action	Forms irreversible complex with β-lactamase
Activity rendered	Cidal
Route of administration	PO
Distribution	Well; no CNS penetration
Half-life	1 hour → q8h or q12h
Excretion	Renal, biliary
Adverse effects	Nausea, vomiting, diarrhea in 5-10% of patients; allergic skin reactions

AMPICILLIN-SULBACTAM

Parameter	Description
Mechanism of action	Forms irreversible complex with β-lactamase
Activity rendered	Cidal
Route of administration	IV
Distribution	Well; CNS penetration
Half-life	1 hour → q6h
Excretion	Renal
Adverse effects	Nausea, diarrhea, rash; transient eosinophilia, transaminase elevation

β-LACTAM/β-LACTAMASE INHIBITORS

Parameter	Description
Spectrum of activity	Effective versus: anaerobes, *Haemophilus influenzae* *Neisseria* sp., *Moraxella catarrhalis* MSSA, enterics to variable extent Piperacillin-tazobactam with greatest potency Not effective versus MRSA
Interesting stuff	An antimicrobial susceptibility testing diagnostic tool for microbiologists (stay tuned)

PENEM CLASS

Subclass (if appropriate)	Agent(s)
penem	faropenem
carbapenem	imipenem
	ertapenem
	meropenem
	doripenem

PENEM CLASS

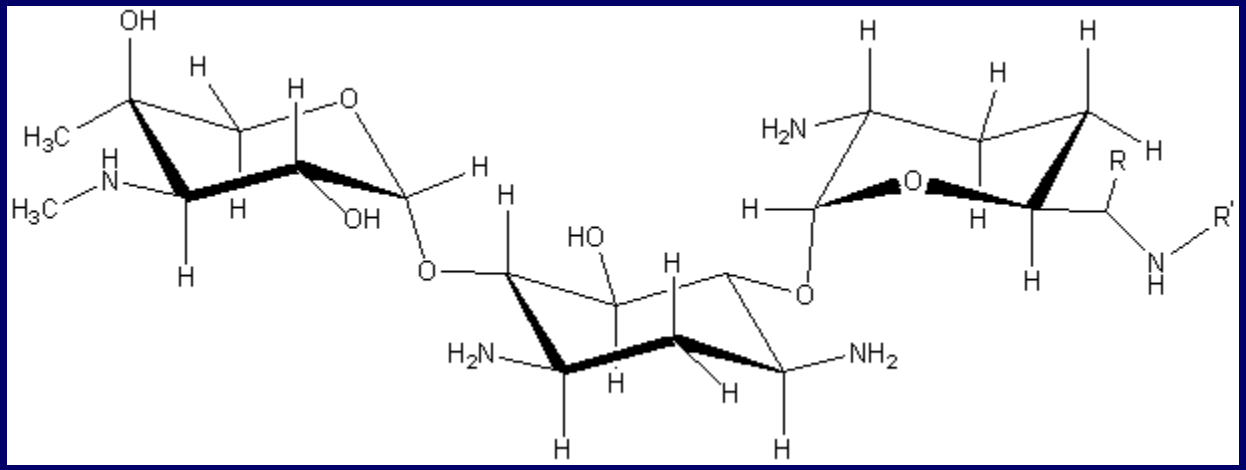
Parameter	Description
Mechanism of action	Bind to penicillin-binding proteins 1 and 2, causing cell elongation and eventual lysis
Activity rendered	Cidal
Route of administration	IV
Distribution	Well; imipenem, meropenem with CNS penetration
Half-life	1-4 hrs → q8h or q24h
Excretion	Renal
Adverse effects	Nausea, vomiting, diarrhea 5%; drug fever, rash, urticaria 3%; seizures 1%; other reversible effects

PENEM CLASS

Parameter	Description
Spectrum of activity	Gram-positives (including penicillin-resist *S. pneumo*) Gram-negatives (including β-lactam- and aminoglycoside-resistant enterics, ESBL) Not effective versus MRSA, vancomycin-resistant *Enterococcus* spp., *Stenotrophomonas maltophilia* Most potent β-lactam versus anaerobes
Interesting stuff	Widest spectrum of antibacterial activity of currently-available antimicrobials; imipenem administered with cilastatin (a dehydropeptidase I inhibitor)

AMINOGLYCOSIDE CLASS

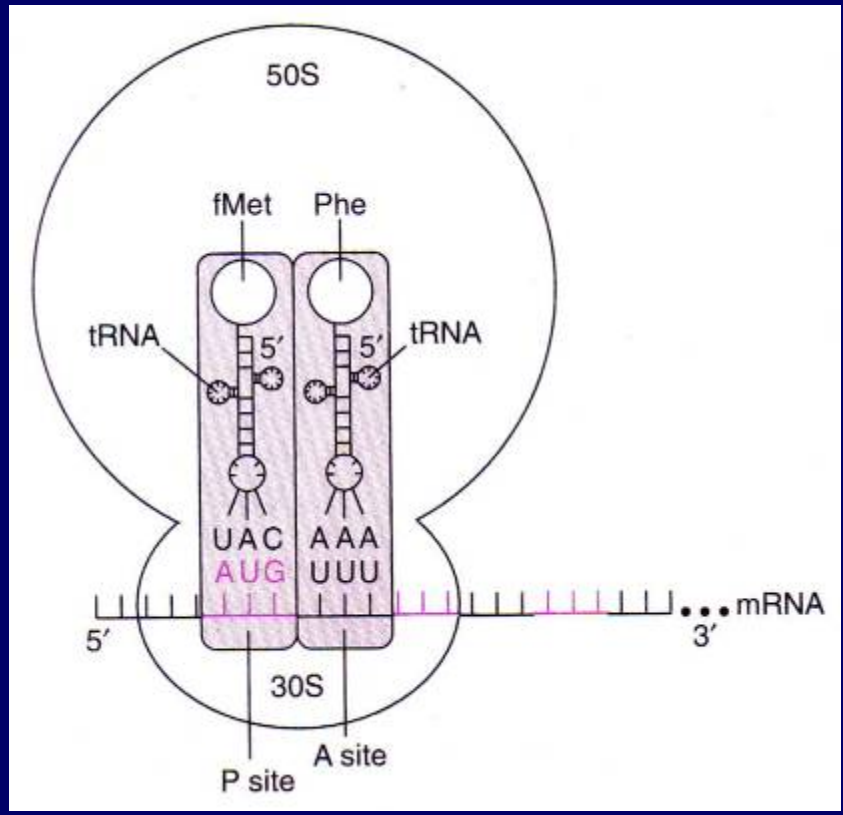
Subclass (if appropriate)	Agent(s)
NONE	gentamicin
	tobramycin
	amikacin
	streptomycin
	kanamycin



