Antimicrobial Resistance: The Therapeutic Challenge

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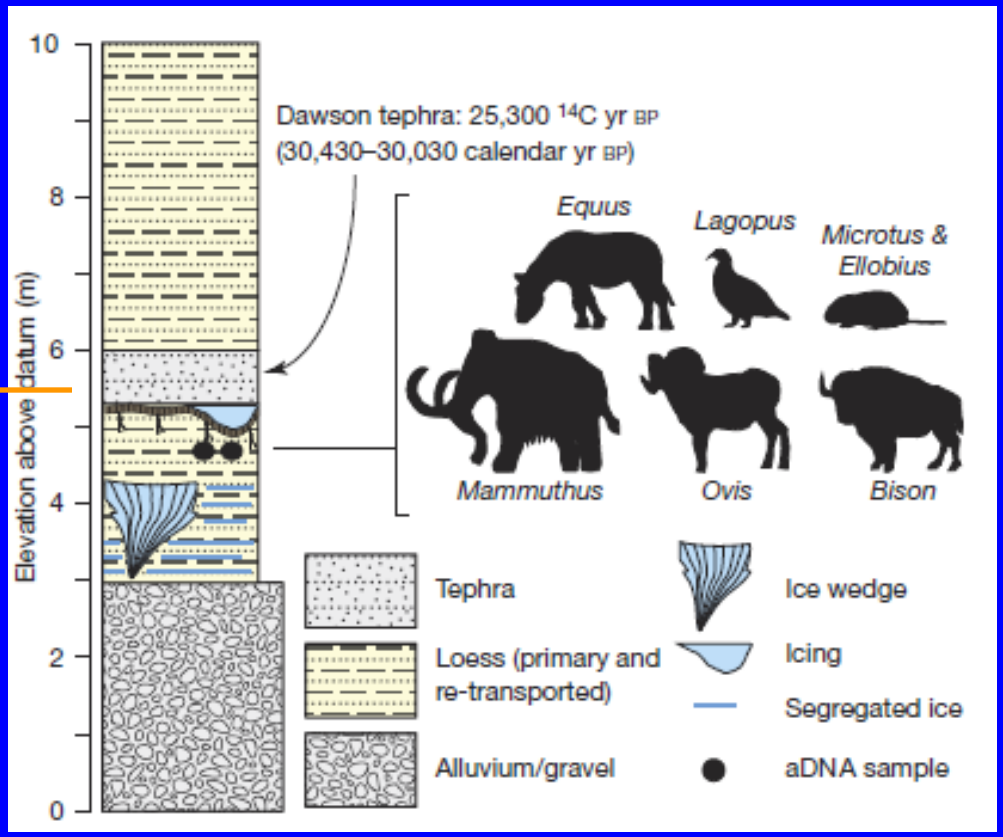
Reservoirs of Resistance Genes are Ancient

tetM
bla (TEM-like)
vanHAX



D'Costa VM et al. Nature 2011; 477:457

Risk Factors for Infection with Drug-Resistant Bacteria

Antimicrobial therapy in preceding 90 days

Current hospitalization for ≥ 5 days

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

Immunosuppression

The prevalence of antimicrobial resistance is determined by:

- Microbial ingenuity
  - –Devising resistance mechanisms
  - –Fitness strategies
- Antimicrobial selection pressures
- Transmission of resistant organisms or resistance genes

Mechanisms of Acquisition of Resistance to Antimicrobials

- Mutation in chromosomal genes
  - All pathogens
- Acquisition of new genes from other bacteria
  - Mobile genetic elements (most pathogens)
    - Plasmids, transposons, bacteriophage
    - Integrons, insertion sequences - multiple resistance gene capture elements
  - Transformation by DNA of related organisms (*S. pneumoniae*, *N. gonorrhoeae*)

How Resistance is Effected

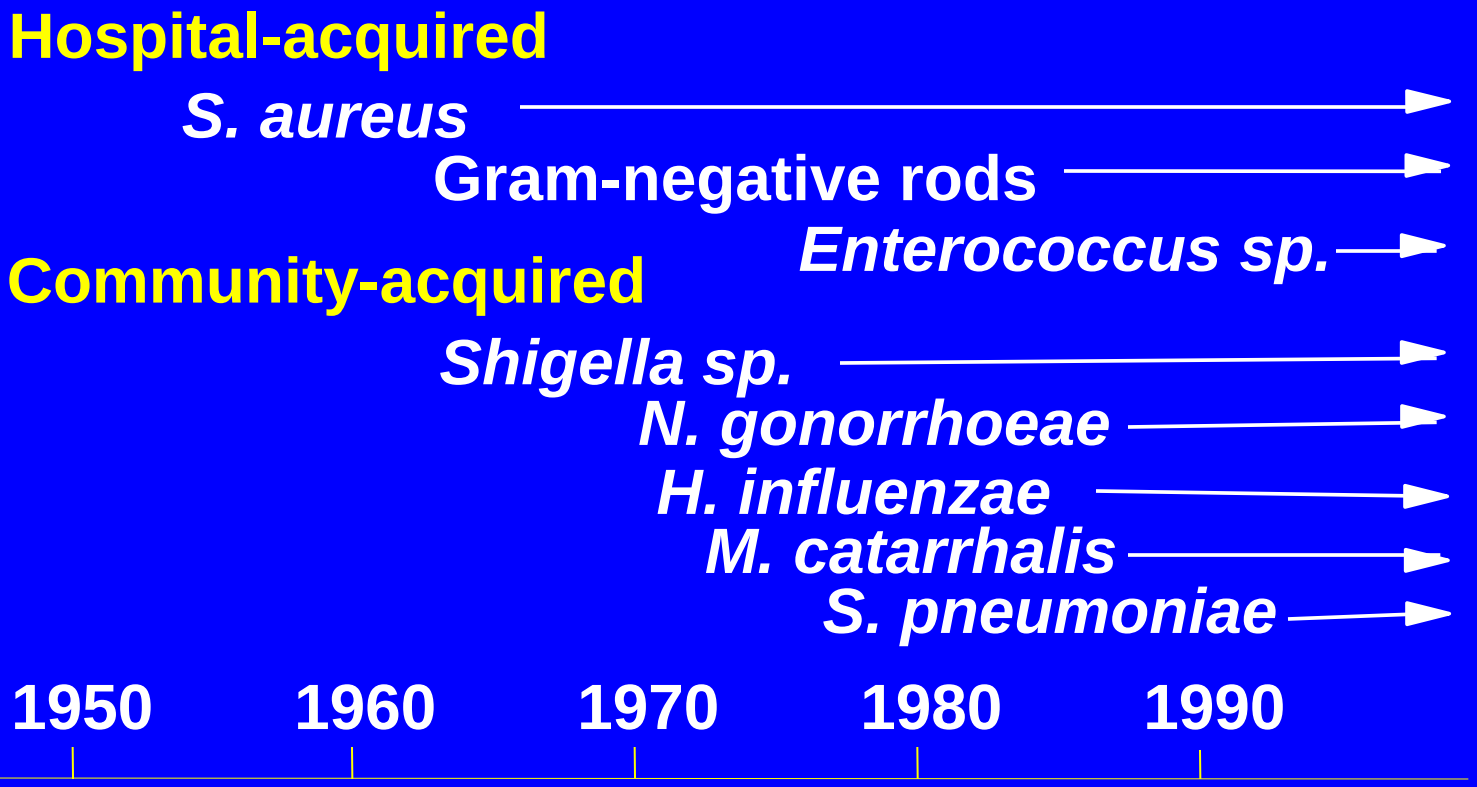
Target Alteration or Substitution

Altered Drug Access to Target

Drug Inactivation

Combinations of Above

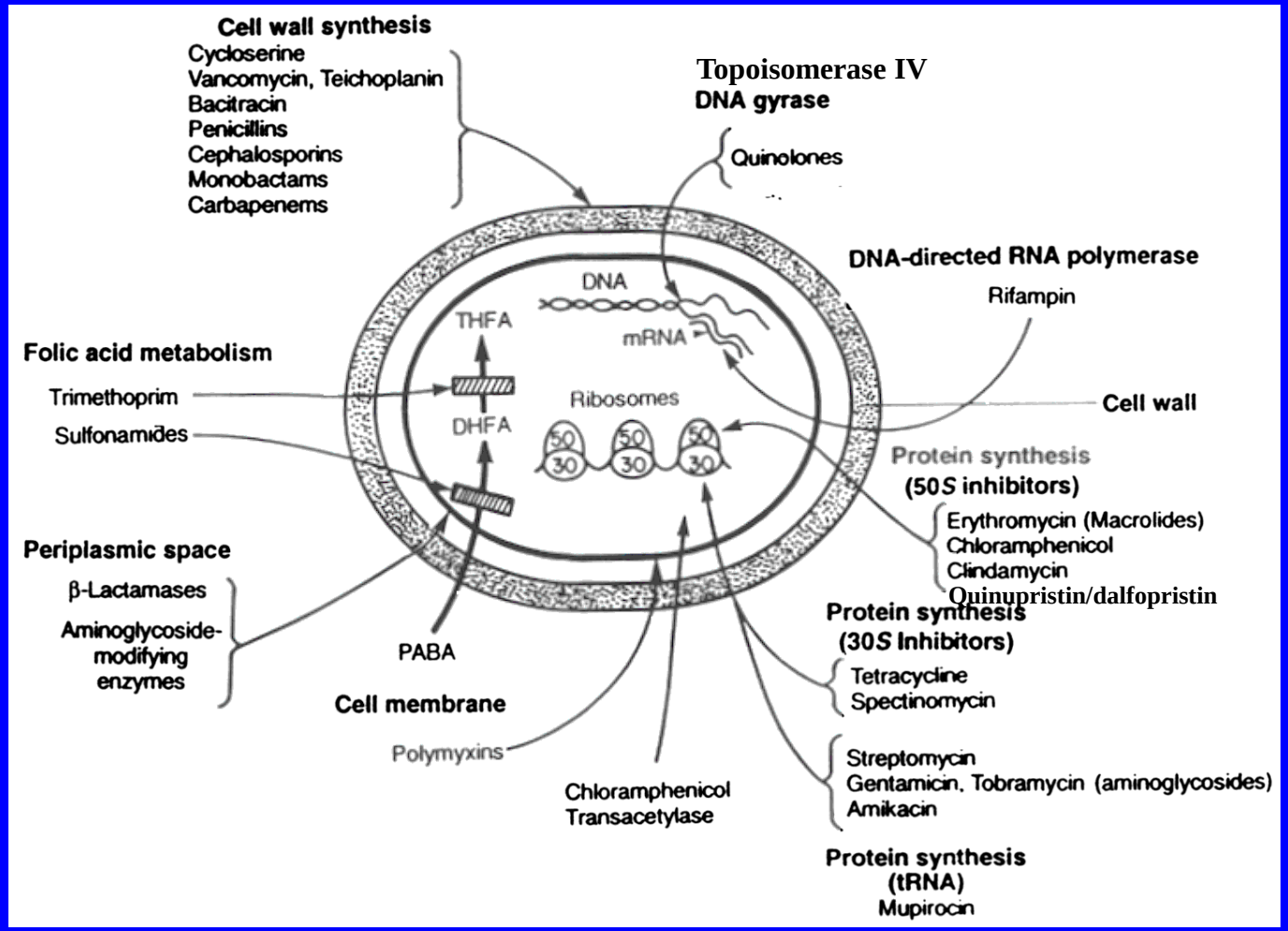
Emergence of Antibiotic-Resistant Bacteria



