Antibiotics 101 for Laboratory Professionals: Part One

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OUTLINE

I. Trying to understand the choice

II. Selected classes of antimicrobials

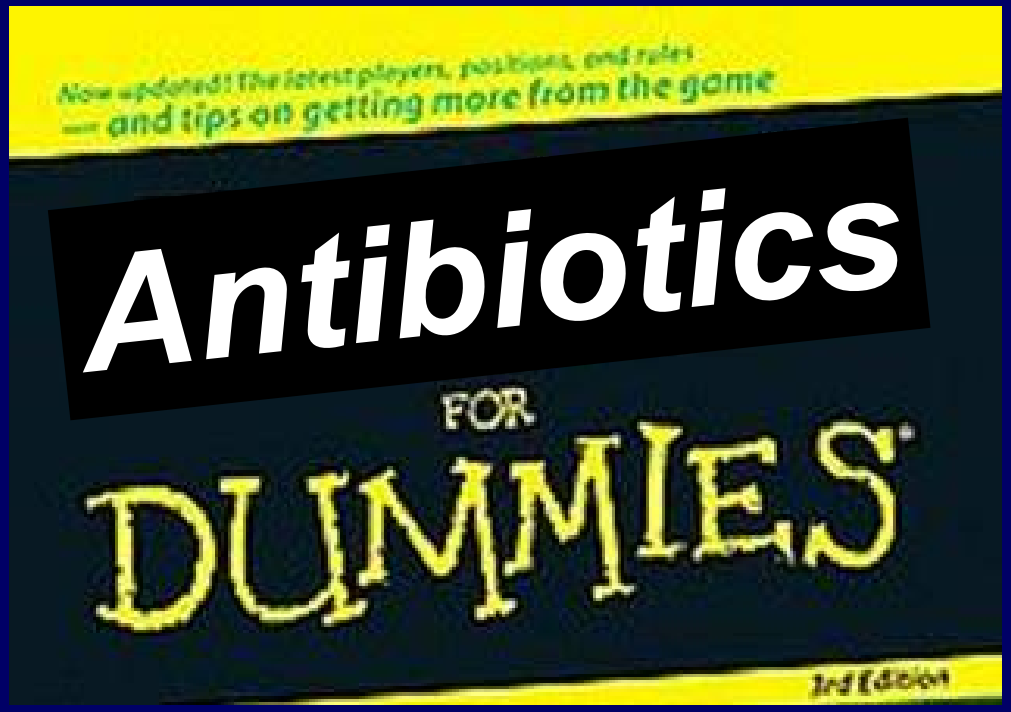
III. Bacterium-specific examples of resistance

   A. *Streptococcus pneumoniae*

   B.

   C.

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



…including myself

Trying to Understand the Choice

EARLY EVIDENCE FOR AST

- *Staphylococcus aureus* bacteremia
- Favorable outcome in 60% of patients treated with a drug that inhibited the organism *in vitro*
- No patients responded clinically when treated with a drug that did not inhibit the organism *in vitro*

Antibiot. Ann. **1958-1959:** 748-756; 1959

NOWADAYS: 90-60 Rule

- Infections due to “susceptible” isolates respond to therapy ~90% of time

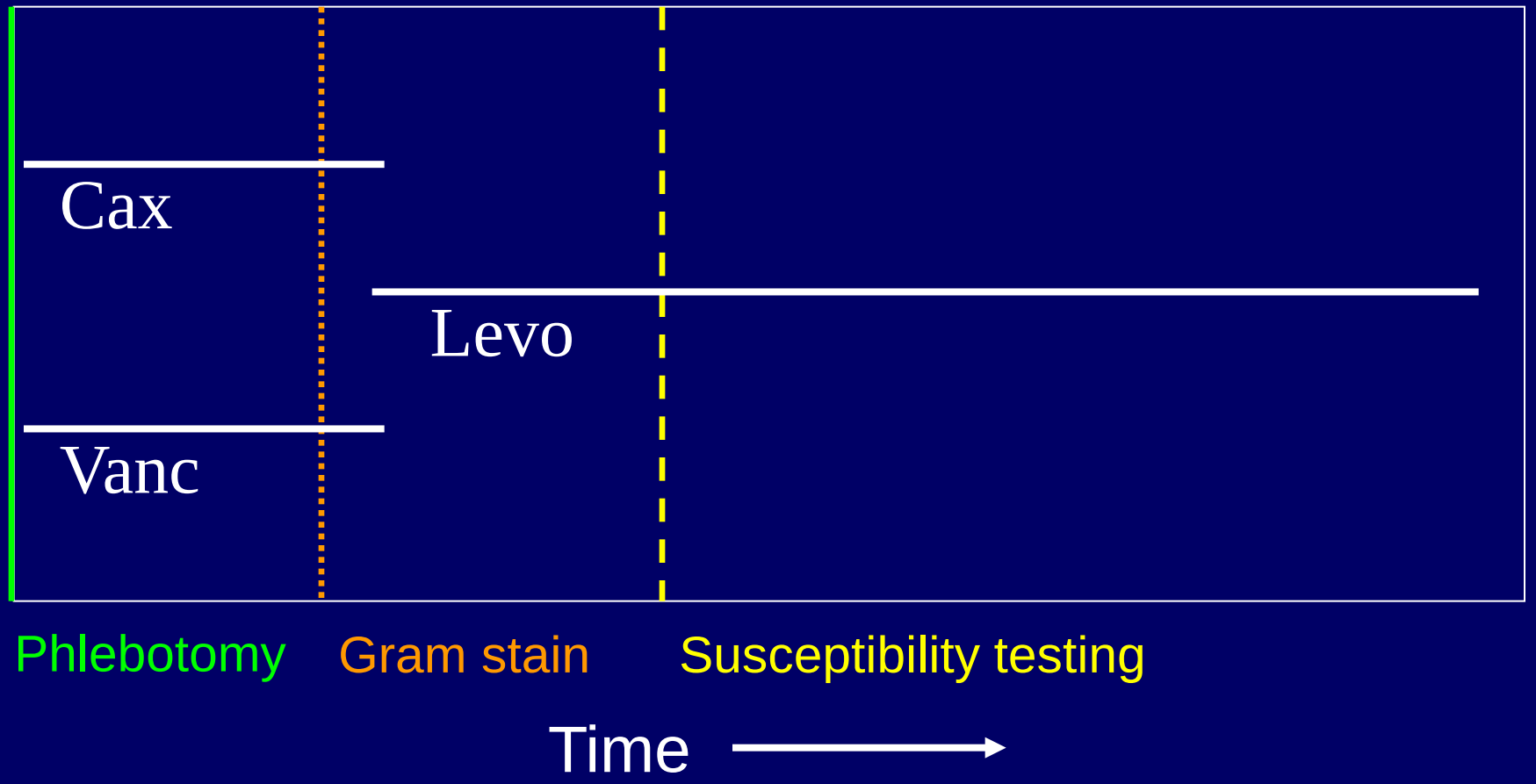
- Infections due to “resistant” isolates respond to therapy ~60% of time

Clin. Infect. Dis. **35:** 982-989; 2002

Laboratory utilizes *in vitro* testing systems to PREDICT antimicrobial effectiveness *in vivo*, independent of confounding factors

FACTORS TO CONSIDER

- Antimicrobial susceptibility testing (AST)
- Spectrum of therapy (empiric therapy)



INITIATION OF THERAPY

Interval	Cumulative Percentage of Events Occurring Within:	
	6 hours	12 hours
Phlebotomy to Gram stain	63.8†	81.4*
Gram stain to susceptibility testing	45.0†	61.1*
After release of susceptibility results	10.0†	17.4*

† $P < 0.001$; * $P < 0.05$

J. Clin. Microbiol. **41:** 495-497; 2003

FACTORS TO CONSIDER

- Antimicrobial susceptibility testing (AST)
- Spectrum of therapy (empiric therapy)
- Availability

Cannot Enter Urinary Tract

macrolides
clindamycin
chloramphenicol

Cannot Enter CNS

fluoroquinolones
1st & 2nd generation cephems
clindamycin
macrolides
tetracycline

FACTORS TO CONSIDER

- Antimicrobial susceptibility testing (AST)
- Spectrum of therapy (empiric therapy)
- Availability
- Route of administration

Administration		**Example**
Medical Lingo	*Colloquial*	
IM	butt	ceftriaxone (also IV)
PO	oral	cephalexin
PO or parenteral	oral or IV	levofloxacin
parenteral	IV	vancomycin

FACTORS TO CONSIDER

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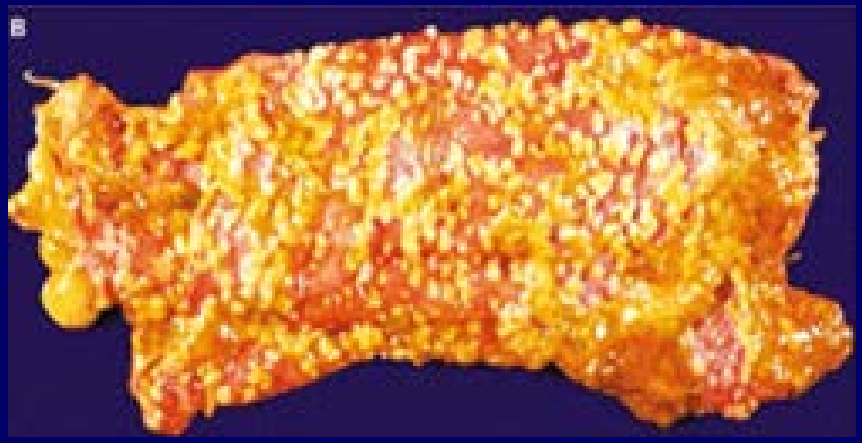