AMINOGLYCOSIDE CLASS

- Irreversible binding to 30S ribosomal subunit; ribosomes unavailable for protein synthesis

- Misreading of genetic code; resultant production of nonsense proteins



AMINOGLYCOSIDE CLASS

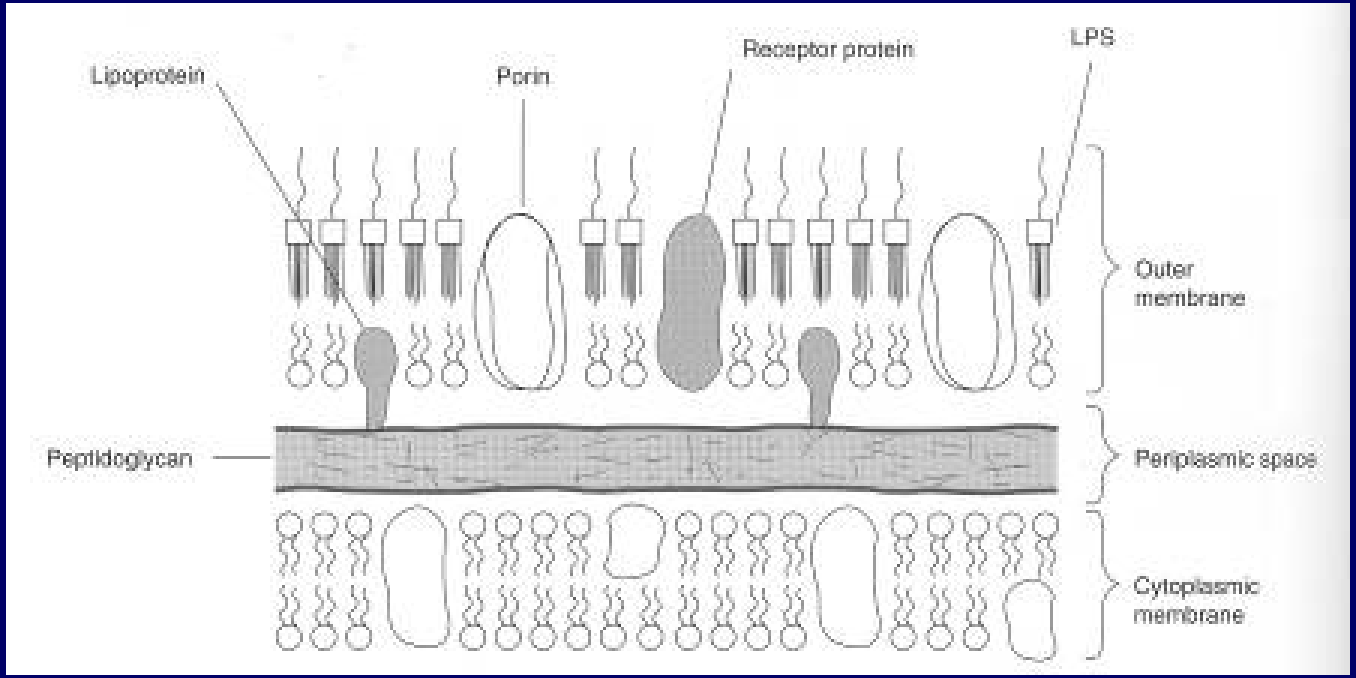
Parameter	Description
Mechanism of action	1. Bind irreversibly to 30S ribosomal subunits; ribosomes unavailable for protein synthesis 2. Cause misreading of genetic code; nonsense proteins
Activity rendered	Cidal
Route of administration	IV
Distribution	Extracellular; no CNS
Half-life	2-3 hours → q24h
Excretion	Renal
Adverse effects	Nephrotoxicity (variable and reversible); auditory, vestibular toxicity (irreversible in 3-5% of patients)

AMINOGLYCOSIDE CLASS

Parameter	Description
Spectrum of activity	Synergy w/ β-lactam/vancomycin vs. Gram-positives Streptomycin: *Mycobacterium tuberculosis* Suspected agents of bioterrorism Gentamicin < tobramycin < amikacin (important vs. *Pseudomonas*, *Acinetobacter*) NO anaerobes; NO Gram-positive monotherapy
Interesting stuff	Energy-dependent uptake; can be facilitated by vancomycin or β-lactam therapy (synergy)

LIPOPEPTIDE CLASS

Subclass (if appropriate)	Agent(s)
polymyxin	polymyxin B
	polymyxin E (colistin)



POLYMYXIN SUBCLASS

Parameter	Description
Mechanism of action	1. Bind to phosphorylated head groups of lipid A, disrupting cell membranes and losing osmolarity 2. Disruption of biofilm formation
Activity rendered	Cidal
Route of administration	IV
Distribution	Well; except CNS, pleural fluid, synovial fluid
Half-life	~3 hrs (colistin) ~7 hrs polymyxin B → q8h or q12h
Excretion	Renal
Adverse effects	Neurotoxicity (parasthesia, dizzy, vertigo, ataxia, slurred speech, confusion); nephrotoxicity (20%)