Cohen;Science 1992;257:1050

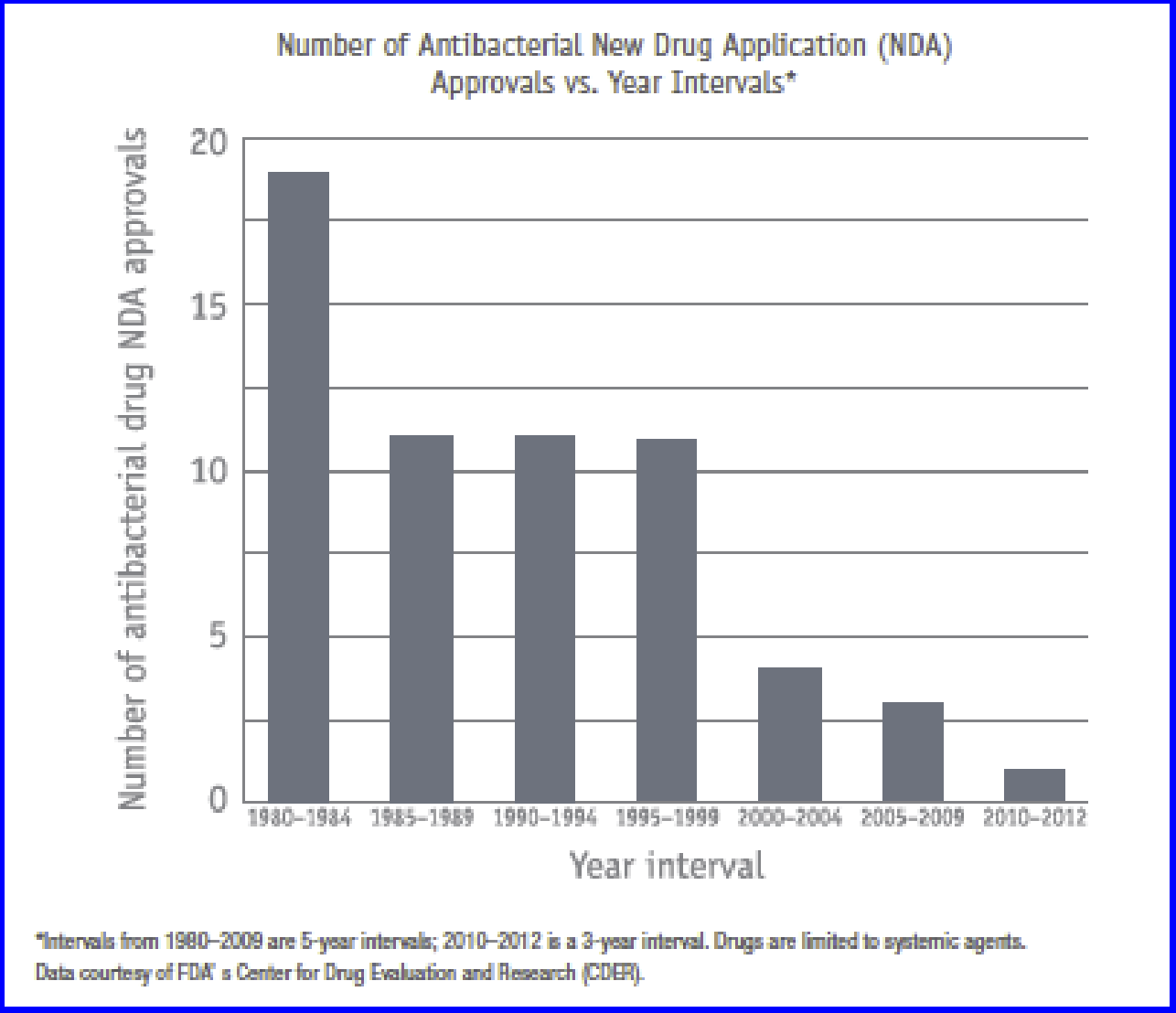
CDC
CENTERS FOR DISEASE CONTROL AND PREVENTION

Sites of Action of Antimicrobial Agents in Clinical Use



Neu HC. Science 1992; 257:1064-73

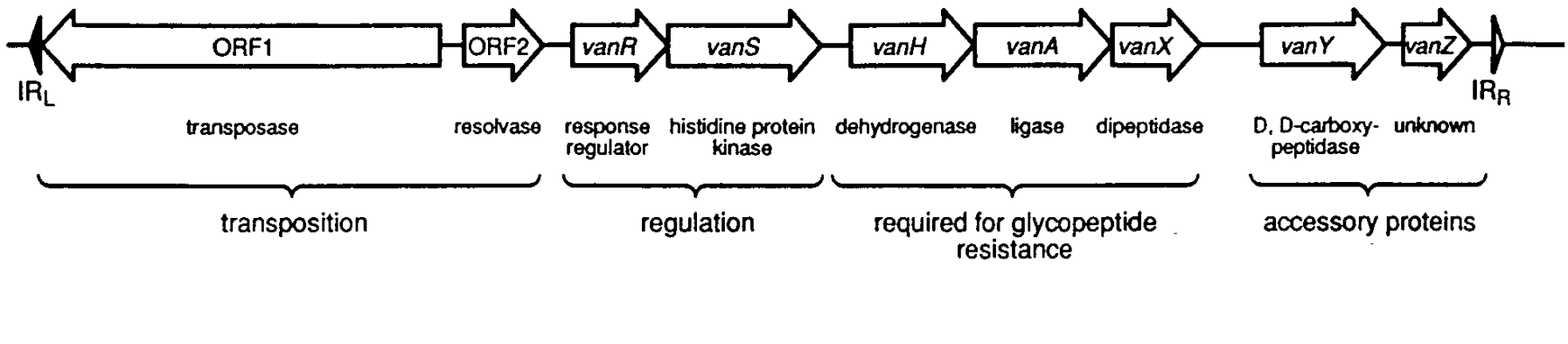
The Diminishing Antibacterial Pipeline



Major Clinical Problems with Antibiotic-Resistant Bacteria

- Vancomycin-Resistant Enterococci
- Methicillin-Resistant *Staphylococcus aureus*
- Cephalosporin-Resistant *Klebsiella*, *Enterobacter*, *Pseudomonas* and other Gram-negative Bacteria
- Carbapenem-Resistant Gram-Negative Bacteria

Glycopeptide Resistance Transposon Tn*1546* from *Enterococcus faecium*



Woodford N *et al*. Clin Microbiol Rev. 1995; 8:585-615

Pernicious Properties of VRE

- Ease of Co-Selection by Exposure to a Range of Antibiotics Because of Multidrug Resistance
- Ability to Contaminate and Survive on Environmental Surfaces
- Ability to Contaminate the Hands of Health Care Workers during Patient Care Contacts
- Facility for Cryptic Colonization of GI Tract