Pseudomembranous colitis caused by *Clostridium difficile*

FACTORS TO CONSIDER

- Antimicrobial susceptibility testing (AST)
- Spectrum of therapy (empiric therapy)
- Availability
- Route of administration
- Majority of excretion

Fluoroquinolone	Percentage Excretion	
	Renal	Biliary
levofloxacin	+++	-
ciprofloxacin	+++	+++++

Salmonella spp. report

ampicillin
trimethoprim-sulfa
ciprofloxacin

FACTORS TO CONSIDER

- Antimicrobial susceptibility testing (AST)
- Spectrum of therapy (empiric therapy)
- Availability
- Route of administration
- Majority of excretion
- Dosing/half-life

easier for patient
reduced pharmacy co$t

FACTORS TO CONSIDER

- Antimicrobial susceptibility testing (AST)
- Spectrum of therapy (empiric therapy)
- Availability
- Route of administration
- Majority of excretion
- Dosing/half-life
- Synergy β-lactam/aminoglycoside
  rifampin

FACTORS TO CONSIDER

- Antimicrobial susceptibility testing (AST)
- Spectrum of therapy (empiric therapy)
- Availability
- Route of administration
- Majority of excretion
- Dosing/half-life
- Synergy
- Side effects

hypersensitivity
hematologic
gastrointestinal
renal
otic
pregnancy

MORE FACTORS TO CONSIDER

- FDA indications

Acute bacterial sinusitis due to *S pneumoniae*, *H influenzae*, or *M catarrhalis*

Community-acquired pneumonia due to methicillin-susceptible *S aureus*, *S pneumoniae* (including multidrug-resistant *S pneumoniae* [MDRSP]), *H influenzae*, *H parainfluenzae*, *K pneumoniae*, *M catarrhalis*, *C pneumoniae*, *L pneumophila*, or *M pneumoniae*. MDRSP isolates are strains resistant to two or more of the following antibacterials: penicillin (MIC ≥ 2 μg/mL), 2nd generation cephalosporins, eg, cefuroxime, macrolides, tetracyclines, and trimethoprim/sulfamethoxazole

LEVAQUIN® (levofloxacin) Tablets/Injection Product Insert (excerpt)

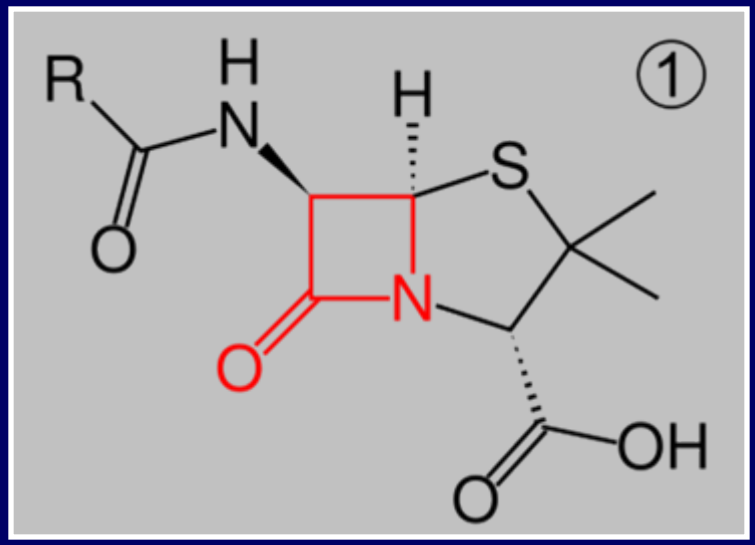
MORE FACTORS TO CONSIDER

- FDA indications
- Co$t
- Polymicrobial infections
- Cidal vs. static

Selected Classes of Antimicrobials

TWO BASIC SUBDIVISIONS

- β-lactam
- Non-β-lactam



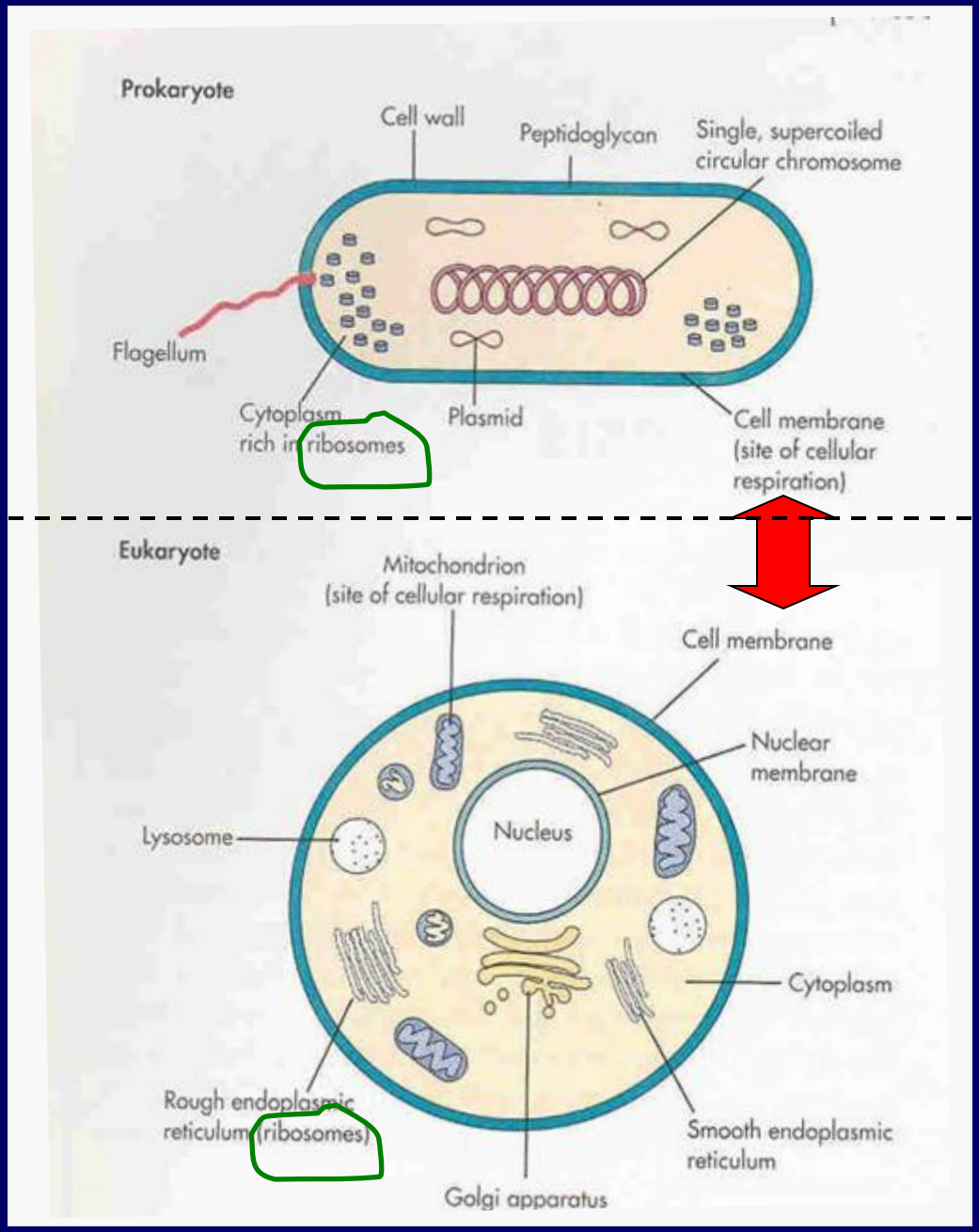
TWO BASIC SUBDIVISIONS

- β-lactam

Penicillins	Cell wall synthesis

- Non-β-lactam

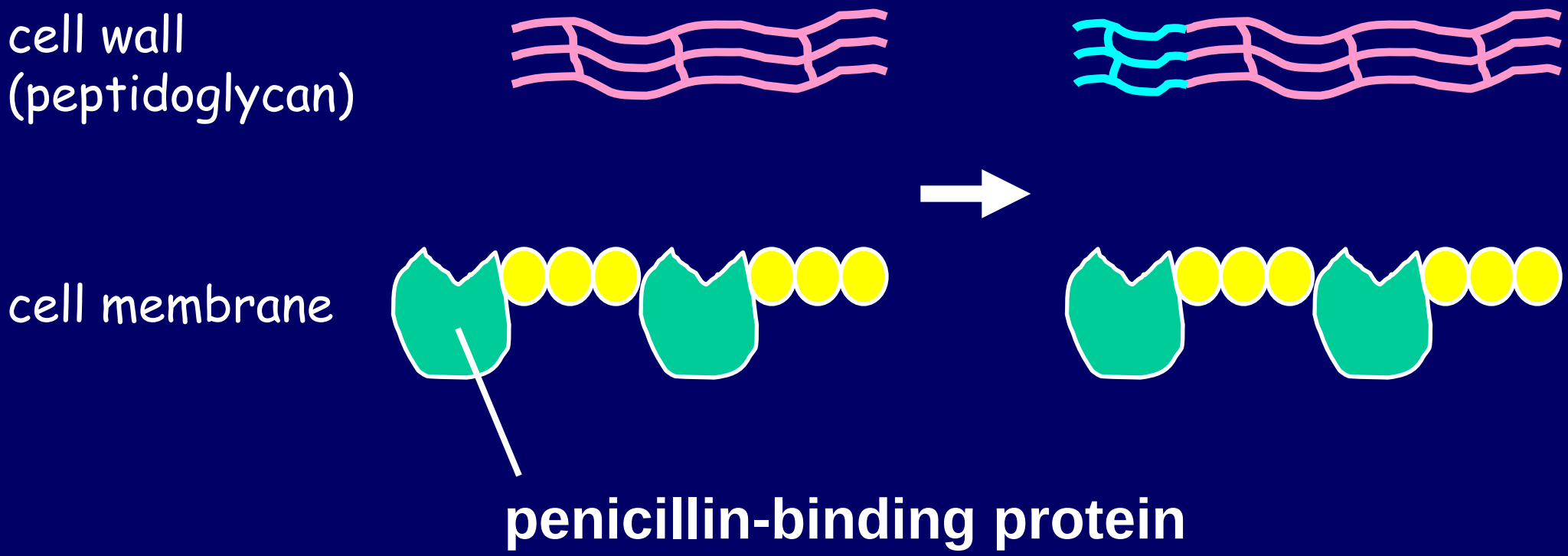
Macrolides	Protein synthesis
Tetracycline	
Folate inhibitors	DNA replication
Fluoroquinolones	