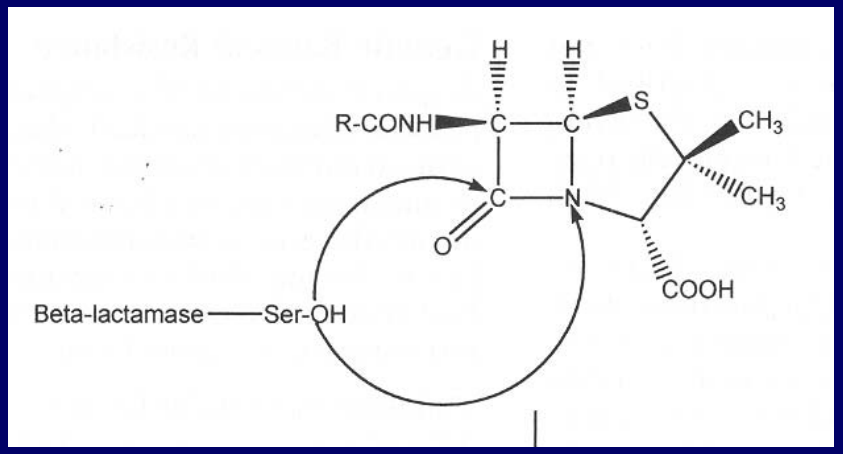
POLYMYXIN SUBCLASS

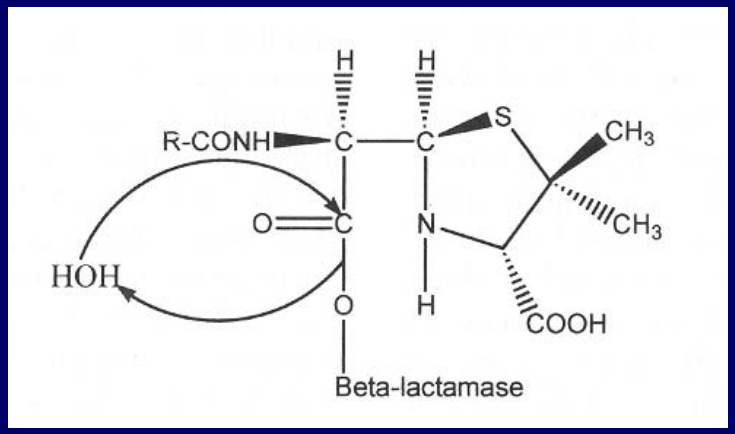
Parameter	Description
Spectrum of activity	Only Gram-negative bacilli (especially *Pseudomonas aeruginosa*) Synergy with trimethoprim-sulfamethoxazole for serious infections caused by resistant *Serratia* spp., *P. aeruginosa*, *S. maltophilia*, *Burkholderia cepacia* Pan-resistant Gram negative bacilli
Interesting stuff	"We're going back to 40 years ago!?!?"

Mechanisms of Resistance

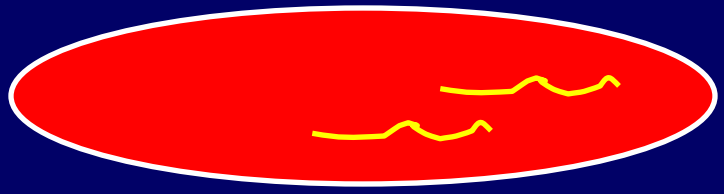
KEY DATES IN CEPHEM RESISTANCE

- 1940s First β-lactamase identified (*E. coli*)



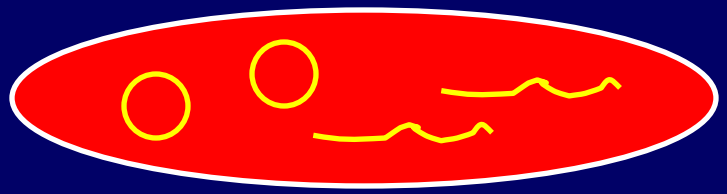


- 1950s Chromosomal-derived β-lactamases in Gram-negatives



KEY DATES IN CEPHEM RESISTANCE

- 1960s First plasmid-derived β-lactamase found in *E. coli* (TEM-1)



Pseudomonas aeruginosa
Haemophilus influenzae
Neisseria gonorrhoeae
Other Enterobacteriaceae

Chromosomal β-lactamase found in *Klebsiella pneumoniae* (SHV-1)