Major Clinical Problems with Antibiotic-Resistant Bacteria

- Vancomycin-Resistant Enterococci (VRE)
- Methicillin-Resistant *Staphylococcus aureus* (MRSA)
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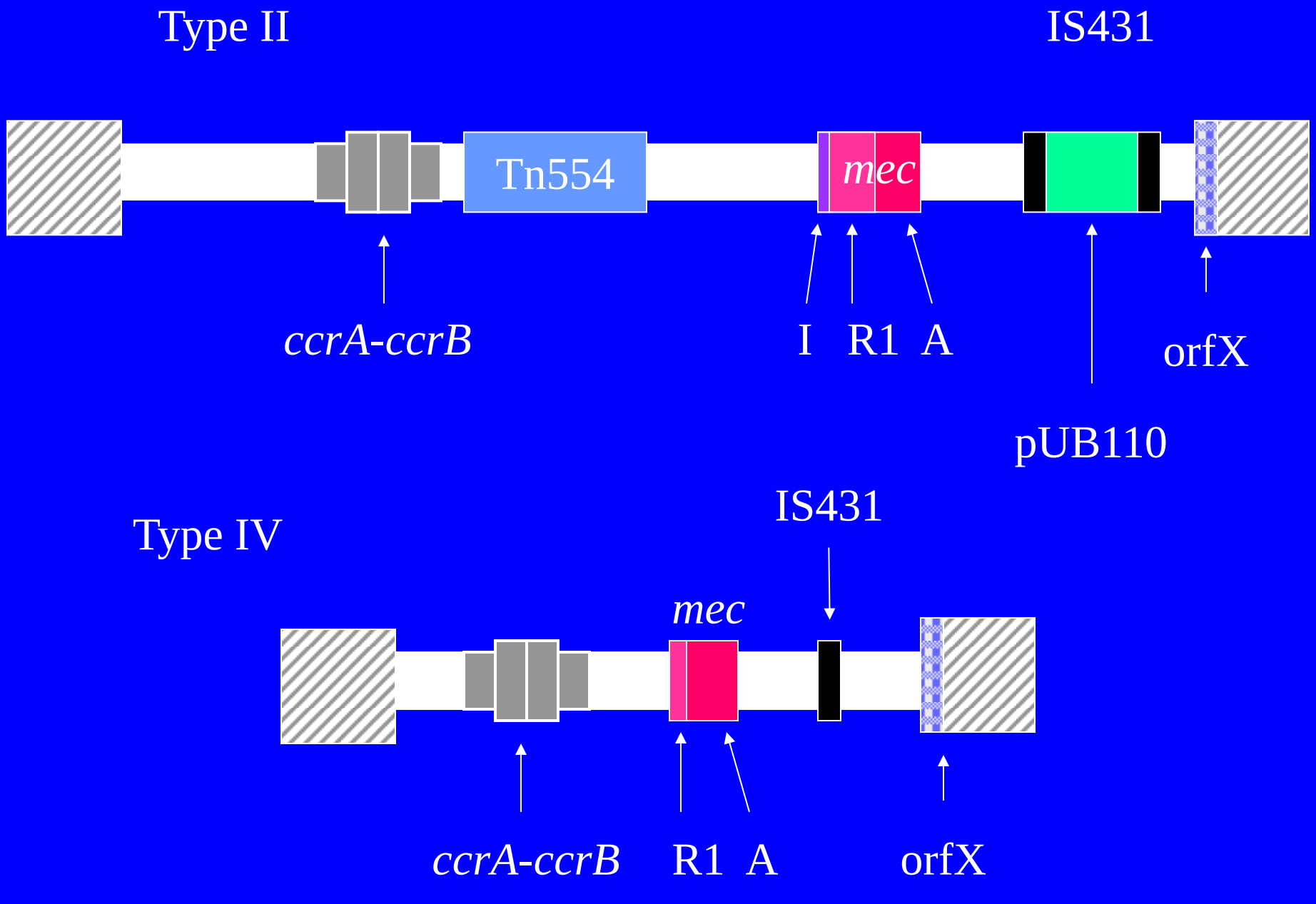
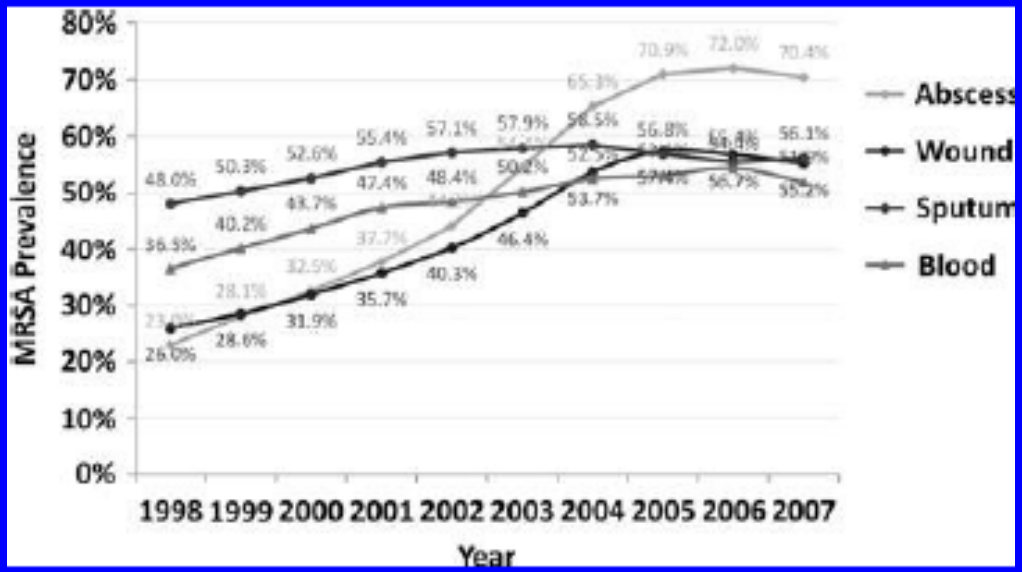
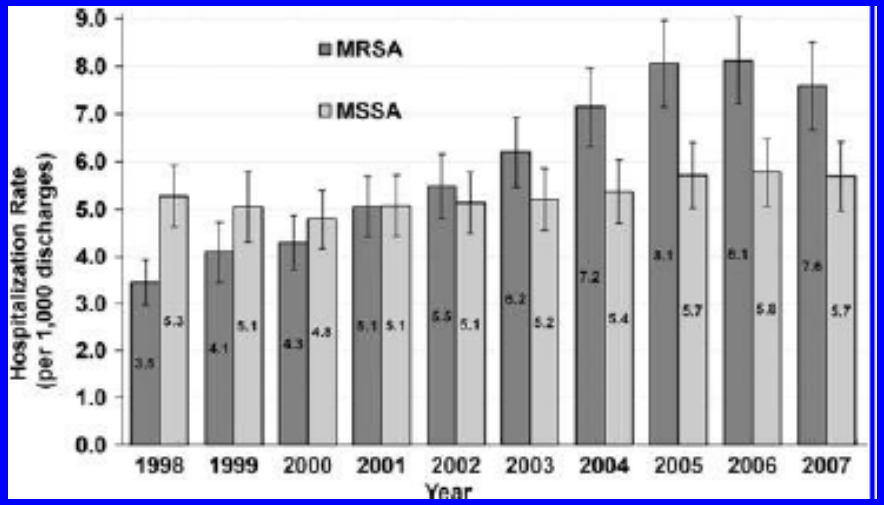
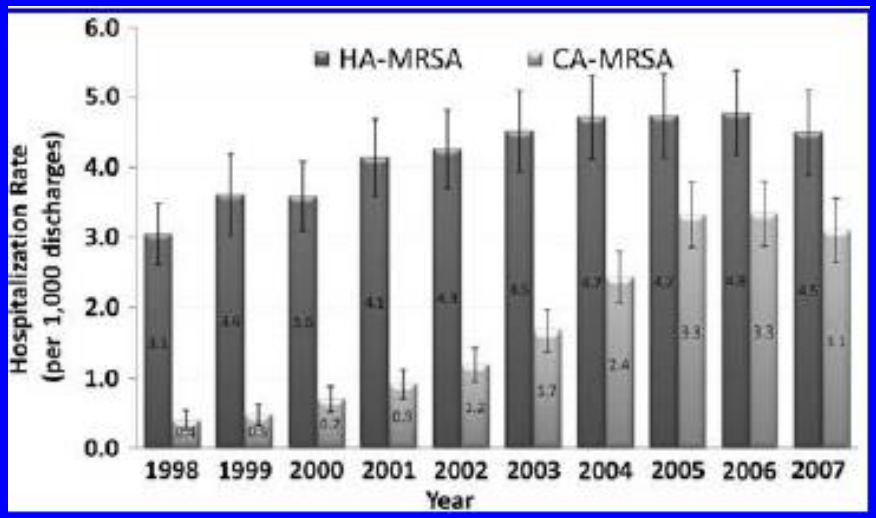
- Carbapenem-Resistant Gram-Negative Bacteria


Type II
IS431
Tn554
mec
ccrA-ccrB
I
R1
A
orfX
pUB110
Type IV
IS431
mec
ccrA-ccrB
R1
A
orfX

Emergence of Methicillin-Resistant *Staphylococcus aureus* (MRSA)







Mera RM et al. Microb Drug Resist 2011; 17:321

Intermixing of Hospital and Community Strains of MRSA

Type	Number (%)		
	Hospital-Onset	Community-Onset	
		Healthcare-Associated	Community-Associated
USA100	160 (74)	303 (62)	35 (23)
USA300	34 (16)	108 (22)	100 (67)
Other	22 (10)	74 (15)	15 (10)

Klevens RM et al. JAMA 2007; 298:1763

Trends in Reduced Susceptibility to Vancomycin

Year	Percent of Isolates (n) with MIC ≥ 2μg/ml	
	MRSA	MSSA
2004	5.6 (1158)	2.6 (1367)
2005	2.8 (1411)	1.5 (1519)
2006	3.3 (1531)	2.1 (2081)
2007	3.8 (2028)	2.8 (2916)
2008	9.2 (1481)	4.1 (2867)
2009	11.1 (640)	5.6 (1005)

Hawser SP et al. Int J Antimicrob Agents 2011; 37: 219

Vancomycin-Intermediate *Staphylococcus aureus*

(MIC = 4-16 μg/ml)

- Susceptibility breakpoint changed to ≤ 2 μg/ml
- Drug sequestration mechanism by multiple mutations that generate thickened and poorly cross-linked cell wall that binds vancomycin
- Associated with prolonged use of vancomycin
- Variably stable resistance phenotype
- Has been associated with treatment failures
  - Worse outcomes also seen at MIC = 2 μg/ml

Howden BP et al. Clin Infect Dis. 2004; 38:521
Moise-Broder PA et al. Clin Infect Dis. 2004; 38:1700
Sakoulas G et al. J Clin Microbiol. 2004; 42:2398

Vancomycin-Resistant MRSA

- 14 independent cases since 2002 in US patients
  - –Michigan 8, New York 1, Pennsylvania 1, Delaware 4
  - –DM 10, CRF 5, obesity 4
  - –VRSA from ulcers or wounds 12; most had prior MRSA + VRE
  - –Healthcare-associated strains 13 (USA100 most often)

- Acquisition of *van* gene cassette on Inc18-like plasmid from *Enterococcus faecalis* 8; less often from *E. faecium* (2) or *E. gallinarum* (1)

- Recipient MRSA often carried pSK41-like plasmids that facilitate transfer of Inc18-like plasmid *van* genes

- Median vancomycin MIC = 512 (32-1024) µg/ml. Remained susceptible to linezolid, daptomycin, and SXT

- Transmission not documented.

Sievert DM et al. Clin Infect Dis. 2008; 46:668
Tenover FC. Clin Infect Dis. 2008; 46:675
Zhu W et al. Antimicrob Agents Chemother. 2013; 57:212
Limbago BM et al. J Clin Microbiol. 2014; 52:998

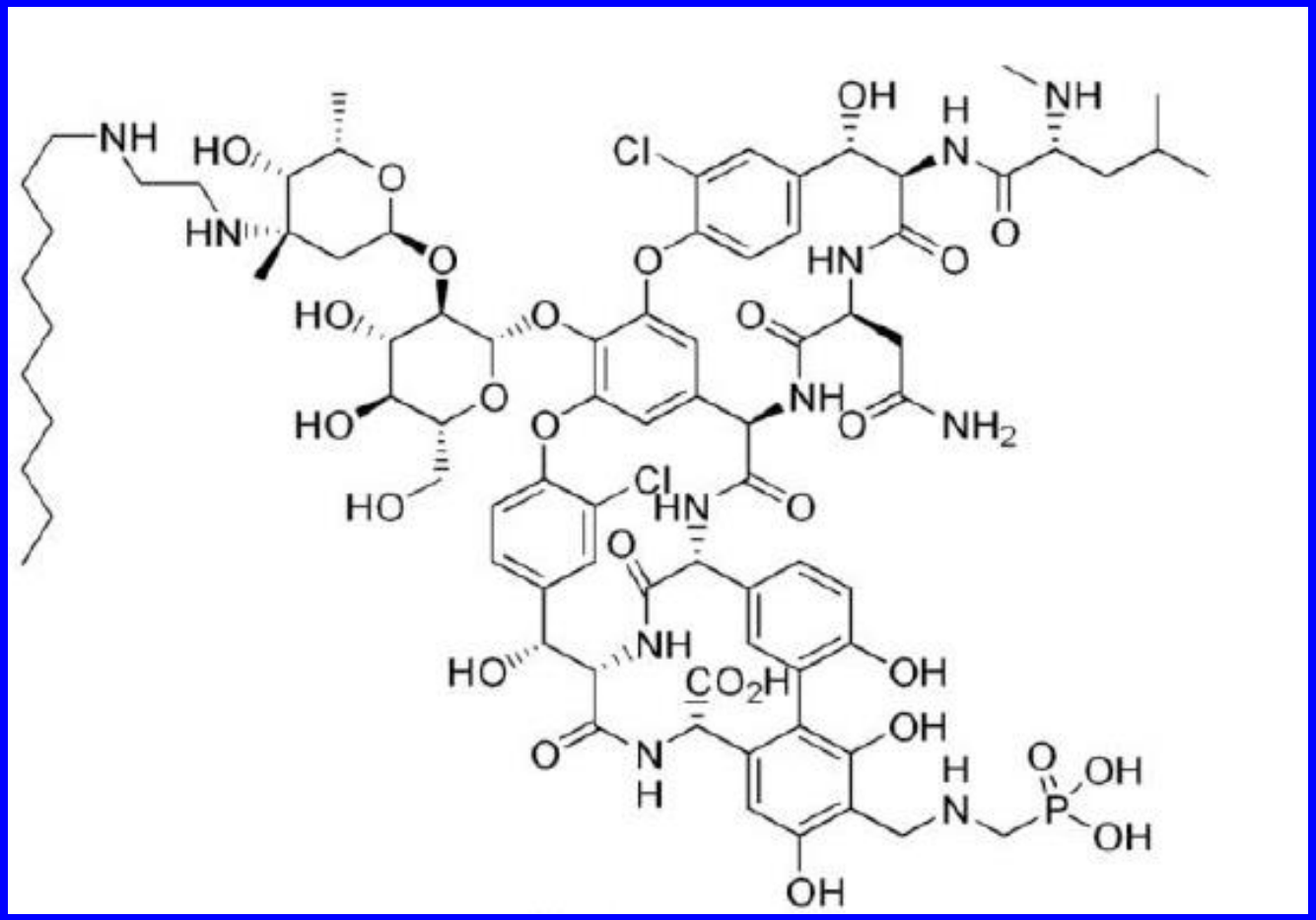
Newer Agents with Gram-Positive Activity Including MRSA