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

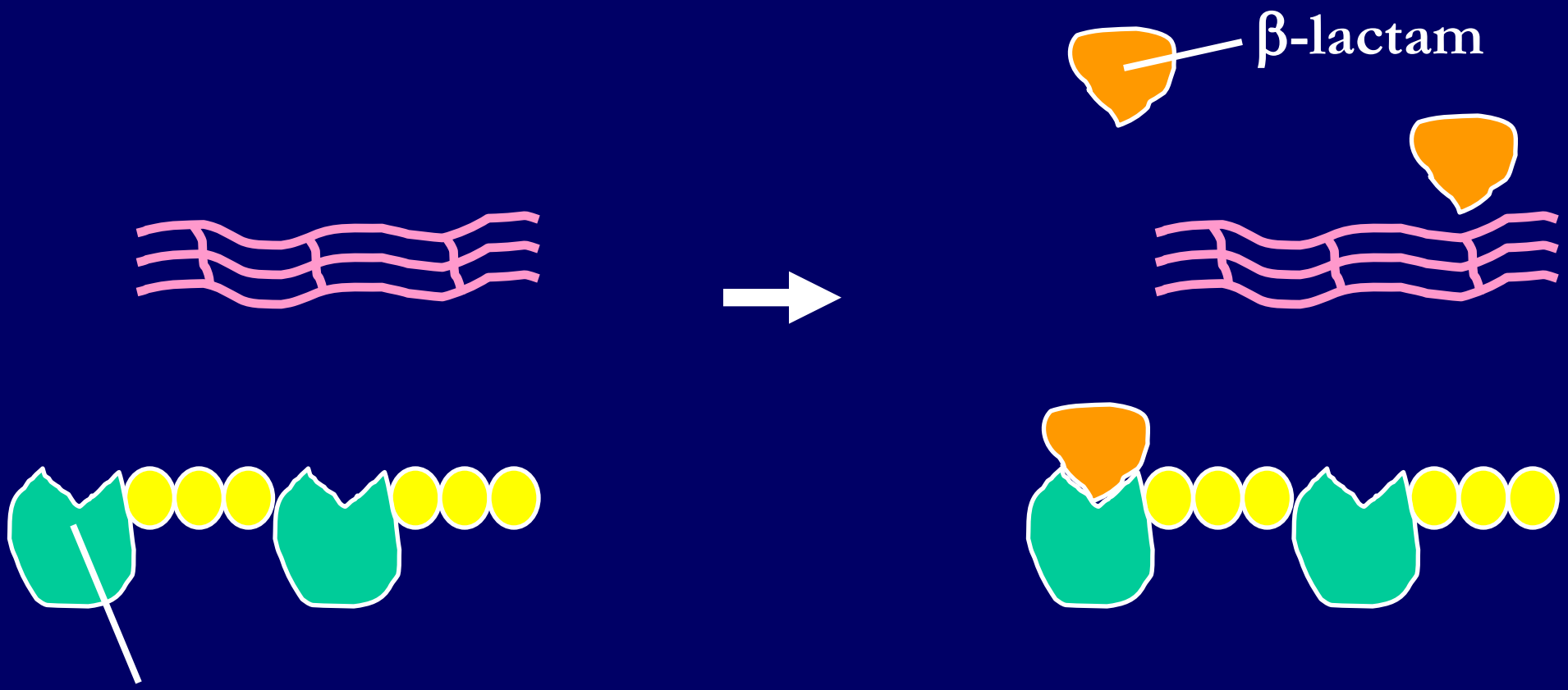
PENICILLIN CLASS

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

CELL WALL SYNTHESIS



CELL WALL SYNTHESIS



penicillin-binding protein

PENICILLIN 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; amoxicillin vs. ampicillin
Distribution	Well; CNS penetration
Half-life	0.5 to 1.5 hours → q4h or q6h
Excretion	Mostly renal; ampicillin with great biliary
Adverse effects	Allergic skin rash, drug fever, diarrhea, severe anaphylaxis is rare

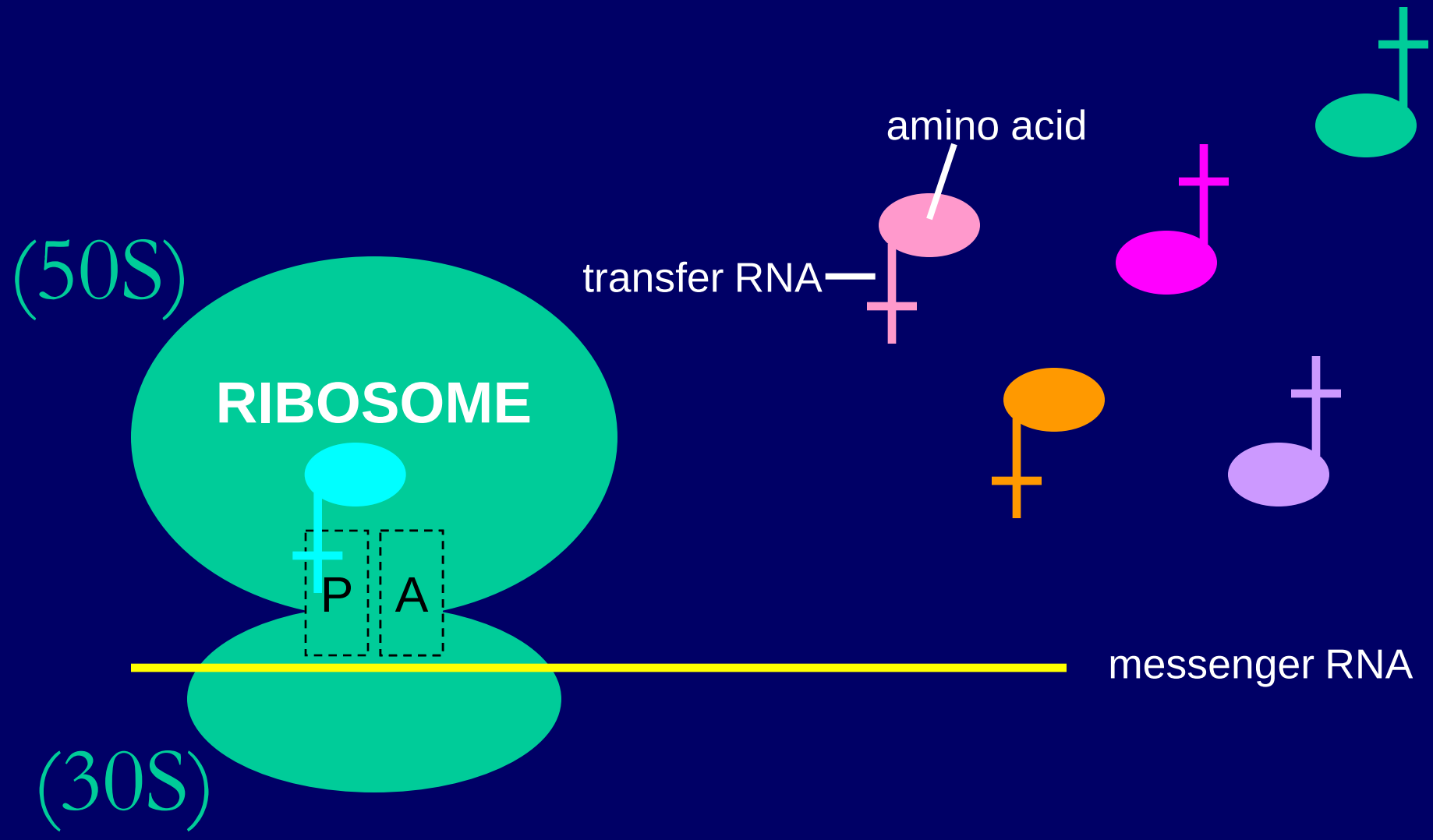
PENICILLIN CLASS

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	Otitis media (stay tuned)