KEY DATES IN CEPHEM RESISTANCE

- 70s,80s

Extended-spectrum beta-lactams

ceftazidime cefotaxime
ceftriaxone aztreonam

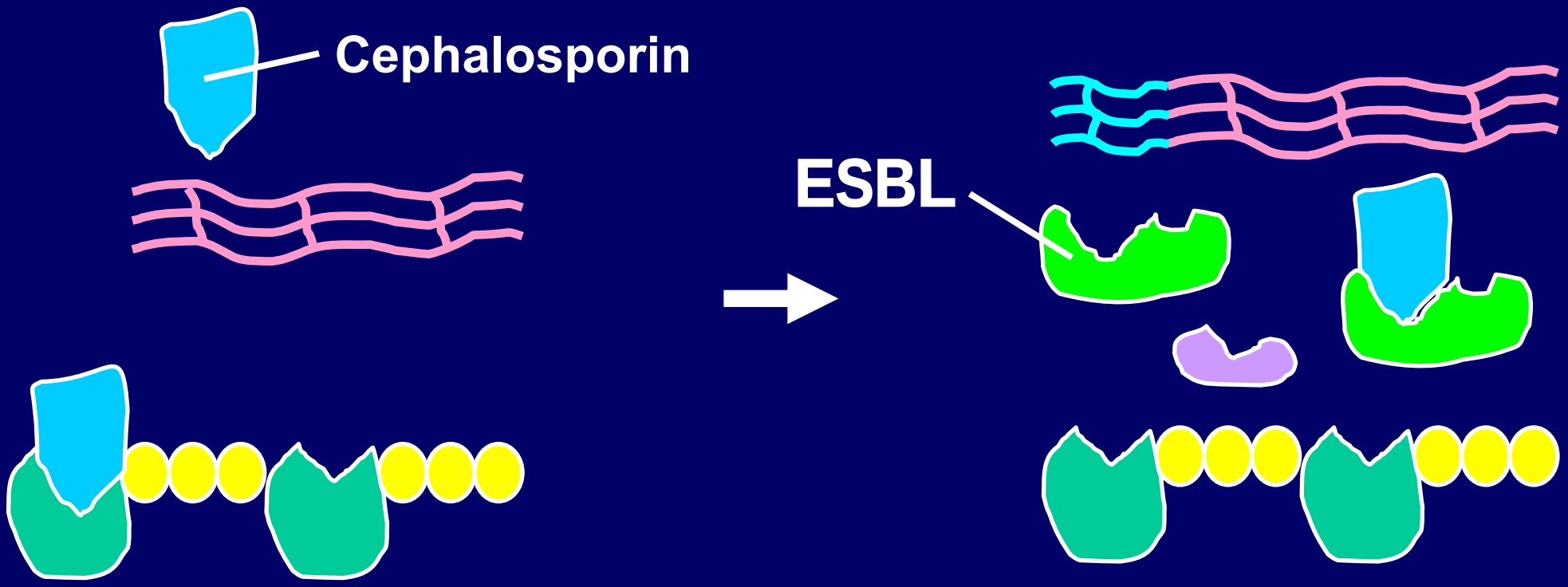
- 1985

Plasmid-derived SHV-2 β-lactamase isolated from *Klebsiella* in Germany

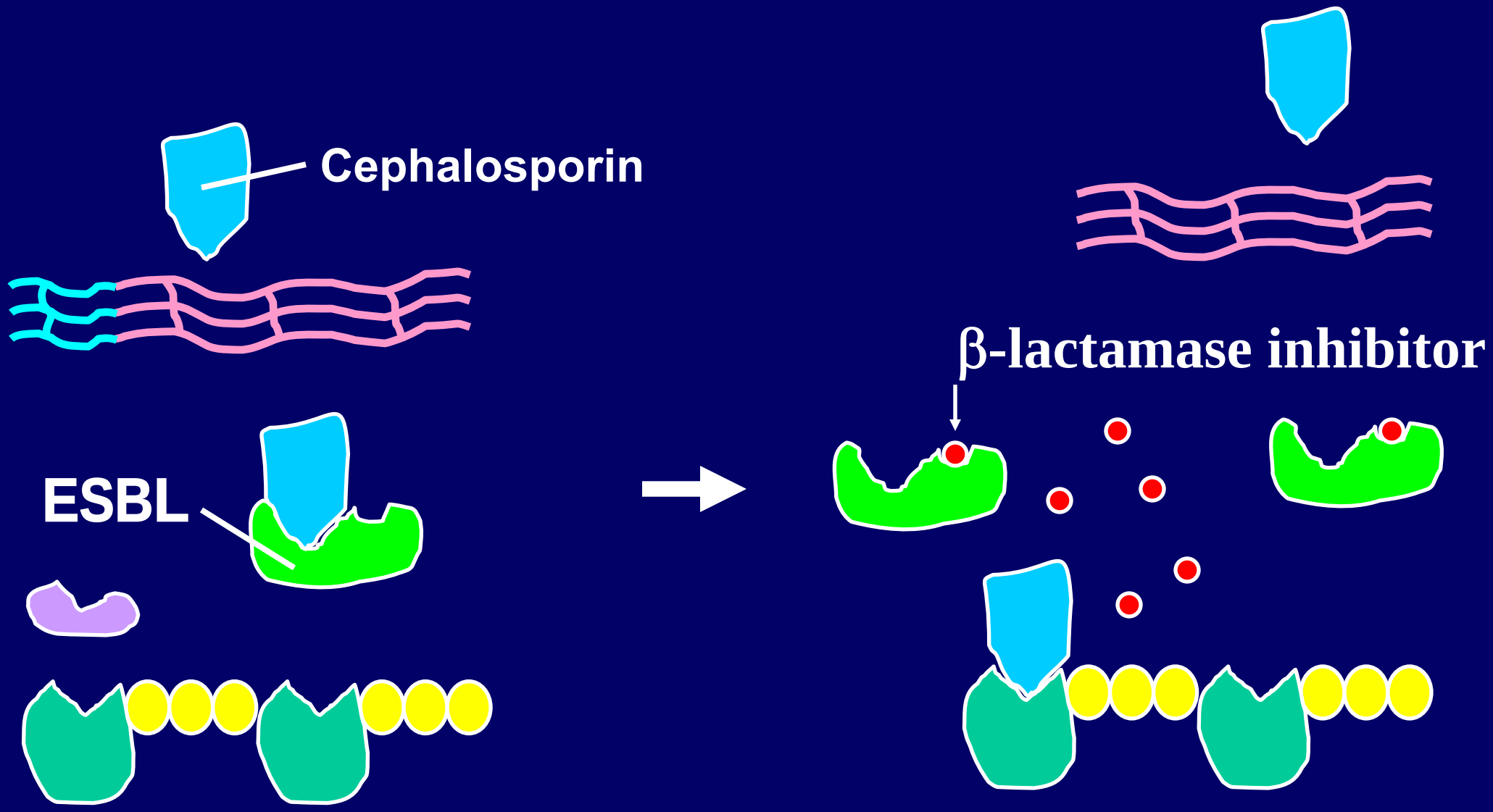
Hydrolyzed new extended-spectrum beta-lactam antimicrobials