- β-Lactams
  - Ceftaroline
- Lipoglycopeptides
  - Telavancin
  - Dalbavancin
  - Oritavancin
- Cyclic lipopeptide
  - Daptomycin
- Oxazolidinones
  - Linezolid
  - Tedizolid

Ceftaroline

- Fifth generation "anti-MRSA" cephalosporin
- Spectrum similar to that of ceftriaxone but improved Gram-positive activity
  - Higher affinity for PBP2a in MRSA and PBP2x and other PBPs in penicillin- and cephalosporin-resistant *Streptococcus pneumoniae*
  - Activity for MRSA, as well as vancomycin-intermediate *S. aureus* (VISA), hetero-VISA, VRSA, and strains of *S. aureus* that are non-susceptible to daptomycin and linezolid
- Not active for enterococci, AmpC-overproducing or ESBL-producing Enterobacteriaceae, *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, or *Bacteroides fragilis*

Telavancin (Lipoglycopeptide)



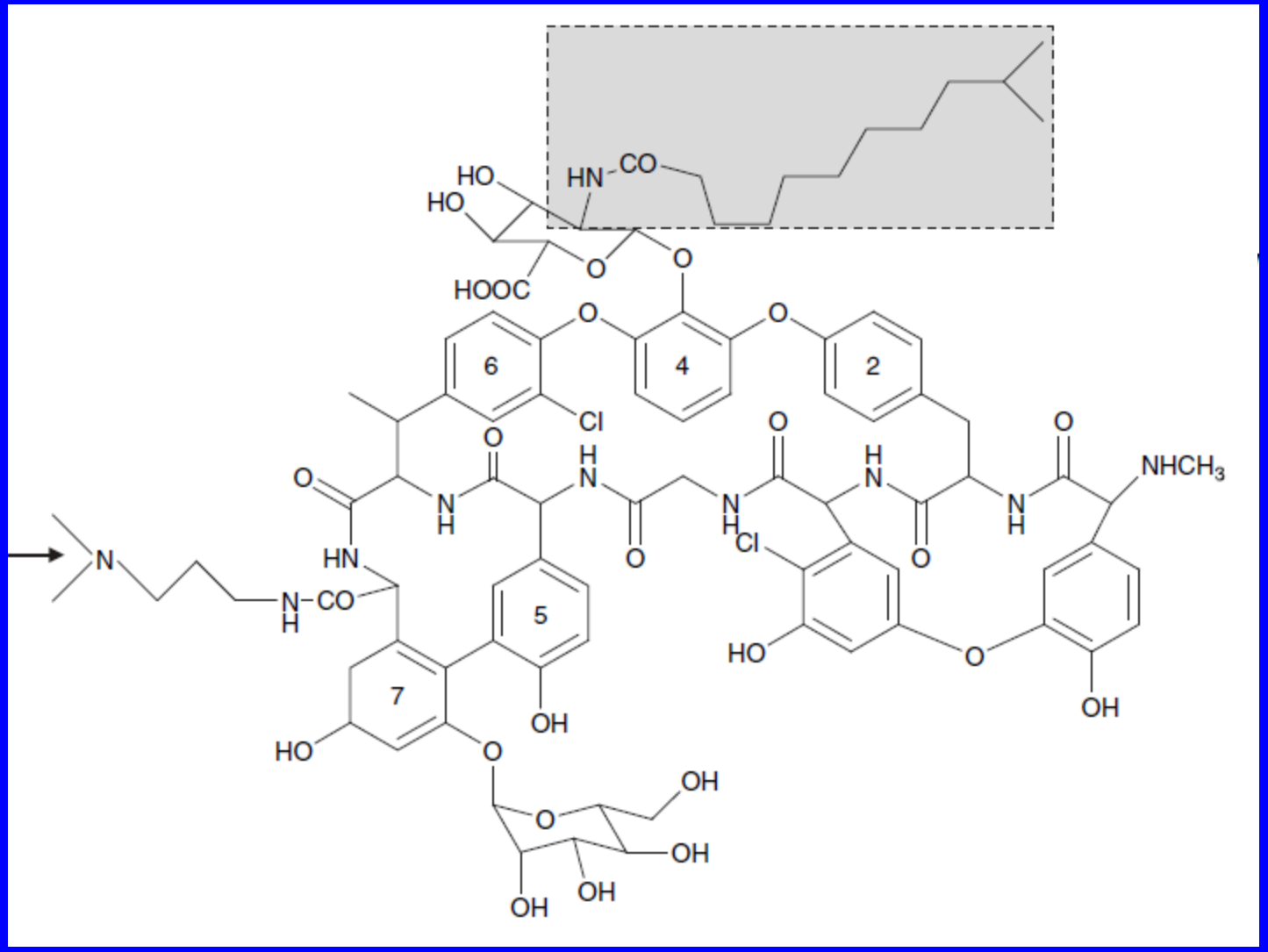
Telavancin
Mechanisms of Action and Resistance

- Binds to the D-Ala-D-Ala pentapeptide terminus of cell wall precursors (as does vancomycin) and blocks transglycosylation
- Lipid side chain
  - Improves binding to cell wall precursors
  - interacts with cell membrane and triggers its depolarization
- Bactericidal
- Resistance
  - VanA and VanB enterococci and staphylococci
  - Has activity against VISA strains (8x > vancomycin)

Telavancin Spectrum of Activity

- Staphylococci (MIC 0.25-1.0 μg/ml)
- Streptococci (MIC 0.03-0.06 μg/ml)
- Enterococci (MIC 0.25-1.0 μg/ml)
  - Not VRE
- *Clostridium perfringens* (MIC 0.125 μg/ml)
- *Clostridium difficile* (MIC 0.25 μg/ml)
- *Peptococcus* sp. (MIC 0.25 μg/ml)
- Not active against gram-negative bacteria

Dalbavancin
(Lipoglycopeptide)



Dalbavancin

- FDA approved for serious skin infections - May 2014
- Gram-positive spectrum:
  - Potency relative to vancomycin:
  - *S. aureus* 16x, includes VISA strains
  - *S. pyogenes* 16x, group B strep 4x
  - Enterococci 16x – not active vs VRE
- Dosing: 1 gm IV day 1, 500 mg IV day 8
  - $t_{½}$ = 147-258 h
  - severe renal impairment reduce dose to [750 mg then 375 mg]; no adjustment in hepatic failure
- Most common AEs: nausea 2.5%; treatment-limiting AEs 2.1%

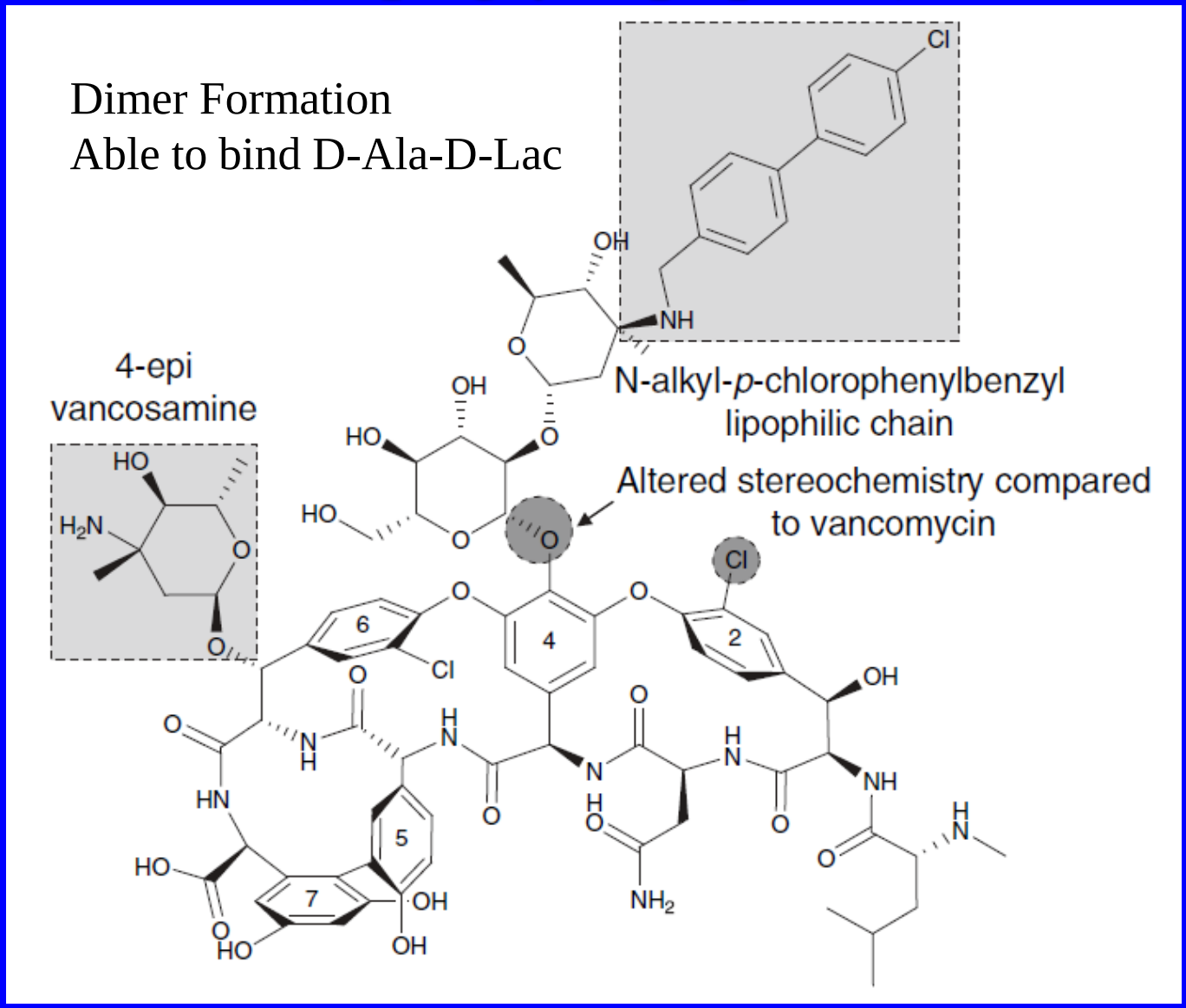
Zhanel GG et al. Drugs 2010; 70:859
Boucher HW et al. NEJM 2014; 370:2169

Dalbavancin

- Acute bacterial skin infections
  - Phase III randomized, double-blind trial, n = 1312
  - Non-inferior to vancomycin (1 gm or 15 mg/kg Q12h) then PO linezolid (600 mg Q12h)
  - Similar in at 48 – 72 h and end of therapy (10-14 d) in subgroups with cellulitis, abscess, MSSA, MRSA (97%), *S. pyogenes* 100%
- Catheter-related staphylococcal bacteremia
  - Phase II randomized ,open-label trial, n =75
  - Catheters removed at baseline: 15/23 (65%) vs 18/28 (64%)
  - *S. aureus* 16/26 (62%) vs 21/28 (75%); coag-neg staph 13 each
  - Significantly better overall success relative to vancomycin 87% vs 50%
  - Microbiologic success at 21 days after treatment period 96% vs 79%

Zhanel GG et al. Drugs 2010; 70:859
Boucher HW et al. NEJM 2014; 370:2169
Raad I et al. Clin Infect Dis. 2005; 40:374

Oritavancin (Lipoglycopeptide)