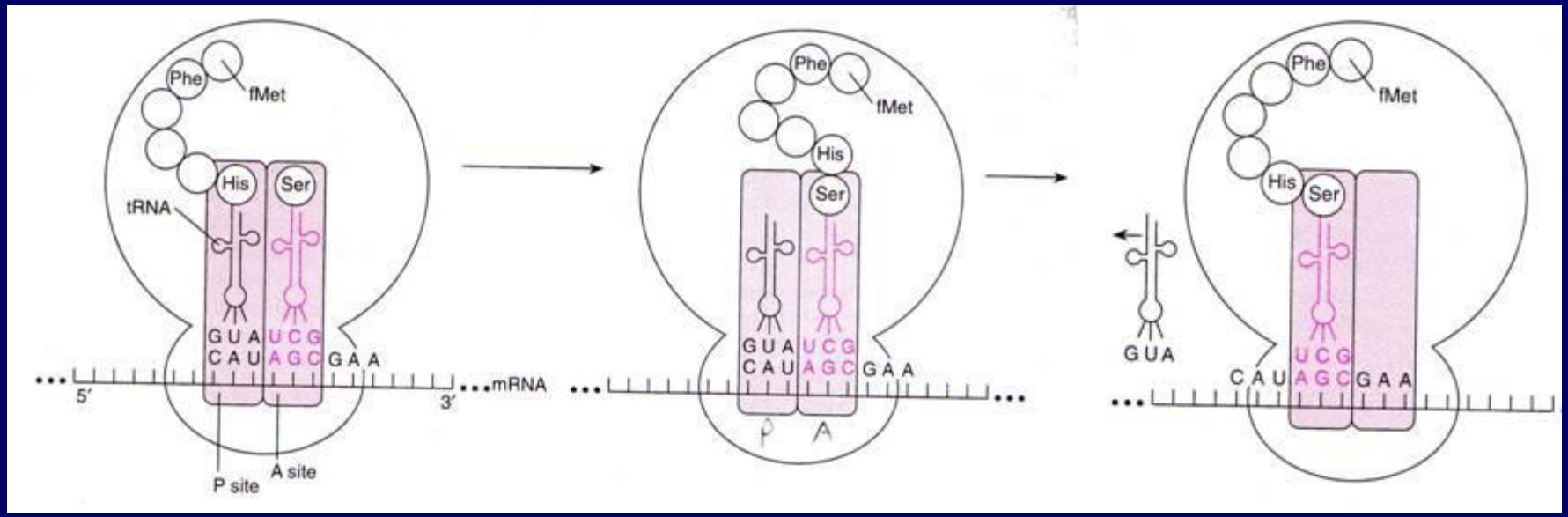
MACROLIDE CLASS

Subclass (if appropriate)	Agent(s)
NONE	erythromycin
	azithromycin
	clarithromycin

PROTEIN SYNTHESIS



MACROLIDE CLASS



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

MACROLIDE CLASS

Parameter	Description
Mechanism of action	Bind reversibly to 50S ribosomal subunits, blocking the translocation reaction of polypeptide chain elongation
Activity rendered	Static
Route of administration	PO or IV
Distribution	Well, especially tissue and intracellular; no CNS
Half-life	1.5-48 hours; azithromycin 2-4 days in tissue
Excretion	Renal and biliary
Adverse effects	Nausea, vomit, diarrhea, hypersensitivity; reversible hearing loss with high dose + renal insufficiency

MACROLIDE CLASS

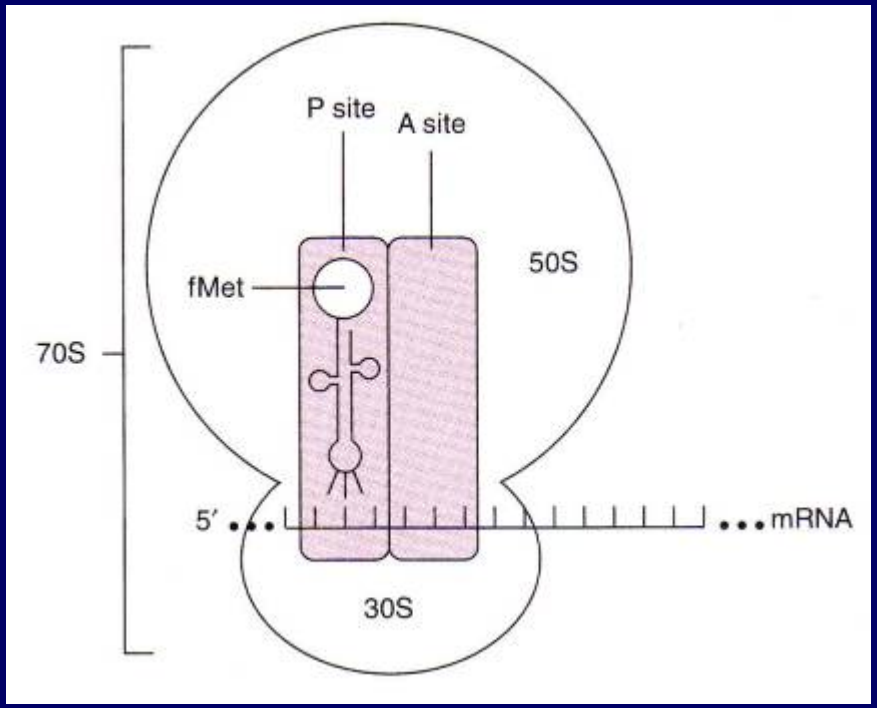
Parameter	Description
Spectrum of activity	Mostly Gram positive; anaerobes Atypical pneumonia: *Chlamydia pneumoniae*, *Mycoplasma pneumoniae*, *Legionella pneumophila* URT: *S. pneumoniae*, *H. influenzae*, *Bordetella pertussis*, *Moraxella catarrhalis* STD: *C. trachomatis*, *N. gonorrhoeae*, syphilis
Interesting stuff	~50% resistance rate in β-hemolytic streptococci; emerging problem in penicillin-allergic patients (moms with group B)

TETRACYCLINE CLASS

Subclass (if appropriate)	Agent(s)
NONE	tetracycline
	doxycycline
	minocycline

TETRACYCLINE MECHANISM

- Energy-dependent entry
- Inhibit attachment of aminoacyl-tRNA to ribosome acceptor site



TETRACYCLINE CLASS

Parameter	Description
Mechanism of action	Bind reversibly to 30S ribosomal subunit, preventing attachment of aminoacyl~tRNA to the A site in the RNA-ribosome complex; energy-dependent penetration of cell membrane
Activity rendered	Static
Route of administration	PO or IV
Distribution	Well, especially in tissue and human milk; no CNS
Half-life	8-22 hours → q6h or q12h
Excretion	Renal and biliary
Adverse effects	Nausea, vomit, esophageal ulcerations; permanent tooth discoloration when given during development

TETRACYCLINE CLASS

Parameter	Description
Spectrum of activity	Broad spectrum (including anaerobes and MRSA) Tick drug: *Rickettsia* spp. *Borrelia burgdorferi* *Coxiella burnetii* typhus Skin & soft tissue infections; intraabdominal infections STD and pelvic inflammatory disease
Interesting stuff	Absorption improved in fasting state (antacids, food impair absorption); avoided in pregnancy & in kids under 8

FOLATE PATHWAY INHIBITORS

Subclass (if appropriate)	Agent(s)
NONE	sulfonamides
	trimethoprim
	trimethoprim-sulfamethoxazole

FOLATE SYNTHESIS

- Overall goal: pyrimidine synthesis (DNA)
- Two-step process

FOLATE PATHWAY INHIBITORS

Parameter	Description
Mechanism of action	Sulfonamides: competitive inhibition of PABA conversion into dihydrofolate Trimethoprim: inhibition of dihydrofolate reductase (DHFR)
Activity rendered	Cidal
Route of administration	PO or IV (for trimethoprim-sulfamethoxazole)
Distribution	Well; CNS penetration
Half-life	10-12 hours → q6h to q12h
Excretion	Renal
Adverse effects	(more commonly due to sulfonamide component) Mild GI, allergic skin rash (3%); hematopoietic changes