Extended-Spectrum Beta-Lactamase

OBLIGATORY CARTOON



OBLIGATORY CARTOON



THERAPEUTIC BENEFIT

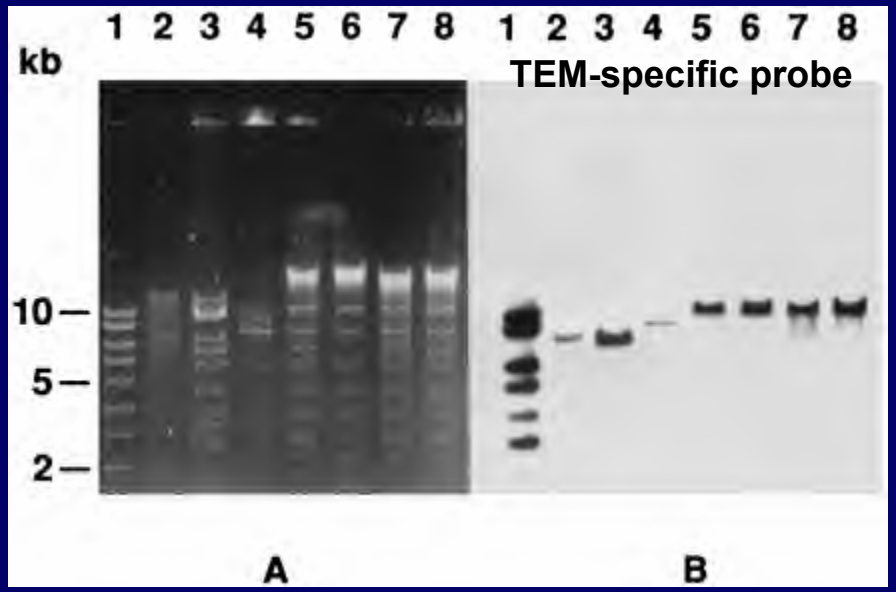
- *K. pneumoniae* bacteremia (18.7% ESBL)
- 32 patients administered cephalosporin within five days of ESBL detection

Outcome	Susceptible	Intermediate	Overall
Failure	54%	100%	59%
Mortality	14%	50%	19%

J. Clin. Microbiol. **39:** 2206-2212; 2001

EPIDEMIOLOGICAL BENEFIT

- Single French ICU patient
- TEM-24 ESBL



2. TEM-3 plasmid DNA
3. TEM-24 plasmid DNA
4. TEM-5 plasmid DNA
5. *Proteus mirabilis* TEM-24
6. *Providencia rettgeri* TEM-24
7. *Klebsiella pneumoniae* TEM-24
8. *Enterobacter aerogenes* TEM-24

Antimicrob. Agents Chemother. **43:** 2069-2073; 1999

DETECTION OF ESBL

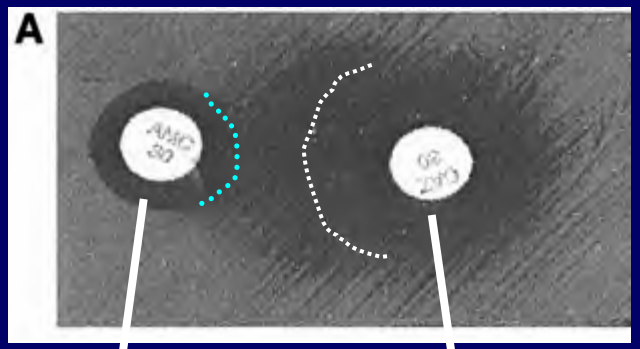
- Gold standard: enzyme detection

- Phenotypic methods; screening drugs

aztreonam
ceftazidime
cefpodoxime

DETECTION OF ESBL--"Method 1"