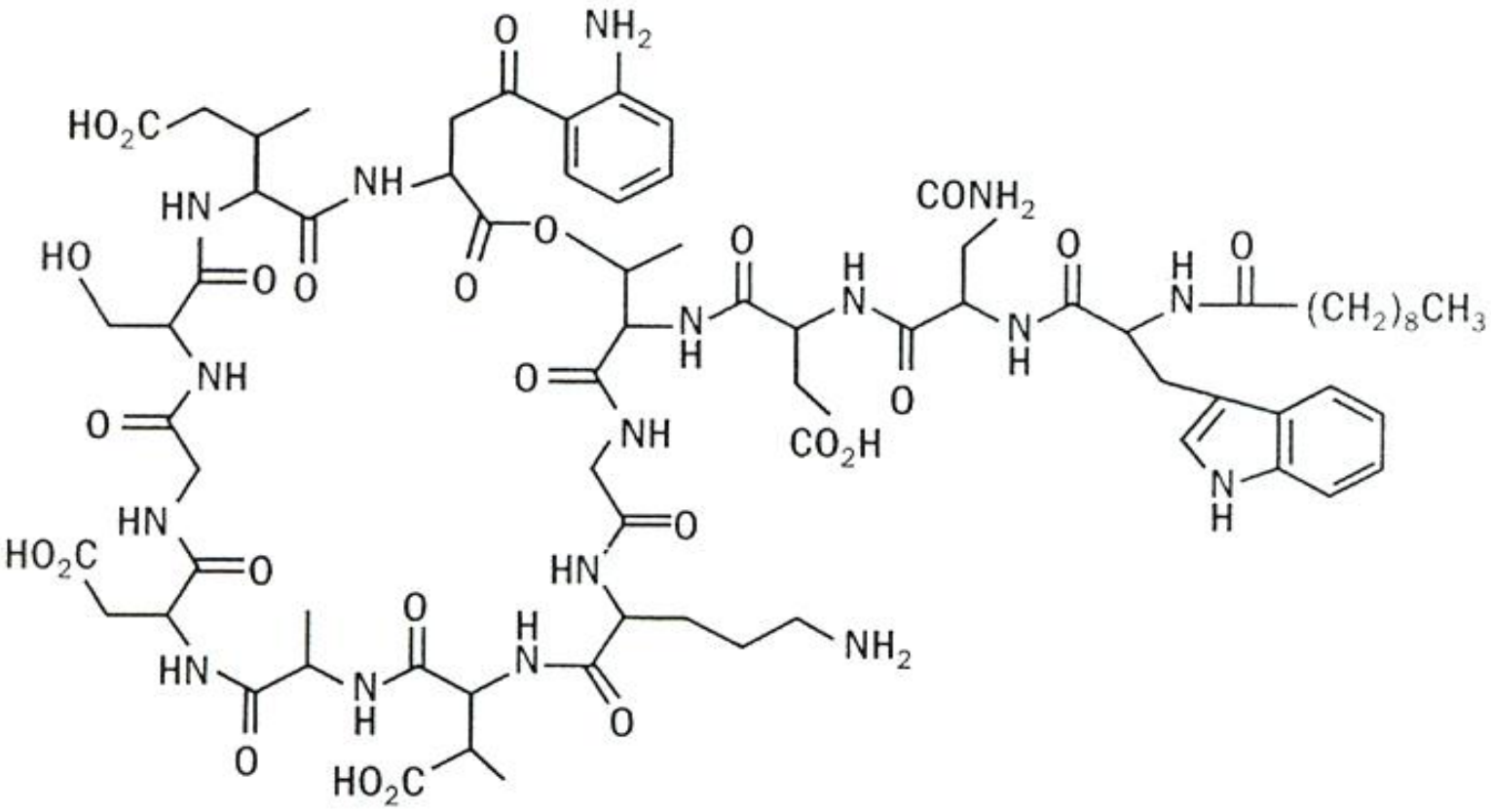


Oritavancin

- FDA approved for complicated skin infections – August 2014
- Gram-positive spectrum:
  - Potency relative to vancomycin: *S. aureus* 8x, includes VISA strains, *S. pyogenes* 4x, group B strep 4x
  - Enterococci : vancomycin S - 32-64x, vancomycin R – 512-2048x
- Dosing: 1200 mg IV single dose – requires 3 h infusion
  - $t_{½}$ = 390 h; no adjustment in renal failure, hemodialysis, or mild to moderate hepatic failure
- Most common AEs: nausea (11 vs 9%), headache (7.2 vs 7.9%); treatment-limiting AEs (3.8 vs 5.8%); LFT ↑ in some studies
- Non-inferior to vancomycin (1 gm or 15 mg/kg Q12h x 7-10d) in acute bacterial skin infections (2 randomized, double-blind trials:
- n = 968 and 1019)
  - Similar in at 48 – 72 h and post-therapy (7-14 d) evaluations overall and in subgroups with MSSA (83%) MRSA (81%); streptococci (78% vs 89%)

Zhanel GG et al. Drugs 2010; 70:859; Corey GR et al. NEJM 2014; 370:23
Corey GR et al. Clin Infect Dis. 2015; 60:254

Daptomycin Structure (Cyclic Lipopeptide)



Daptomycin
Mechanisms of Action and Resistance

- Binds to bacterial cell membrane in Ca^{++}-dependent manner with subsequent:
  - membrane depolarization
  - K^{+} release from cytoplasm
  - cell death
- Acquired resistance
  - infrequent in vitro
  - resistant mutants with changes in membrane potential and charge
  - has been associated with clinical failure in rare patients
  - seen in some patients developing VISA on vancomycin therapy without vancomycin exposure

Hayden MK et al. J Clin Microbiol. 2005; 43:5285
Marty FM et al. J Clin Microbiol 2006; 44:595
Sakoulas G et al. Antimicrob Agents Chemother 2006; 50:1581
Mwangi MM et al. Proc Natl Acad Sci USA 2007; 104:9451

Daptomycin
Spectrum of Activity

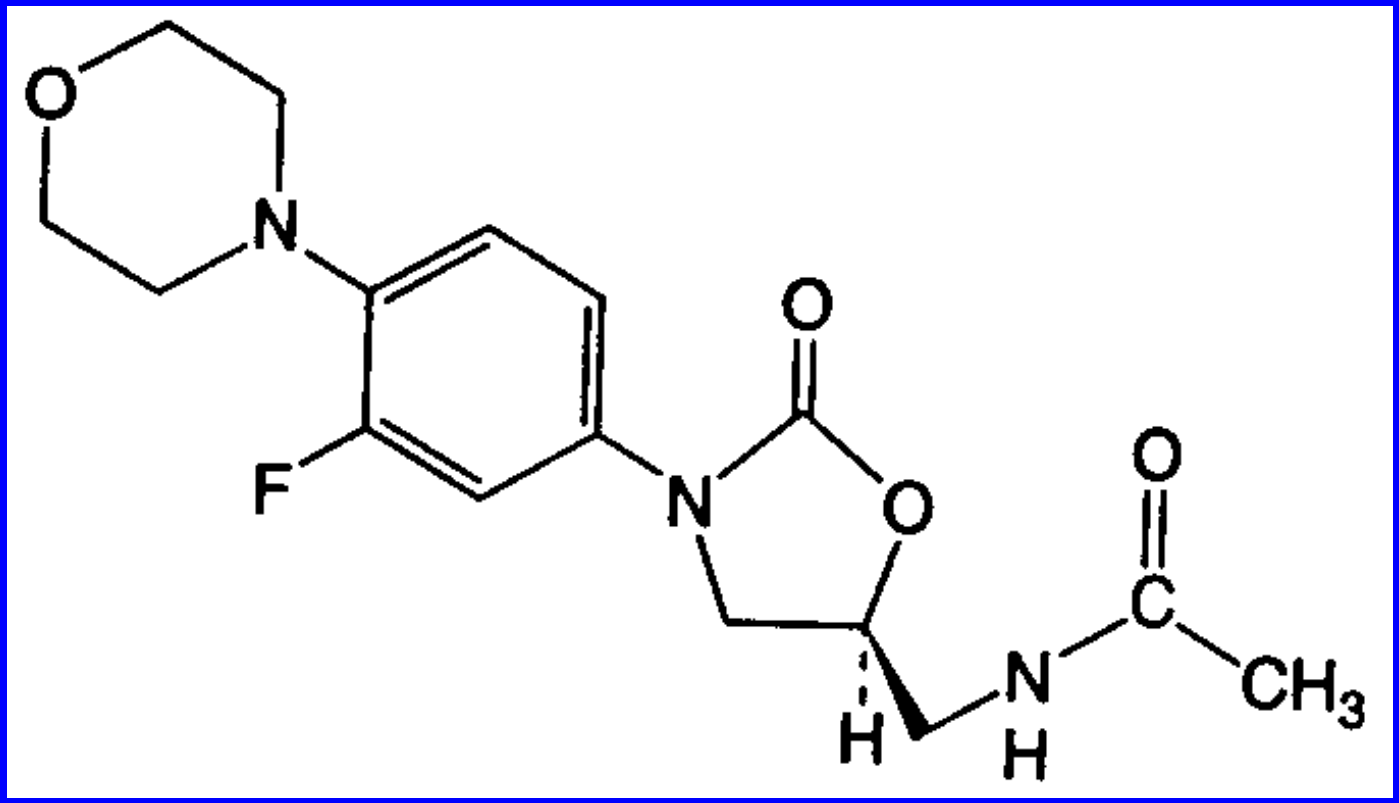
- *Staphylococcus aureus*, coagulase-negative staphylococci (MIC 0.5 μg/ml)
- Streptococci (MIC 0.25 μg/ml)
- Enterococci – *E. faecalis* (MIC 1-2 μg/ml), *E. faecium* (MIC 4 μg/ml)
- *Clostridium* spp. and peptococci (MIC 0.5-1 μg/ml)
- No activity against gram-negative bacteria

Daptomycin + β-Lactams for Refractory MRSA Bacteremia

- Case series
  - 7 patients: 5 unknown source (neg TEE, CTs, MRIs), 1 TV endocarditis (IVDU), skin abscess/empyema
  - 7/7 failed vancomycin 1st line
  - 7/7 failed daptomycin 2nd line (+ gentamicin 2)
  - 3/7 failed daptomycin + gentamicin 3rd line
  - 7/7 cleared BCs with daptomycin + nafcillin as 3rd or 4th line
  - 5/7 cure, 2/7 relapse
    - relapse isolates: MICs vanco 2-3 μg/ml, dapto 1-1.5 μg/ml
- Retrospective analysis of case registry (56 MRSA cases)
  - Daptomycin with and without β-lactam - similar outcomes
- Mechanism
  - Added β-lactam found to:
    - Decrease bacterial positive surface charge - ?due to release lipoteichoic acids
    - Increase daptomycin binding and bactericidal activity

Dhand A et al. Clin Infect Dis. 2011; 53:158
Moise PA et al. Antimicrob Agents Chemother. 2013; 57:1192

Linezolid Structure (Oxazolidinone)



Linezolid - Mechanisms of Action and Resistance

- Inhibition of protein synthesis - prevents formation of initiation complex of mRNA, N-formyl-methionyl tRNA, and ribosome
- Bacteriostatic
- Acquired resistance (staphylococci and enterococci)
  - no cross resistance with macrolides, streptogramins
  - mutations in 23S rRNA, G2576U (central loop domain V) or G2447T or ribosomal protein L3 or L4
  - associated with prolonged or repeated courses of treatment and for enterococci with nosocomial spread
  - plasmid-encoded Cfr methylase that modifies ribosome, conferring resistance to linezolid and chloramphenicol