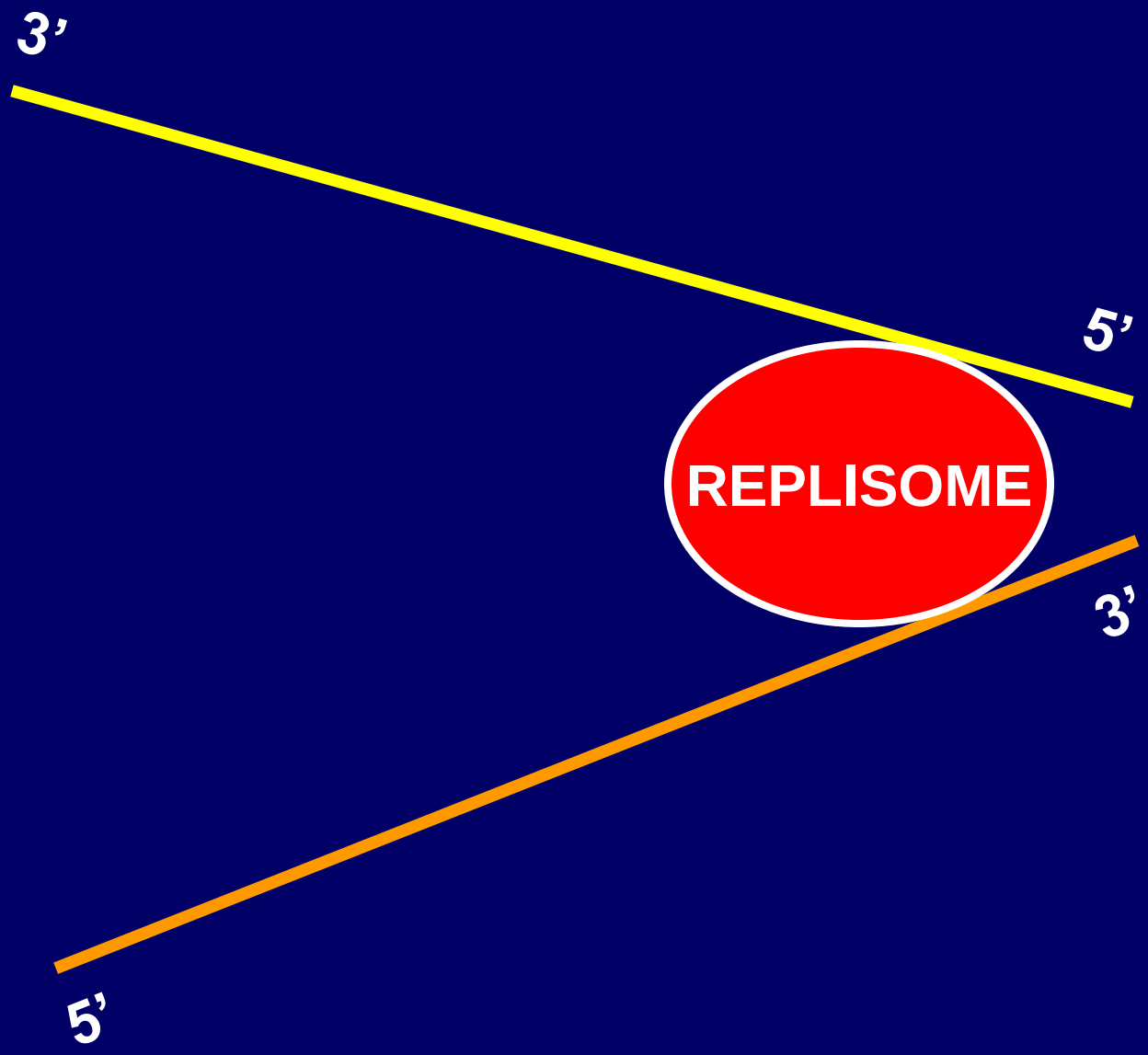
FOLATE PATHWAY INHIBITORS

Parameter	Description
Spectrum of activity	Broad spectrum (except *Pseudomonas aeruginosa*) UTI etiologies except *Enterococcus* spp. Enteric pathogens Acute otitis media, sinusitis, acute bronchitis, pneumonia (*S. pneumoniae*, *H. influenzae*, *M. catarrhalis*)
Interesting stuff	Fungal therapy & prophylaxis *(Pneumocystis carinii*) AIDS patients have higher frequency of adverse reactions (70%)

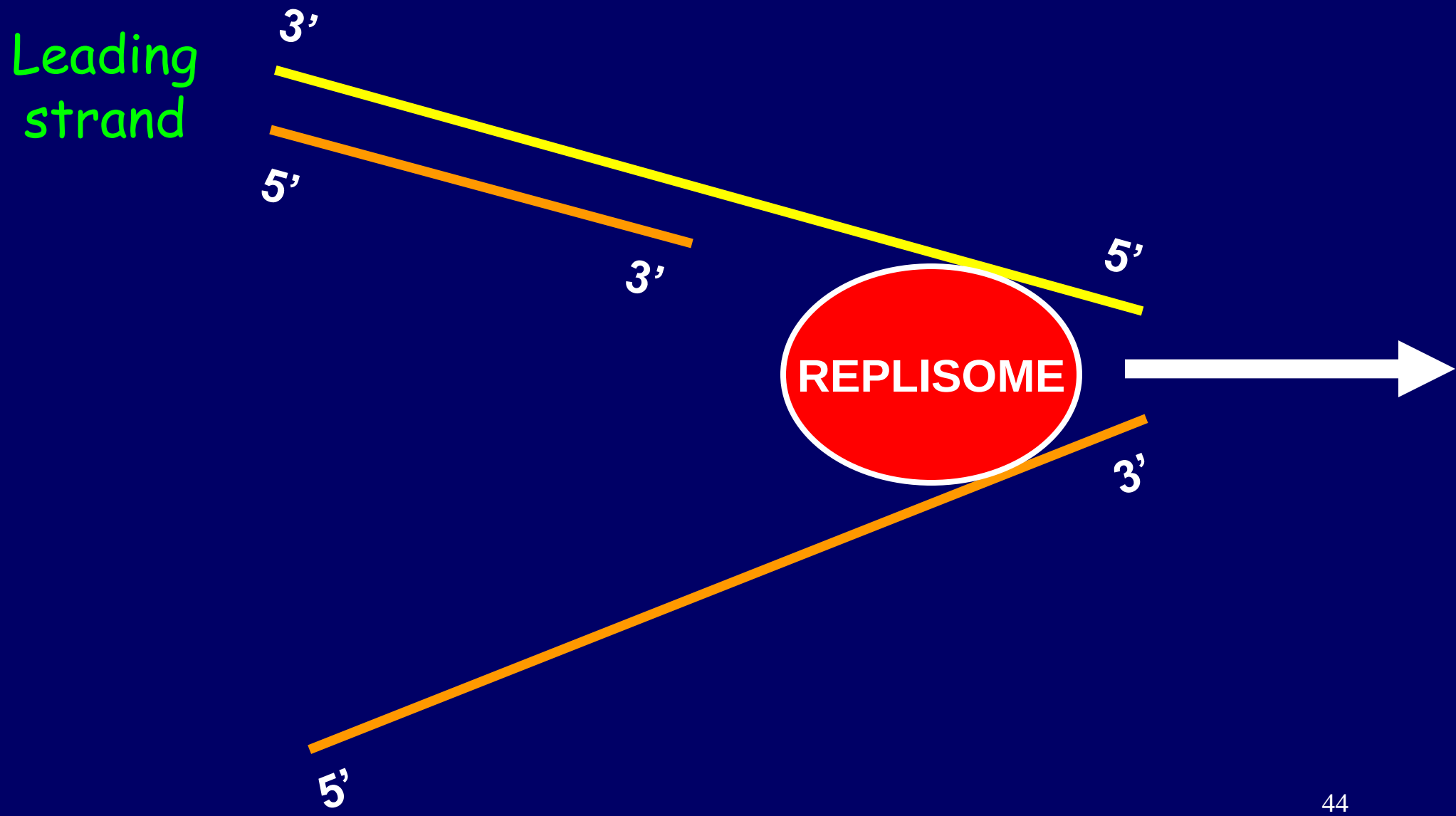
QUINOLONE CLASS

Subclass (if appropriate)	Agent(s)
quinolone	nalidixic acid
fluoroquinolone	ofloxacin
	norfloxacin
	ciprofloxacin
	levofloxacin
	moxifloxacin
	gatifloxacin
	trovafloxacin
	temafloxacin, grepafloxacin