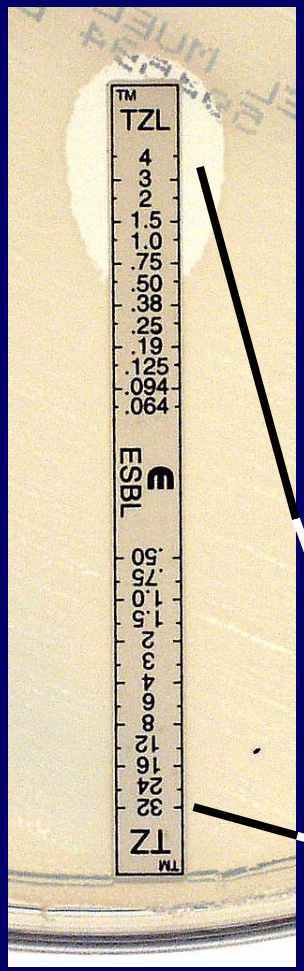
Double-disk potentiation



ceftazidime

amoxicillin-clavulanic acid

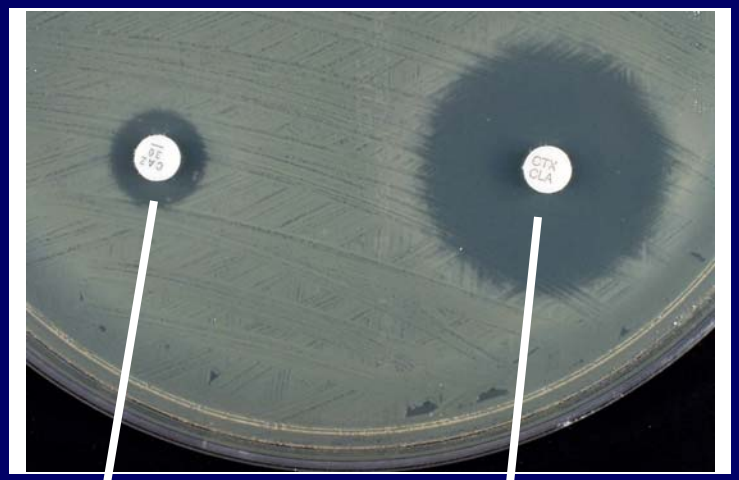
Etest



ceftazidime + clavulanic acid

ceftazidime

Disk diffusion

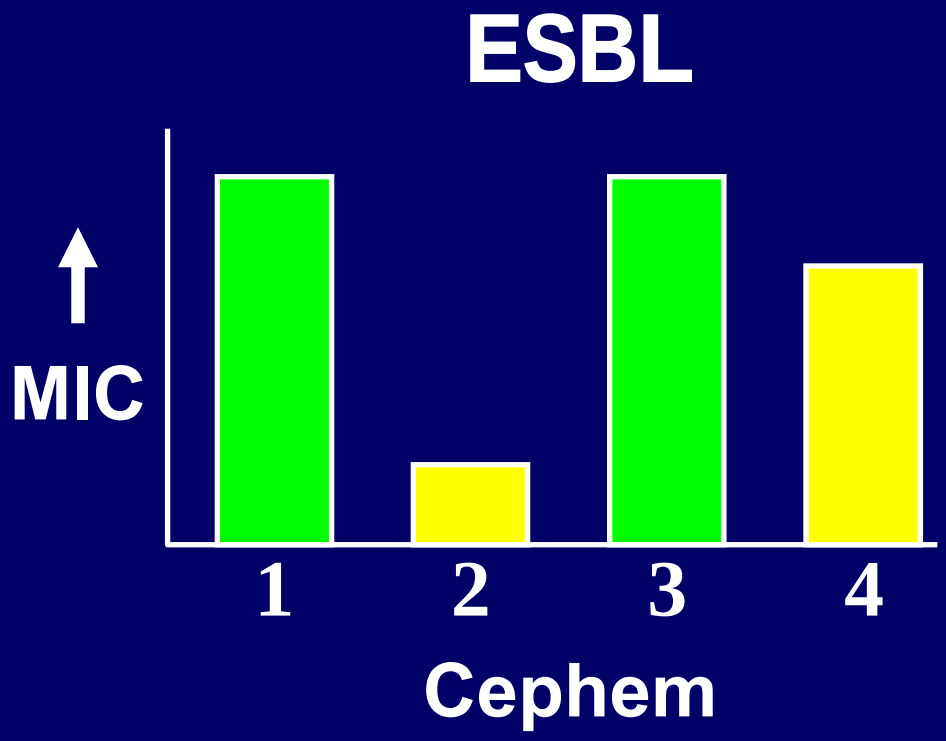


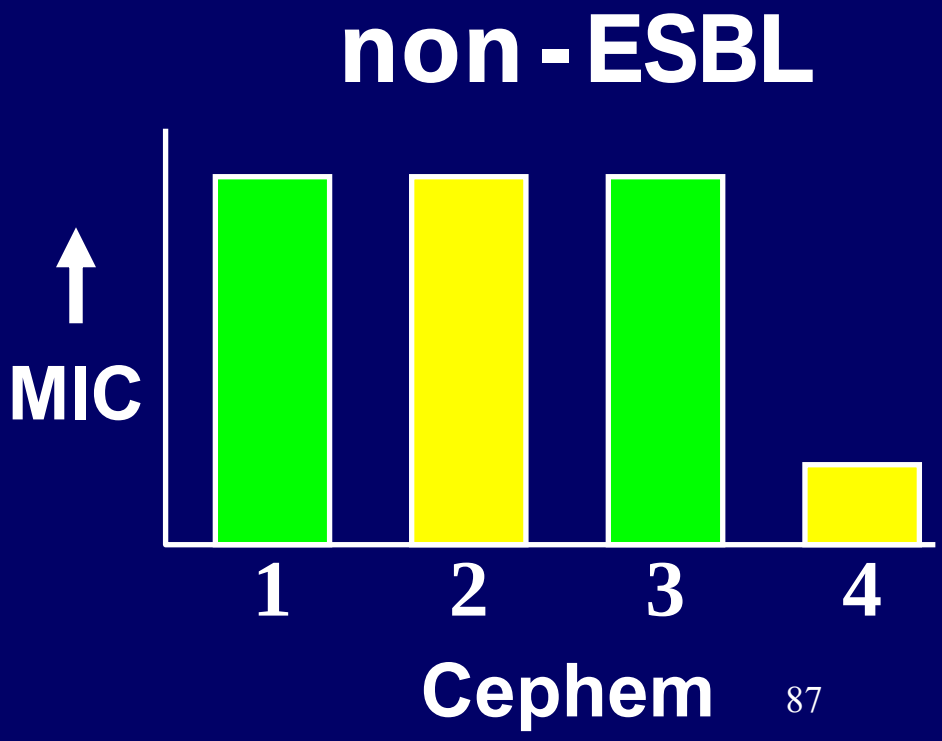
ceftazidime

ceftazidime + clavulanic acid

DETECTION OF ESBL--"Method 2"