Jones RN et al. Diag Microbiol Infect Dis. 2009; 65:404
Endimiani A et al. Antimcrob Agents Chemother. 2011; 55:1684
Gu B et al. J Antimicrob Chemother. 2012; 68:4

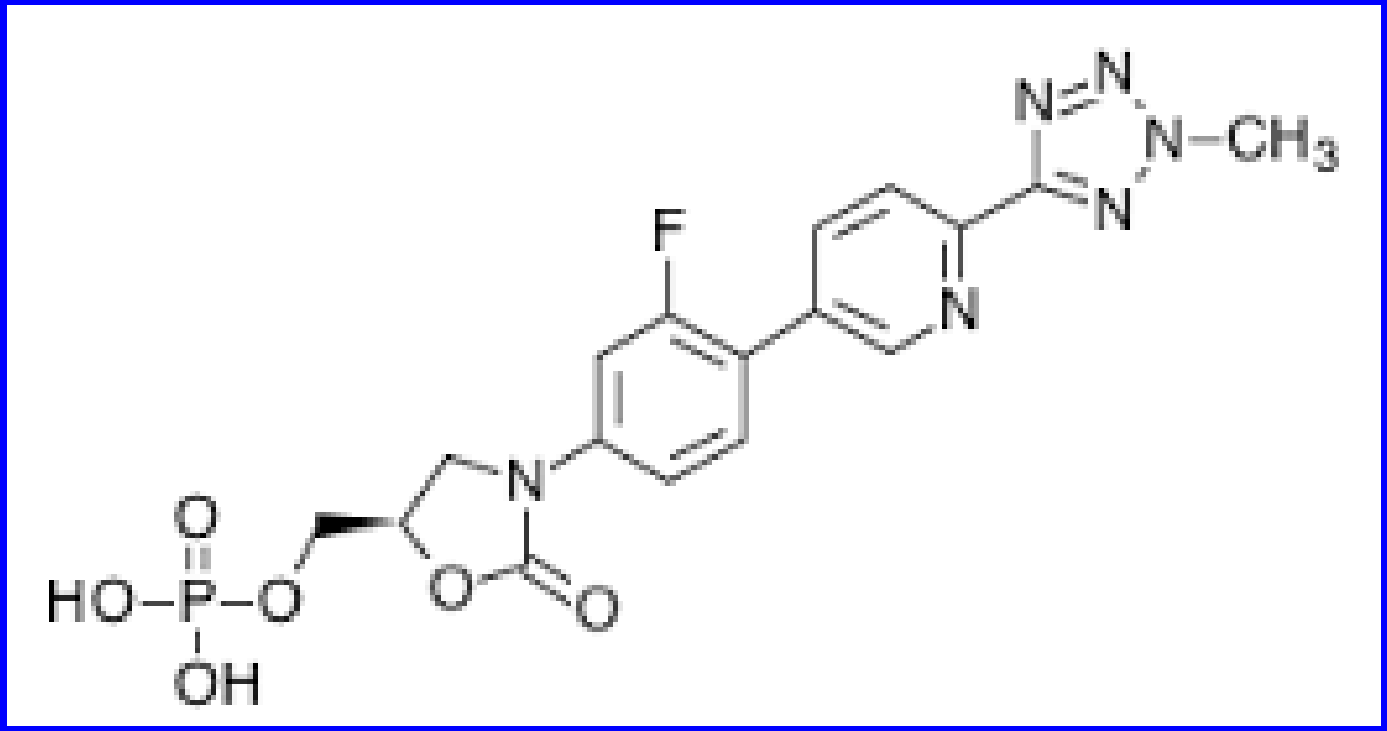
Linezolid: Spectrum of Activity

- Staphylococci (including MRSA, VISA,[a] VRSA[b])
- Streptococci (including PRSP[c]) and enterococci (*E. faecium* and *E. faecalis*, including VRE)
- *Listeria* spp., *Corynebacterium* spp., *Rhodococcus* spp.
- Anaerobes (clostridia, peptostreptococci, fusobacteria, *Bacteroides fragilis*)
- *Mycobacterium tuberculosis*; atypical mycobacteria - *M. fortuitum* and *M. chelonae* are less susceptible
- *Nocardia* spp.
- Not active against *Enterobacteriaceae*, *P. aeruginosa*
  - Endogenous efflux pumps reduce activity

[a]Vancomycin-intermediate *S. aureus*, [b]Vancomycin-resistant *S. aureus*

[c]Penicillin-resistant *Streptococcus pneumoniae*

Tedizolid Phosphate Structure (Oxazolidinone)



Tedizolid

- FDA approved for serious skin infections June 2014
- 4- to 8-fold more potent than linezolid in vitro
  - Remains active vs some linezolid-resistant strains
- Dose: 200 mg PO or IV once daily
  - 100% oral bioavailability; $t_{½}$ = 10-12 h; fecal excretion; no renal adjustment
- Weak, reversible MAO inhibition in vitro
  - Possibly lower drug-drug interactions because of lower doses and free drug exposure
- Little hematologic toxicity up to 3 weeks
  - Platelets <150,000 - tedizolid 4.9% vs linezolid 10.8% in trials
- Most common AEs: nausea (8%), HA (6%)

Prokocimer P et al. JAMA 2013; 309:559
Prokocimer P et al. AAC 2012; 56:4608
Urbina O et al. Drug Design Devel Ther. 2013;7:243

Costs of Antimicrobials

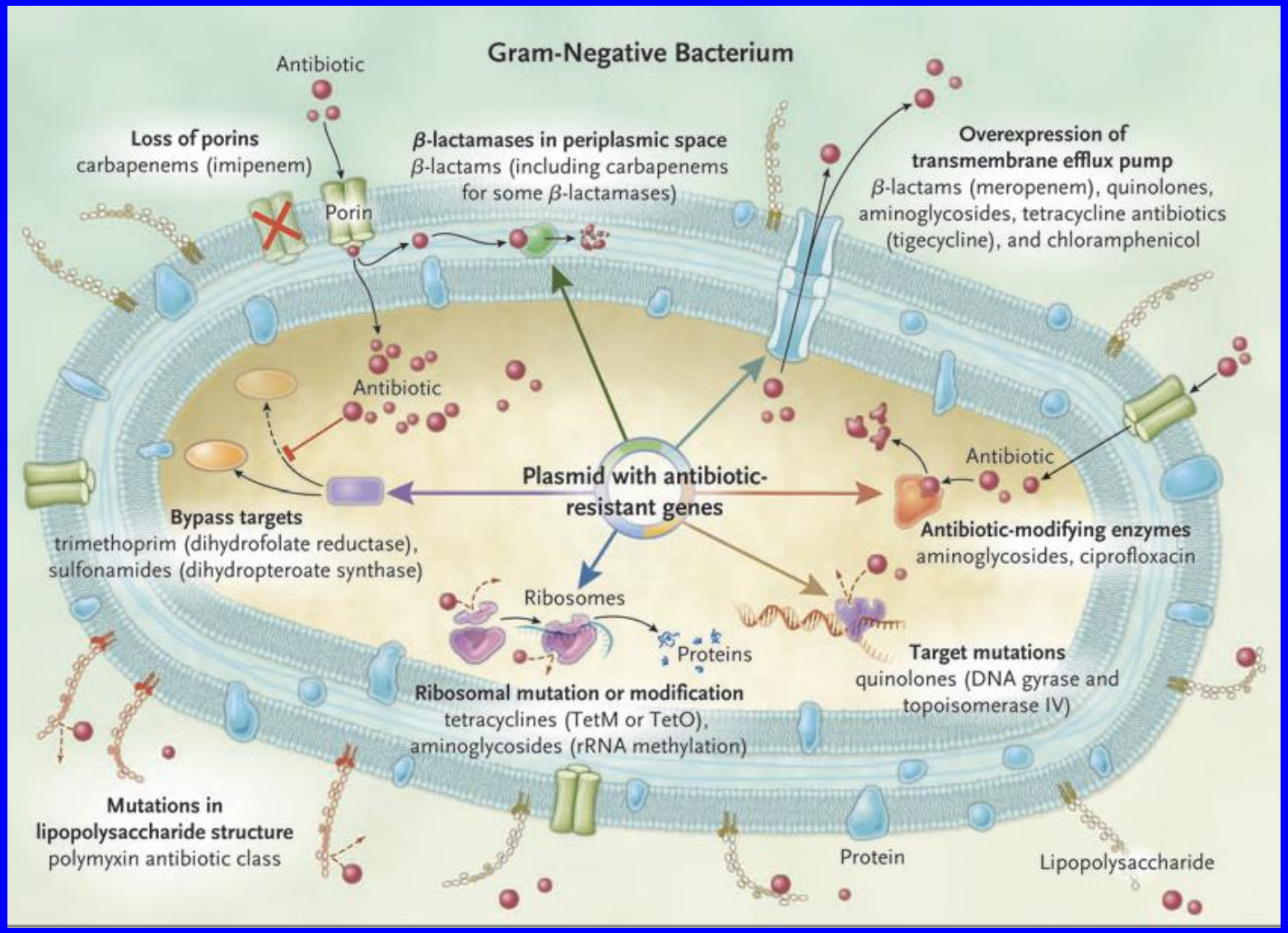
Drug	Dose	Daily Cost
Vancomycin	1000 mg IV Q12h	$15
Ceftaroline	600 mg IV Q12h	$303
Linezolid	600 mg PO Q12h	$364
	600 mg IV Q12h	$296
Tedizolid	200 mg PO Q24h	$354
	200 mg IV Q24h	$282
Quinupristin/ Dalfopristin	7.5 mg/kg IV Q8-12	$1,060-$707[a]
Daptomycin	4-6 mg/kg IV Q24h	$455
Telavancin	10 mg/kg IV Q24h	$390[a]
Dalbavancin	1000 mg IV 2 doses	$3576[b]
Oritavancin	1200 mg IV once	$1160[b]

[a] based on 70 kg person

[b] cost of full course

Average Wholesale Price March 2015

Mechanisms of Antimicrobial Resistance



Peleg AY, Hooper DC. N Engl J Med. 2010;362:1804

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- Carbapenem-Resistant Gram-Negative Bacteria

Effect of *E. coli* Resistance to 3rd-Generation Cephalosporins on 30-day Mortality and LOS