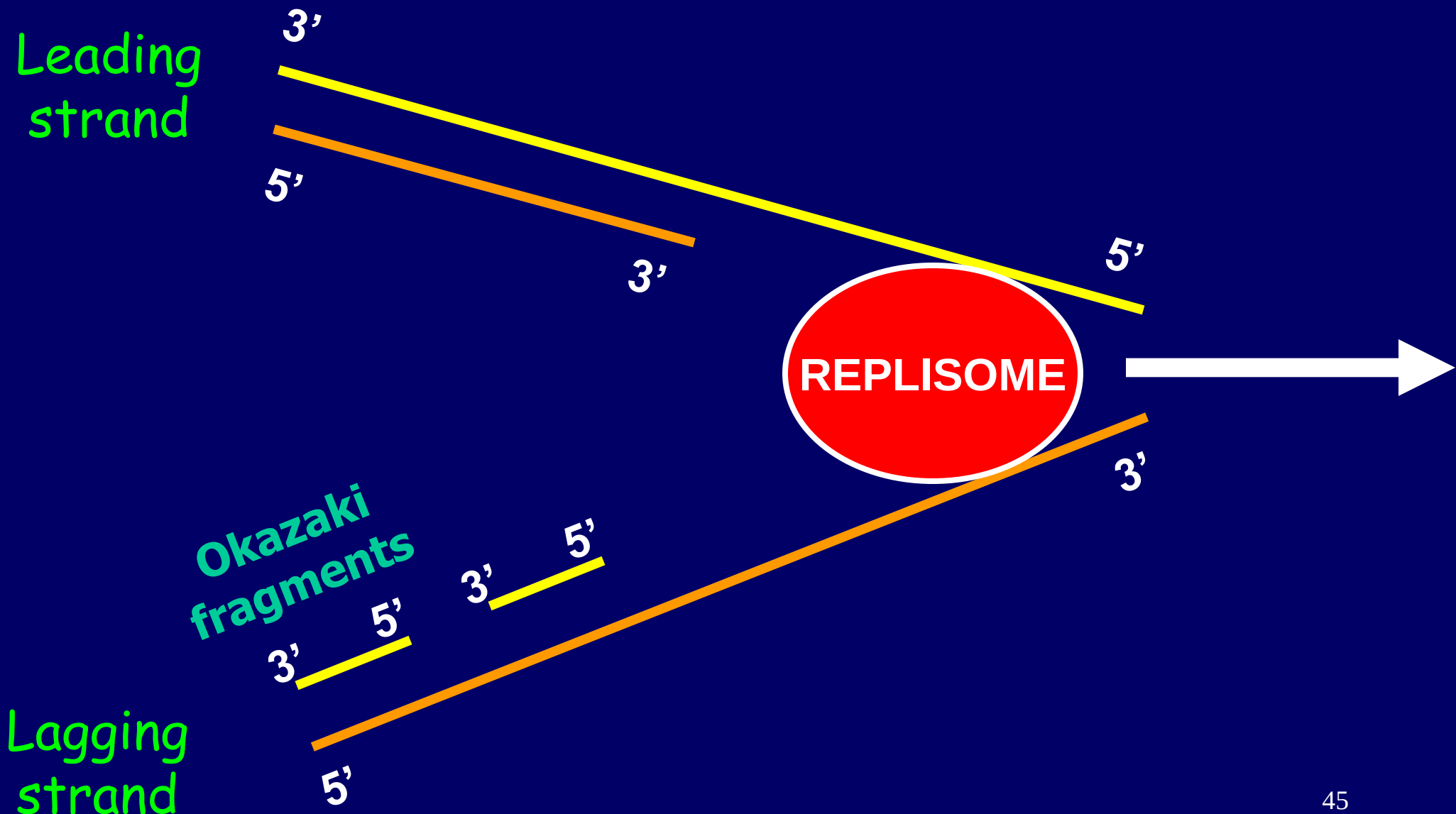
DNA REPLICATION



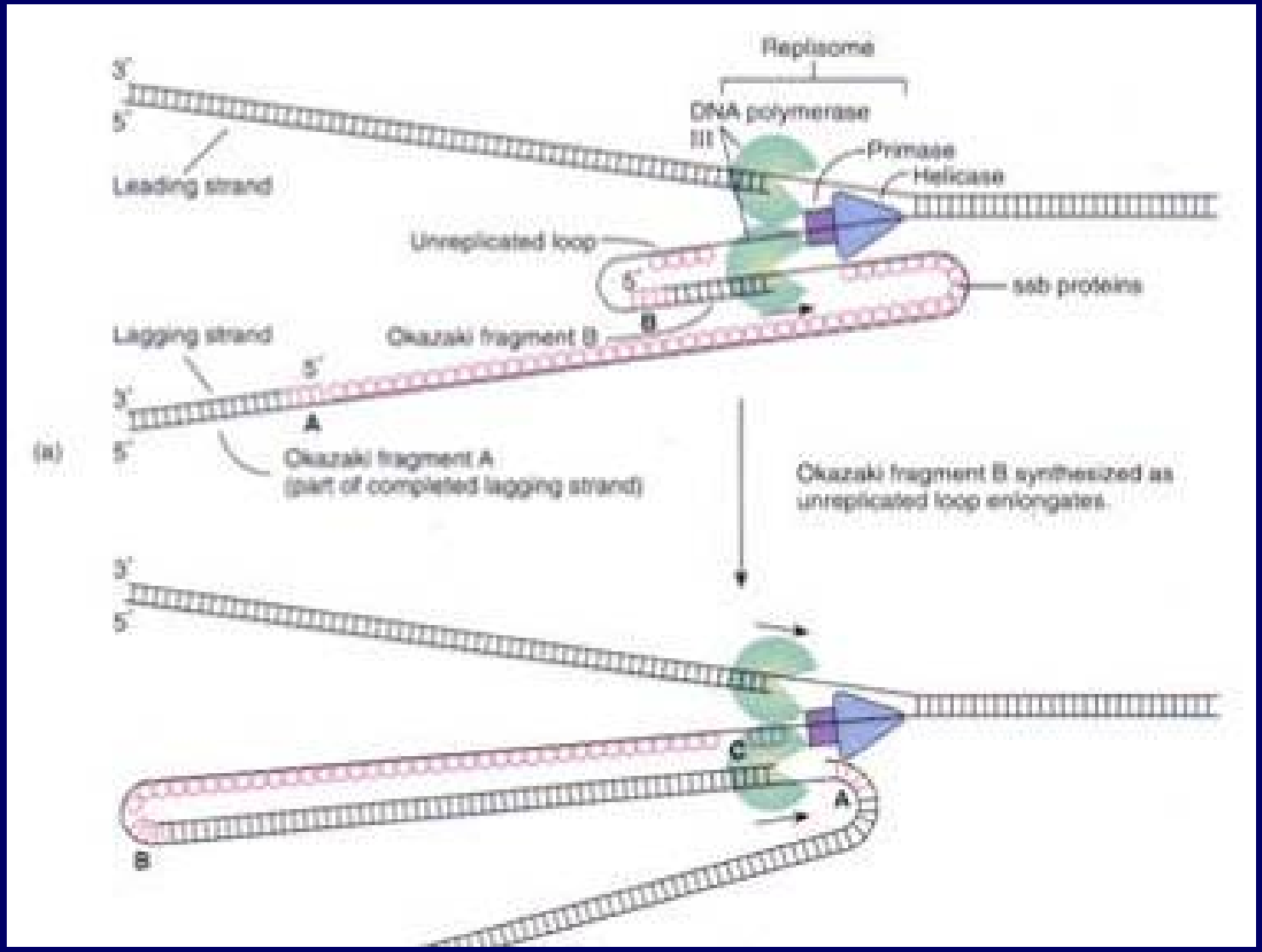
DNA REPLICATION



DNA REPLICATION



DNA REPLICATION



RELAXING/RECOVERY ENZYMES

- DNA topoisomerase IV

parC → Two C subunits
parE → Two E subunits

- DNA gyrase

gyrA → Two GyrA subunits
gyrB → Two GyrB subunits

QUINOLONE CLASS

Parameter	Description
Mechanism of action	1. Binds DNA gyrase (primarily in Gram negatives) 2. Newer agents bind DNA topoisomerase (primarily in Gram positives)
Activity rendered	Cidal
Route of administration	PO or IV
Distribution	Well; levo, gati, moxi CNS; also intracellular delivery
Half-life	3.5 to 20 hours → q12h or q24h
Excretion	Renal; ciprofloxacin also with strong biliary excretion
Adverse effects	Growth plate development; cipro: tendonitis, rupture Nausea, vomit, diarrhea, pseudomembranous colitis?

QUINOLONE CLASS

Parameter	Description
Spectrum of activity	Gram positive and Gram negative coverage--losing activity versus MRSA Otitis media agents *Neisseria gonorrhoeae*, *Chlamydia trachomatis* ciprofloxacin: enteric pathogens, *P. aeruginosa* levofloxacin, moxifloxacin: *S. pneumoniae* gatifloxacin, moxifloxacin: Anaerobes Some activity versus *Mycobacterium* spp.
Interesting stuff	Losing them versus common enteric GNR Canadian studies predict loss versus *S. pneumoniae*

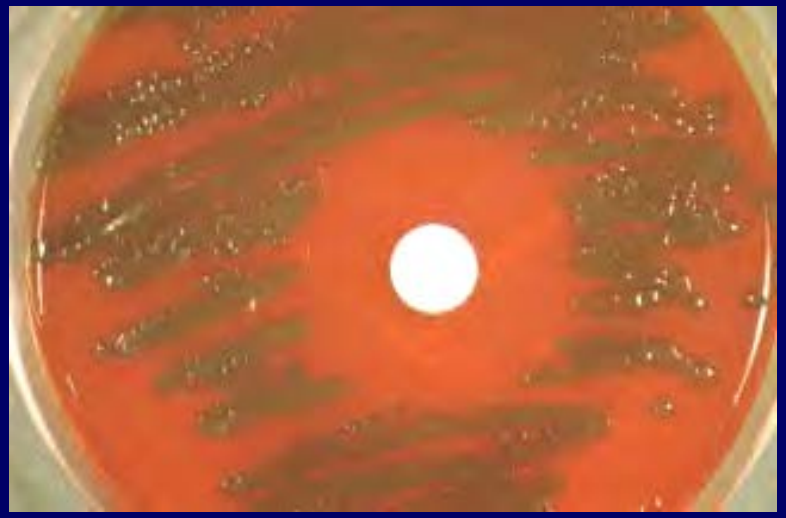
Mechanisms of Resistance

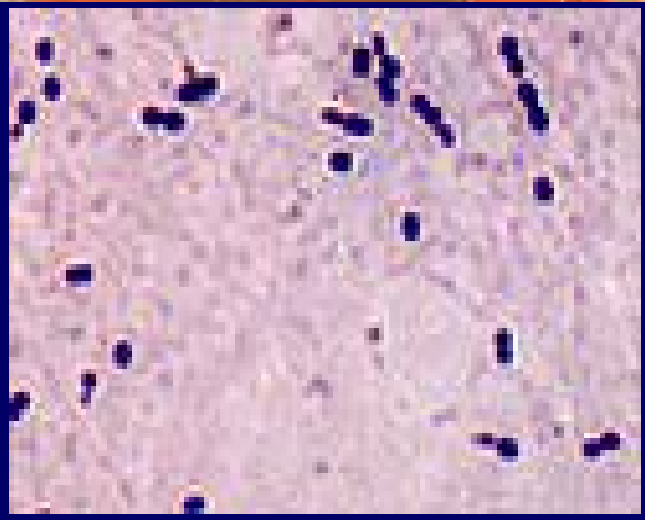
BACTERIUM-MEDIATED RESISTANCE

- Altered target
- Enzymatic inactivation
- Diminished penetration
- Efflux
- Altered physiology