- Antibiogram profiles





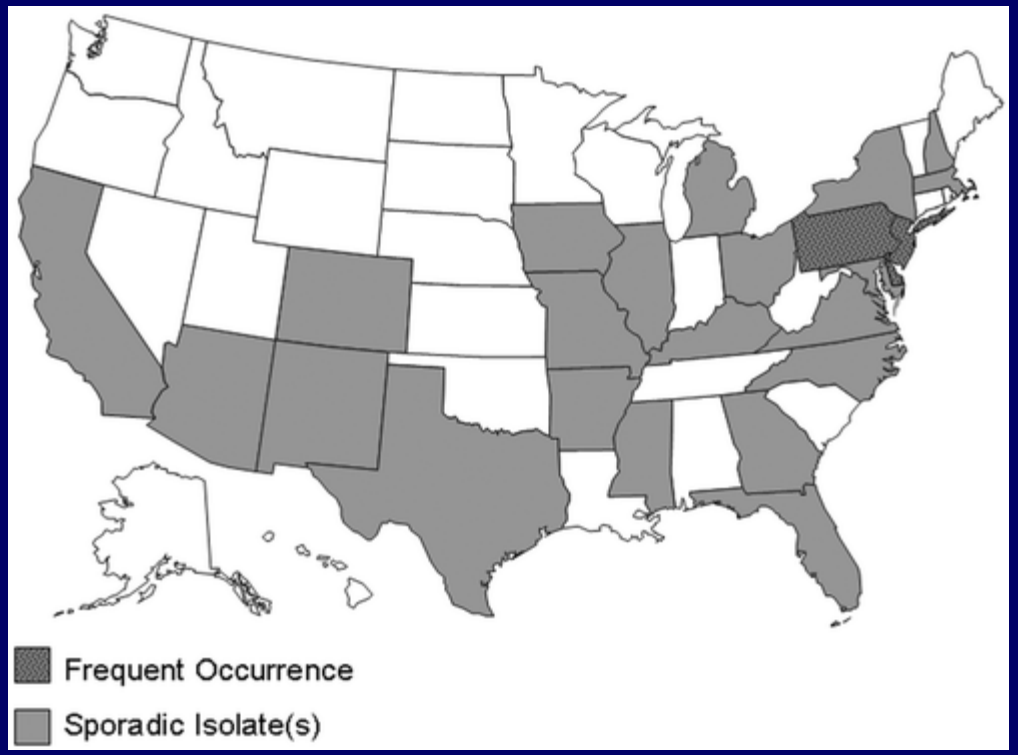
PENEM RESISTANCE

- Alteration of porin channels in bacterial cell wall, reducing permeability

- Carbapenemase production

  Serine carbapenemases (class A β-lactamase)
  Metallo-β-lactamase (class B β-lactamase)
  OXA-type β-lactamase (class D β-lactamase)

Klebsiella pneumoniae CARBAPENEMASE (KPC)



K. pneumoniae carbapenem resistance rate:

1% in 2000
8% in 2008

Infect. Control Hosp. Epidemiol. **29:** 1107-1109; 2008

Klebsiella pneumoniae CARBAPENEMASE

- Confers resistance to all β-lactams and all β-lactam/β-lactamase inhibitor combinations
- *bla*$_{KPC}$ located on plasmids
- Plasmids carrying *bla*$_{KPC}$ contain genes conferring resistance to aminoglycosides and fluoroquinolones

Infect. Control Hosp. Epidemiol. **29:** 1107-1109; 2008

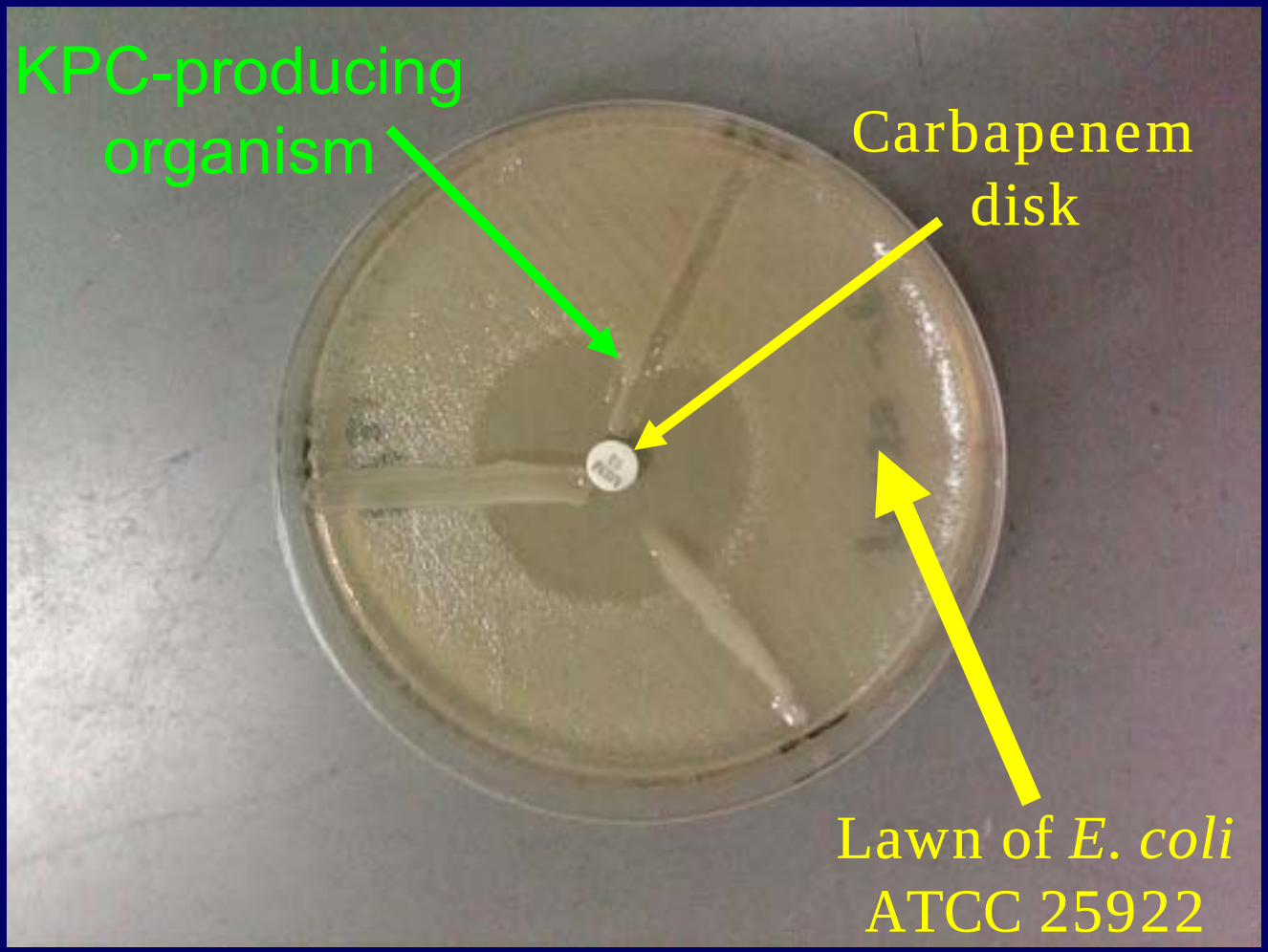
PREVALENCE OF KPC

- New York City hospital with endemicity
- KPC-producing organisms accounted for 26% of *K. pneumoniae* bloodstream infection
- KPC-producing organisms:

  59% susceptible to gentamicin
  52% susceptible to tetracycline
  90% susceptible to polymyxin B

Infect. Control Hosp. Epidemiol. **29:** 1099-1106; 2008

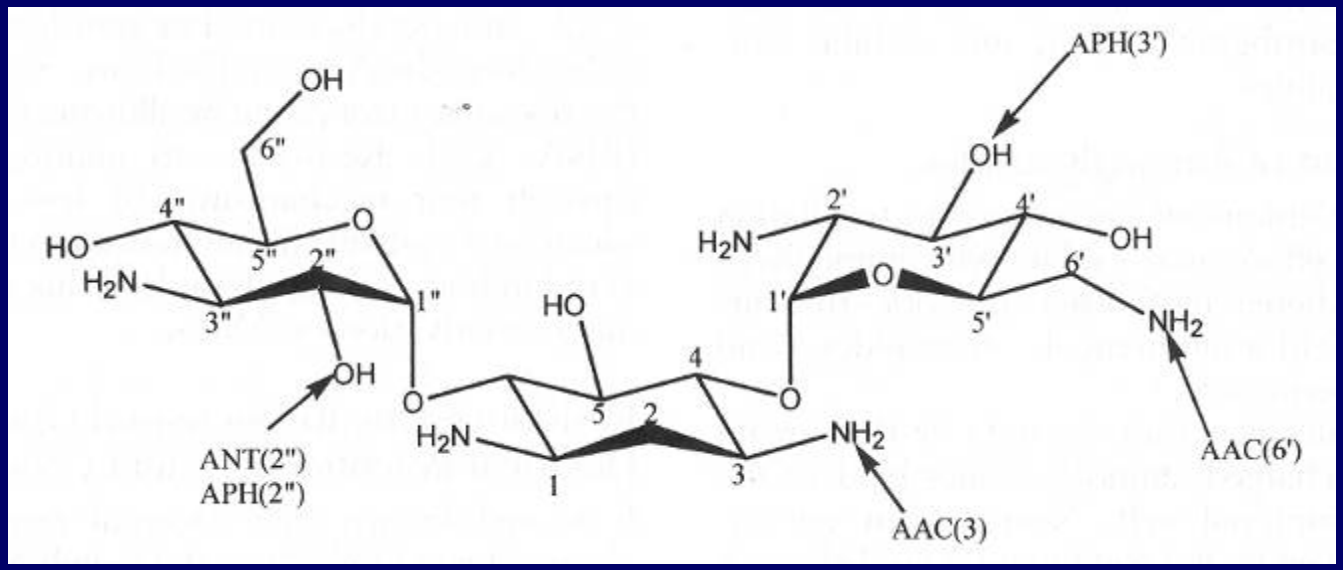
MODIFIED HODGE TEST



AMINOGLYCOSIDE RESISTANCE

- Inactivation via modifying enzymes

  Modify specific amino or hydroxyl groups on AG;
  Results in lower affinity for ribosome



acetyltransferases (AAC)
nucleotidyltransferases (ANT)
phosphotransferases (APH)

AMINOGLYCOSIDE RESISTANCE

- Inactivation via modifying enzymes

  Modify specific amino or hydroxyl groups on AG;
  Results in lower affinity for ribosome

- Modification of ribosome

  Mutations → changes in proteins and 16S rRNA
  Enzymatic methylation of rRNA

- Decreased uptake

  Electron potential (anaerobes, facultatives)
  Divalent cations (competition)
  Efflux

POLYMYXIN RESISTANCE

- Decreased uptake
  - Efflux
  - Cell wall of some organisms prevents uptake
- Modification of phosphate groups of lipid A
- Lipopolysaccharide modifications
  - Alteration of fatty acid content of lipid A
  - Addition of amino, carboxyl groups

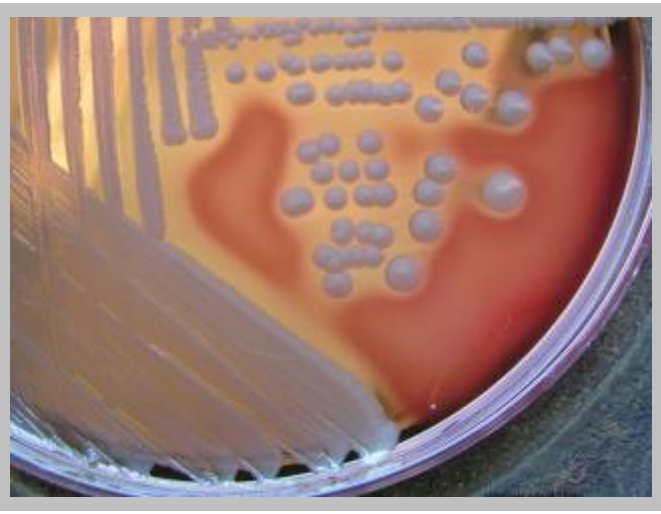
THE END

- Stuff we've done

penicillins
macrolides
tetracyclines
folate pathway inhibitors
quinolones

penicillins (methicillin)
glycopeptides
lincosamides
streptogramins
oxazolidinones

cephems
monobactams
β-lactam/β-lactamase inhibitors
penems
aminoglycosides
lipopeptides


THE END

- Stuff we've done

penicillins
macrolides
tetracyclines
folate pathway inhibitors
quinolones

penicillins (methicillin)
glycopeptides
lincosamides
streptogramins
oxazolidinones

cephems
monobactams
β-lactam/β-lactamase inhibitors
penems
aminoglycosides
lipopeptides

- See you at the Dells