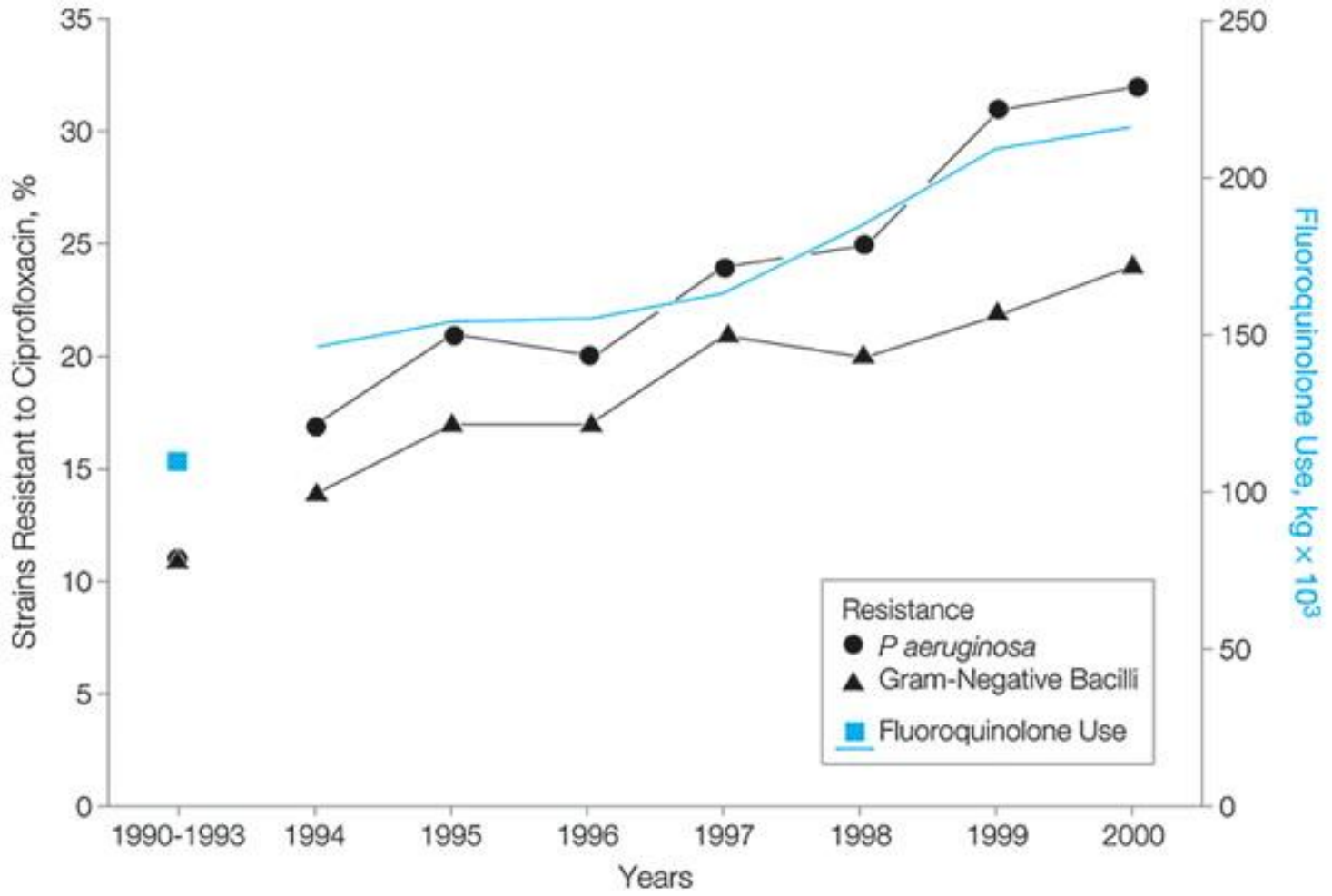
Type of analysis	*n*	HR for effect measure (95% CI)	Effect measure; potential confounders in model
REC versus controls			
univariate	315	7.9 (4.0–15.3)	REC BSI
multivariate	268	5.7 (2.5–13.0)	REC BSI; tracheal tube, central venous catheter, urinary catheter, transfer from another institution, number of indwelling devices
SEC versus controls			
univariate	3193	2.7 (2.2–3.3)	SEC BSI
multivariate	2699	2.0 (1.5–2.5)	SEC BSI; age, emergency admission, tracheal tube, central venous catheter, arterial vascular access, urinary catheter, transfer from another institution, CCI, number of indwelling devices
REC cohort versus SEC cohort comparison of adjusted effect estimates		2.9 (1.2–6.9)	third-generation cephalosporin resistance of *E. coli* BSI

Type of analysis	*n*	Ratio of mean LOS for effect measure (95% CI)	Extra LOS in days for effect measure (95% CI)	Effect measure; potential confounders in model
REC cohort versus SEC cohort comparison of adjusted effect estimates		1.3 (1.0–1.7)	5.0 (0.4–10.2)	third-generation cephalosporin resistance of *E. coli* BSI

Cohorts of BSI cases matched on length of stay before infection

de Kraker MEA et al. J Antimicrob Chemother. 2011; 66:398

Increasing Quinolone Resistance Associated with Increasing Use



Neuhauser MM et al. JAMA 2003; 289:885-8

Ciprofloxacin Resistance in Gram-Negative Bacilli in Intensive Care Units in the United States - 1994-2000

Species	Resistant (%)	Change[A] (%)	Cross Resistance to: Gent	Ceftaz	Imip
					(%, CipR/CipS)
P. aeruginosa	24	+13	66/21	40/14	38/11
Enterobacter spp.	10	+6	49/4	82/32	4/1
K. pneumoniae	12	+7	67/7	65/6	3/0.5
E. coli	3	+2			
All isolates[B]	19	+10			

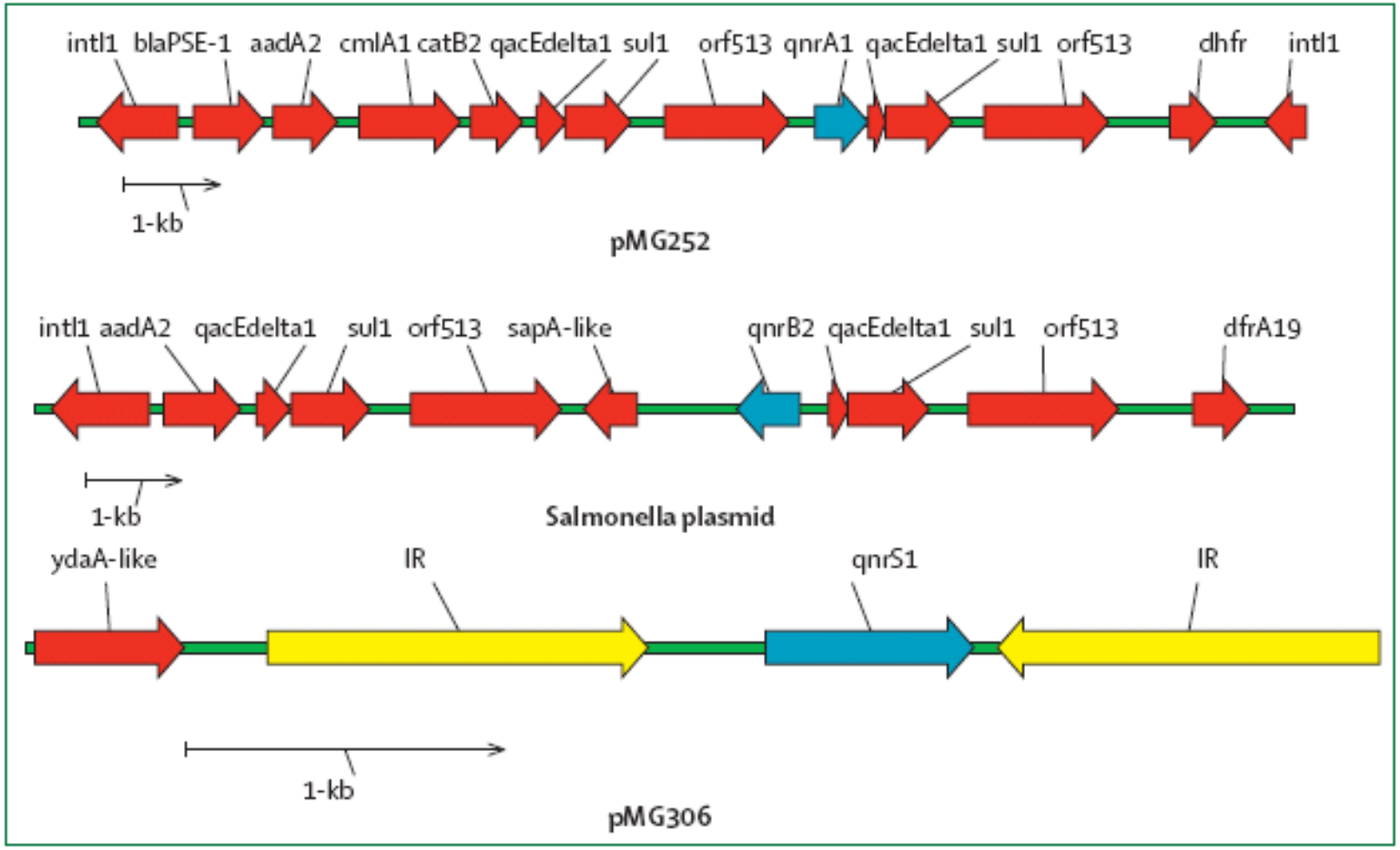
[A]Change relative to 1990-1993 [B]n=35,790

Neuhauser MM *et al*. JAMA 2003; 289:885-888

Mechanisms of Resistance to Fluoroquinolones

- Chromosomal mutations
  - Alterations in DNA gyrase and/or topoisomerase IV
  - Active drug efflux (MDR pumps) +/- reduced porin diffusion channels
- Plasmid-mediated resistance
  - QnrA,B,C,S (pentapeptide repeat proteins)
    - Protects by binding to gyrase and topoisomerase IV
    - In many enteric bacteria on multidrug resistance plasmids
  - Modified aminoglycoside acetyl transferase
    - Acetylates ciprofloxacin and reduces its activity
    - In many enteric bacteria on multidrug resistance plasmids
  - Efflux pumps (QepA, OqxAB)

Plasmid-Encoded Quinolone Resistance: Qnr Genes



Robicsek A et al. Lancet Infect Dis 2006; 6:629-40

Occurrence of Integron-Carrying Enteric Bacteria in ICUs

Variable	No. (%) of ICU Patients	
	Medical (n = 277)	Neurosurgical (n = 180)
Total colonized	19 (7)	12 (7)
Acquired colonization	14 (5)	9 (5)
Time to acquisition (d)	10 ± 10	12 ± 10
Acquisition rate (per 1000 patient-days)	10	8

Nijssen S et al. Clin Infect Dis. 2005; 41:1-9.

Resistance Profiles of Integron-Carrying Enteric Bacteria

Antimicrobial	Percent Resistant	
	Integron (-) (n = 120)	Integron (+) (n = 54)
Piperacillin	24	94*
Ceftazidime	26	33
Cefotaxime	29	44*
Meropenem	0	0
Gentamicin	2	94*
Ciprofloxacin	3	33*

Nijssen S et al. Clin Infect Dis. 2005; 41:1-9.