Streptococcus pneumoniae

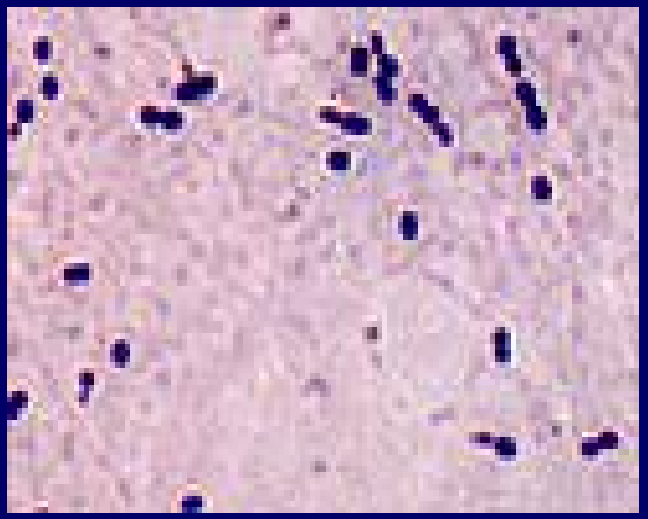
- Community-acquired pneumonia
- Bacteremia
- Otitis media
- Sinusitis
- Meningitis
- Endocarditis





PENICILLIN SUSCEPTIBILITY

Year	% Susceptible
2002	75.9
2003	80.2
2004	74.4
2005	71.0
2006	73.5
2007	62.2



PENICILLIN vs. *S. pneumoniae*

Specimen Source	% Intermediate	% Resistant
Upper respiratory tract	14.1	31.3
Lower respiratory tract	14.0	20.9
Blood	10.7	14.9
CSF/sterile fluid	6.1	24.2

Age (years)	% Intermediate	% Resistant
0-5	13.7	28.9
6-20	10.3	25.3
21-64	11.2	18.8
65 or older	14.2	15.9

Antimicrob. Agents. Chemother. **45:** 1721-1729; 2001

Direct Detection of Bacterial Biofilms on the Middle-Ear Mucosa of Children With Chronic Otitis Media

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Context Chronic otitis media (OM) is a common pediatric infectious disease. Previous studies demonstrating that metabolically active bacteria exist in culture-negative pediatric middle-ear effusions and that experimental infection with *Haemophilus influenzae* in the chinchilla model of otitis media results in the formation of adherent mucosal biofilms suggest that chronic OM may result from a mucosal biofilm infection.

Objective To test the hypothesis that chronic OM in humans is biofilm-related.

Design, Setting, and Patients Middle-ear mucosa (MEM) biopsy specimens were obtained from 26 children (mean age, 2.5 [range, 0.5-14] years) undergoing tympanostomy tube placement for treatment of otitis media with effusion (OME) and recurrent OM and were analyzed using microbiological culture, polymerase chain reaction (PCR)-based diagnostics, direct microscopic examination, fluorescence in situ hybridization, and immunostaining. Uninfected (control) MEM specimens were obtained from 3 children and 5 adults undergoing cochlear implantation. Patients were enrolled between February 2004 and April 2005 from a single US tertiary referral otolaryngology practice.

Main Outcome Measures Confocal laser scanning microscopic (CLSM) images were obtained from MEM biopsy specimens and were evaluated for biofilm morphology using generic stains and species-specific probes for *H influenzae*, *Streptococcus pneumoniae*, and *Moraxella catarrhalis*. Effusions, when present, were evaluated by PCR and culture for evidence of pathogen-specific nucleic acid sequences and bacterial growth, respectively.

Results Of the 26 children undergoing tympanostomy tube placement, 13 (50%) had OME, 20 (77%) had recurrent OM, and 7 (27%) had both diagnoses; 27 of 52 (52%) of the ears had effusions, 24 of 24 effusions were PCR-positive for at least 1 OM pathogen, and 6 (22%) of 27 effusions were culture-positive for any pathogen. Mucosal biofilms were visualized by CLSM on 46 (92%) of 50 MEM specimens from children with OME and recurrent OM using generic and pathogen-specific probes. Biofilms were not observed on 8 control MEM specimens obtained from the patients undergoing cochlear implantation.

Conclusion Direct detection of biofilms on MEM biopsy specimens from children with OME and recurrent OM supports the hypothesis that these chronic middle-ear disorders are biofilm-related.

JAMA. 2006;296:202-211 www.jama.com

OTITIS MEDIA (OM) IS THE most common illness for which children visit a physician, receive antibiotics, or undergo surgery in the United States. Chronic OM includes both OM with effusion (OME) and recurrent OM in which clinical evidence of OM and the middle-ear effusion (MEE) resolves between episodes. Otitis media with effusion can result in conductive hearing loss, which has been linked to the delayed development of speech and socialization skills.[1] *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis* are isolated from approximately 25% of children with OME, but polymerase chain reaction (PCR)-based methods have demon-

Author Affiliations: Center for Genomic Sciences, Allegheny-Singer Research Institute, Pittsburgh, Pa (Drs Hall-Stoodley, Hu, Gieseke, Nistico, Nguyen, Forbes, Stoodley, Post, and Ehrlich and Mr Hayes and Ms Dice); Department of Microbiology and Immunology, Drexel University College of Medicine, Allegheny Campus, Pittsburgh (Drs Hall-Stoodley, Hu, Stoodley, Post, and Ehrlich); Department of Molecular Ecology, Max Planck Institute for Marine Microbiology, Bremen, Germany (Dr Gieseke); Children's Hospital of Pittsburgh, Pittsburgh (Dr Greenberg); and Children's Hospital of Wisconsin, Medical College of Wisconsin, Department of Otolaryngology, Milwaukee (Ms Burrows and Drs Wackym and Kerschner).
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BIOFILM FREQUENCY

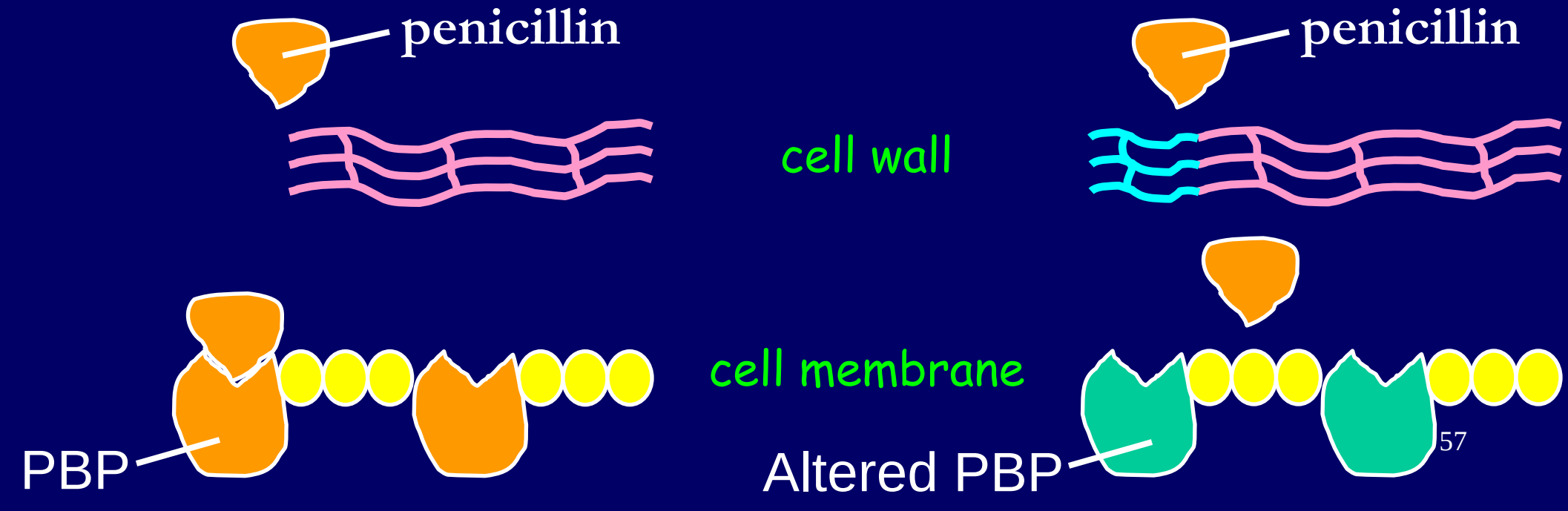
- 93% of ears with recurrent otitis media

- 91% of ears with otitis media with effusion

JAMA. **296:** 202-211; 2006

RECOMBINATION W/ FOREIGN DNA

- PBP of less-susceptible species recombine with native, susceptible species
- Transformation: uptake of “naked” DNA

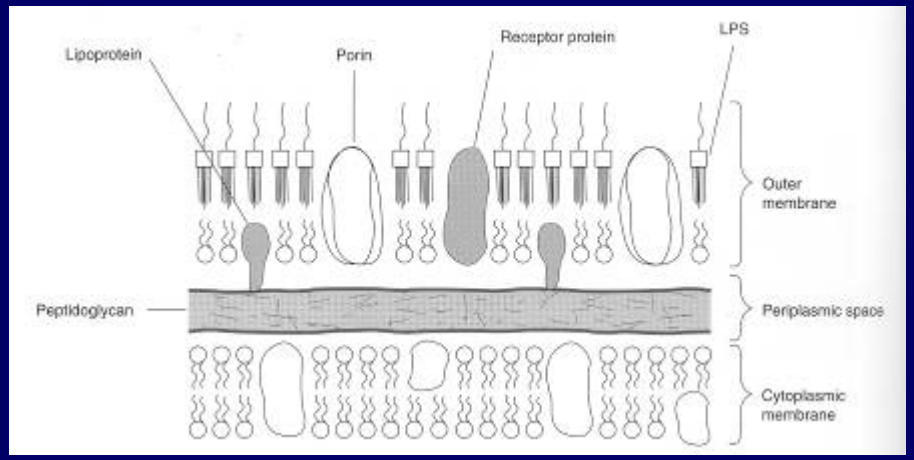


NON-β-LACTAM ANTIMICROBIALS

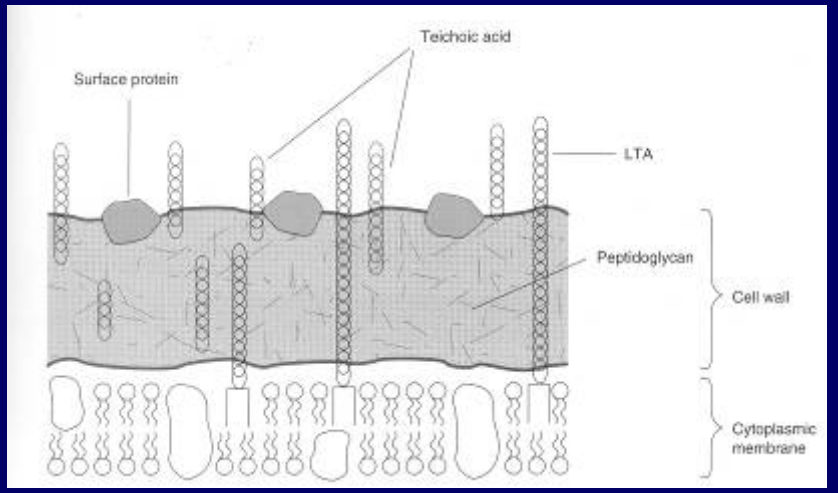
Year	Percentage Susceptible		
	Erythromycin	Tetracycline	Trimethoprim-sulfamethoxazole
2004	75	81	80
2005	69	83	73
2006	80	85	76
2007	58	76	63

MACROLIDE RESISTANCE

- Size matters



Gram negative



Gram positive

- Methylation of ribosome

  ermA → erythromycin ribosomal methylase

- Expression of efflux pumps

  Resistance to macrolides, not clindamycin

TETRACYCLINE RESISTANCE

- Efflux mechanism by which bacterium exchanges tetracycline-cation complex for a proton

- Ribosome protection proteins

  Bind to ribosome
  Change ribosome configuration
  Inhibit binding of tetracycline

TRIMETH-SULFA RESISTANCE

- Intrinsic resistance

  Due to permeability barrier or active efflux, decreased access to target enzymes that assist in manufacture of tetrahydrofolate

  Low affinity for organism-specific target enzymes that assist in manufacture of tetrahydrofolate

  Bacterium with ability to absorb exogenous folate or thymine

TRIMETH-SULFA RESISTANCE

- Intrinsic resistance
- Acquired resistance trimethoprim

  Promoter mutations → enzyme overproduction

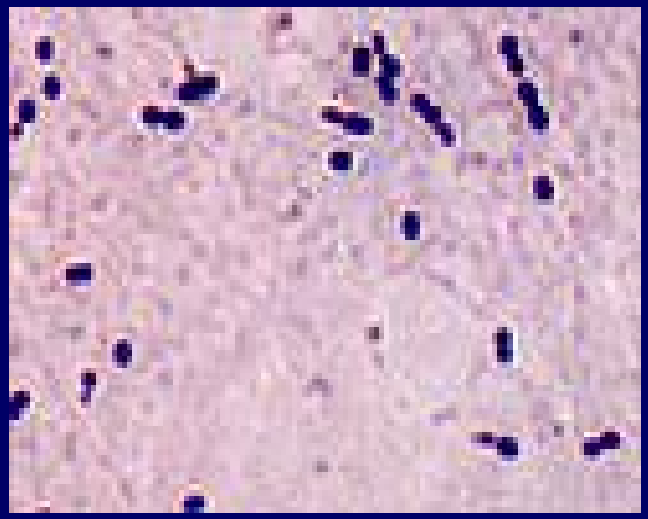
  Point mutations → low affinity of enzyme for drug

- Acquired resistance sulfonamides

  Point mutations → low affinity of enzyme for drug

LEVOFLOXACIN SUSCEPTIBILITY

Year	% Susceptible
2002	97.2
2003	100.0
2004	99.5
2005	100.0
2006	97.3
2007	99.3



LEVOFLOXACIN vs. *S. pneumoniae*

Antimicrobial Susceptibility Breakpoints and First-Step *parC* Mutations in *Streptococcus pneumoniae*: Redefining Fluoroquinolone Resistance

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Emerg. Infect. Dis. **9:** 833-837; 2003

METHODS

- Clinical MIC breakpoints (CLSI)

Levofloxacin:	≤ 2	susceptible
	4	intermediate
	≥ 8	resistant

- Micro/molecular MIC breakpoints

Sequenced *parC*, *gyrA*

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ROLE OF *parC* AND *gyrA*

Table 2. Number of isolates with ParC and GyrA amino acid substitutions and their corresponding levofloxacin MICs

MIC (μg/mL)	No. strains with amino acid substitutions in ParC (%)	ParC and GyrA (%)
8	0/10 (0)	10/10 (100)
≥16	0/15 (0)	15/15 (100)

[a]29/82 isolates were randomly examined for GyrA mutations.

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FREQUENCY OF *parC*

Table 1. ParC amino acid substitutions found in 115 *Streptococcus pneumoniae* isolates with levofloxacin MICs ≥2 µg/mL and corresponding levofloxacin MICs

ParC amino acid substitution	No. isolates inhibited by levofloxacin MIC (µg/mL) of					Total no. of strains
	2	4	8	16	≥32	
Ser79→Phe	28	4	3	9	3	47
Ser79→Tyr	7	1	3	2	1	14
Ser79→Ala	1	0	0	0	0	1
Asp83→Asn	7	0	3	0	0	10
Asp83→Gly	1	0	0	0	0	1
Asp83→Tyr	3	0	0a	0	0	3
Asp83→Val	1	0	0	0	0	1
Asp83→Ala	0	0	1	0	0	1
No. isolates/total with amino acid substitutions	48/82 (59%)	5/8[a] (63%)	10/10	11/11	4/4	78/115 (69%)

[a]One isolate with no ParC amino acid substitution found to have active efflux; two isolates had ParC amino acid substitutions at sites other than Ser79 or Asp83.

Emerg. Infect. Dis. **9:** 833-837; 2003

CONCLUSIONS

- *parC* is first-step mutation in reducing fluoroquinolone susceptibility

- MIC breakpoints do not always predict levofloxacin resistance

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Why is this important?

CLINICAL FAILURE

TABLE 1. MICROBIOLOGIC CHARACTERISTICS OF *STREPTOCOCCUS PNEUMONIAE* ISOLATED BEFORE, DURING, OR AFTER THERAPY WITH ORAL LEVOFLOXACIN FROM FOUR PATIENTS WITH COMMUNITY-ACQUIRED PNEUMONIA.*

PATIENT NO.	SOURCE AND TIME OF CULTURE	SEROTYPE	PFGE PATTERN†	SUSCEPTIBILITY TO LEVOFLOXACIN‡	MINIMAL INHIBITORY CONCENTRATION§			AMINO ACID SUBSTITUTION	
					LEVO-FLOXACIN	MOXI-FLOXACIN	GATI-FLOXACIN	IN PARC	IN GYRA
					μg/ml				
1	Sputum, before treatment	23F	A	S	1 (S)	0.12 (S)	0.25 (S)	—	—
	Sputum, after treatment	23F	A	R	8 (R)	1 (S)	2 (I)	S79F	S81F
2	Sputum, before treatment	6A	B	S	4 (I)	0.25 (S)	0.5 (S)	S79F	—
	Sputum, during treatment	6A	B	R	16 (R)	4 (R)	4 (R)	S79F	S81F
3	Blood, before treatment	14	C	R	16 (R)	4 (R)	2 (I)	S79F	S81Y
	Pleural fluid, during treatment	14	C	R	16 (R)	4 (R)	2 (I)	S79F and D83Y	S81Y
4	Sputum, during treatment	ND	ND	R	16 (R)	4 (R)	8 (R)	S79Y	E85K

N. Engl. J. Med. **346:** 747-750; 2002

FLUOROQUINOLONE RESISTANCE

- Spain: 5.3%

  Antimicrob. Agents. Chemother. **44:** 3481-3482; 2000

- Hong Kong: 12.1%

  Antimicrob. Agents. Chemother. **43:** 1310-1313; 1999

- Northern Ireland: 15.2%

  J. Antimicrob. Chemother. **41:** 420-421; 1998

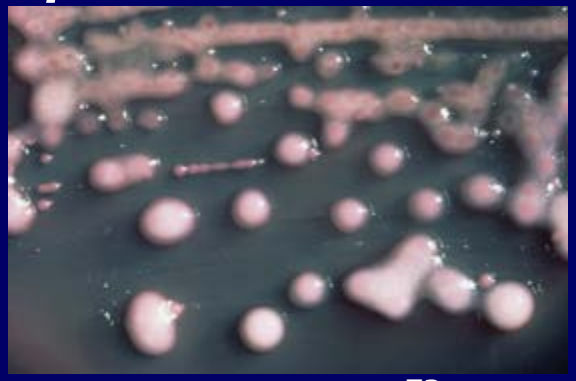
THE END

- Next time (Part Two): *Staphylococcus aureus*

penicillin
oxacillin/nafcillin
vancomycin

clindamycin
synercid
linezolid

Klebsiella pneumoniae



cephems
monobactams
β-lactamase inhibitors

carbapenems
aminoglycosides
polymyxins