Major Clinical Problems with Antibiotic-Resistant Bacteria

- Vancomycin-Resistant Enterococci
- Methicillin-Resistant *Staphylococcus aureus*
- Cephalosporin-Resistant *Klebsiella*, *Enterobacter*, *Pseudomonas* and other Gram-negative Bacteria
- Carbapenem-Resistant Gram-Negative Bacteria

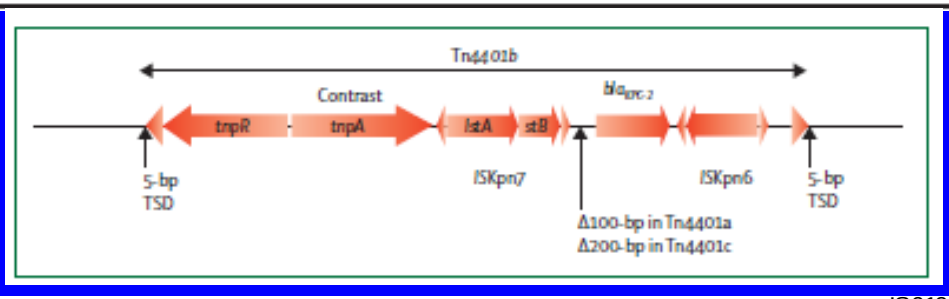
Carbapenem-Resistant Bacteria

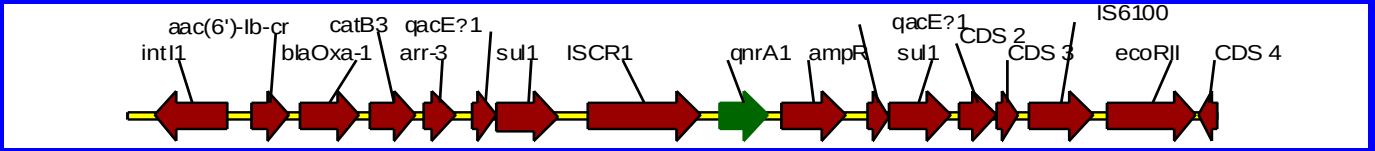
- Generally found in multidrug-resistant *Enterobacteriaceae*, some pan-resistant
  - Most often *Klebsiella pneumoniae*
- Due to carbapenemases
  - most often KPC family of enzymes in US
    - On plasmids generally carrying other resistance genes
    - Act on all β-lactams
    - Weakly inhibited by clavulanate and tazobactam
  - other enzymes (e.g., NDM-1, VIM, et al) found outside US
- May be difficult to detect in clinical laboratory
  - Ertapenem resistance more sensitive for detection but not specific
  - Modified Hodge test
  - New CLSI breakpoints will make detection simpler
- Widespread in some areas (clonal in NYC)
- New CDC guidance for isolation and screening

Nordmann P et al. Lancet Infect Dis. 2009; 9:228
MMWR 2009; 58:256

Carbapenemase-positive Enteric Bacteria

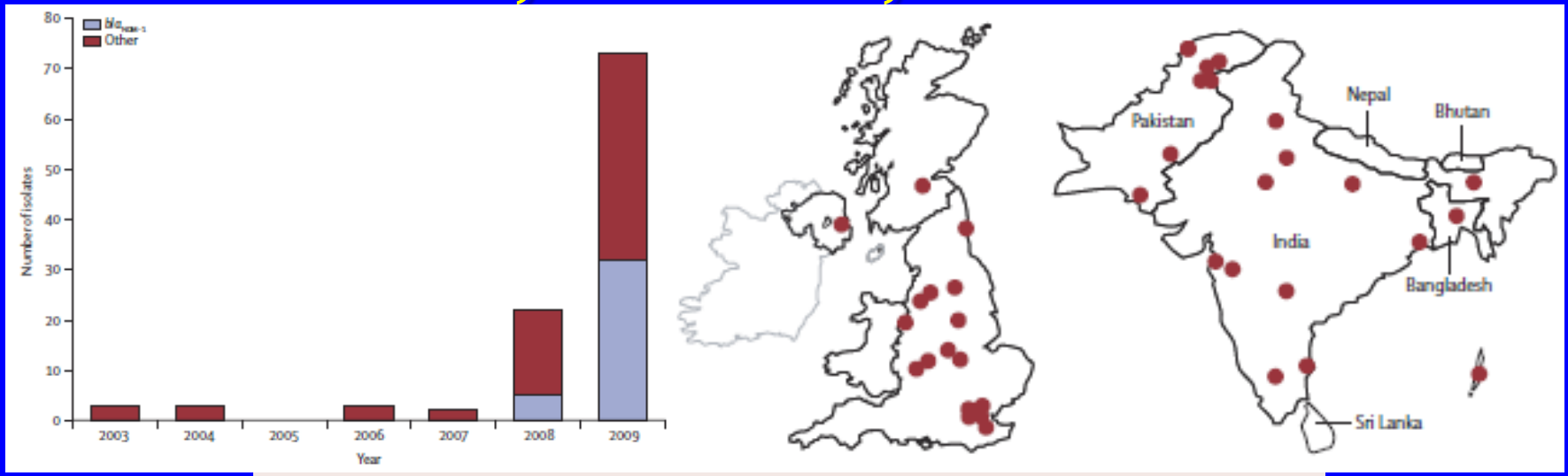
Species	Enzyme	MIC (mg/L)[a] AMP	ETP	IPM	IPM–EDTA	MEM	CAZ	TZP	ATM	CIP	GEN	TOB	AMK	CST
Klebsiella spp.	IMP	>64	>16	>32	0.5	>32	>256	(16)	1	≤0.125	>32	>32	32	≤0.5
Klebsiella spp.	IMP	>64	8	(2)	0.125	4	>256	(16)	≤0.125	4	16	>32	16	≤0.5
E. coli	IMP	>64	8	(2)	0.125	(2)	256	(8)	0.25	>8	>32	>32	2	≤0.5
Enterobacter spp.	KPC-4	>64	>16	>32	>16	>32	>64	>64	>64	>8	1	1	2	1
Klebsiella spp.	KPC-3	>64	>16	32	>16	>32	256	>64	>64	>8	1	32	32	≤0.5
K. pneumoniae	OXA-48	>64	>16	16	8	8	256	>64	>64	>8	1	32	8	1





Livermore DM. J Antimicrob Chemother. 2009; 64:(suppl 1) i29
Nordmann P et al. Lancet Infect Dis. 2009; 9:228
Strahilevitz J et al. Clin Microbiol Rev. 2009; 22:664

Emergence of NDM-1β-Lactamase Isolates in India, Pakistan, and the UK



	UK (n=37)		Chennai (n=44)		Haryana (n=26)	
	MIC_{50}:MIC_{90} (mg/L)	Proportion susceptible*	MIC_{50}:MIC_{90} (mg/L)	Proportion susceptible*	MIC_{50}:MIC_{90} (mg/L)	Proportion susceptible*
Imipenem	32; 128	0%	64; 128	0%	32; 128	0%
Meropenem	32; 32	3%	32; >32	3%	>32; >32	3%
Piperacillin-tazobactam	>64; >64	0%	>64; >64	0%	>64; >64	0%
Cefotaxime	>256; >256	0%	>256; >256	0%	>256; >256	0%
Ceftazidime	>256; >256	0%	>256; >256	0%	>256; >256	0%
Cefpirome	>64; >64	0%	>64; >64	0%	>64; >64	0%
Aztreonam	>64; >64	11%	>64; >64	0%	>64; >64	8%
Ciprofloxacin	>8; >8	8%	>8; >8	8%	>8; >8	8%
Gentamicin	>32; >32	3%	>32; >32	3%	>32; >32	3%
Tobramycin	>32; >32	0%	>32; >32	0%	>32; >32	0%
Amikacin	>64; >64	0%	>64; >64	0%	>64; >64	0%
Minocycline	16; >32	0%	32; >32	0%	8; 16	0%
Tigecycline	1; 4	64%	4; 8	56%	1; 2	67%
Colistin	0·5; 8	89%†	1; 32	94%†	1; 2	100%†

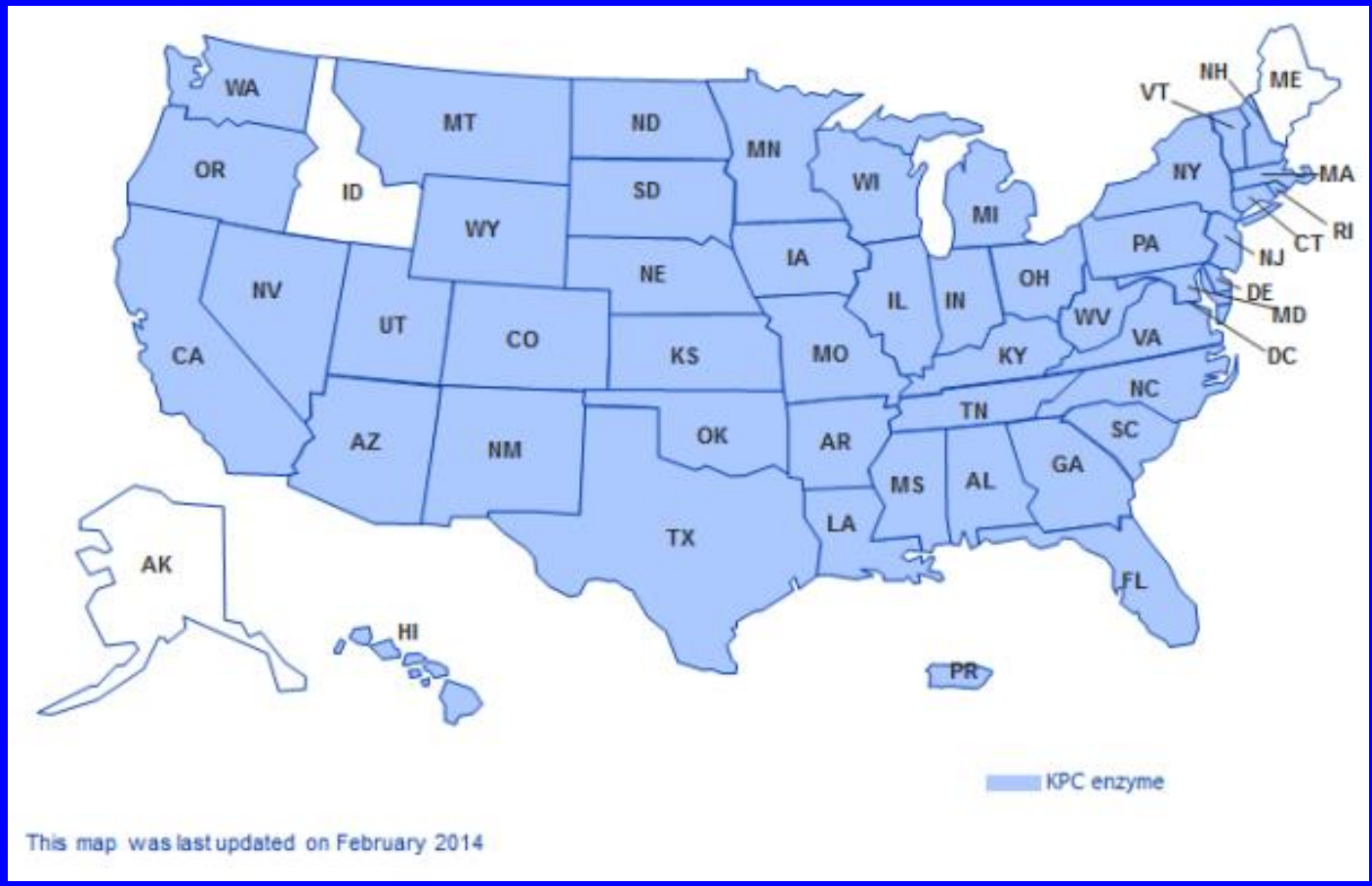
Kumarasamy KK et al. Lancet Infect Dis. 2010; 10:597

Countries with Reported Cases of NDM-1 Positive Bacteria

Triangles = cases linked to Indian subcontinent

Johnson AP, Woodford N. J Med Microbiol. 2013; 62:499-513

States Reporting Carbapenem-Resistant Gram-Negative Bacteria

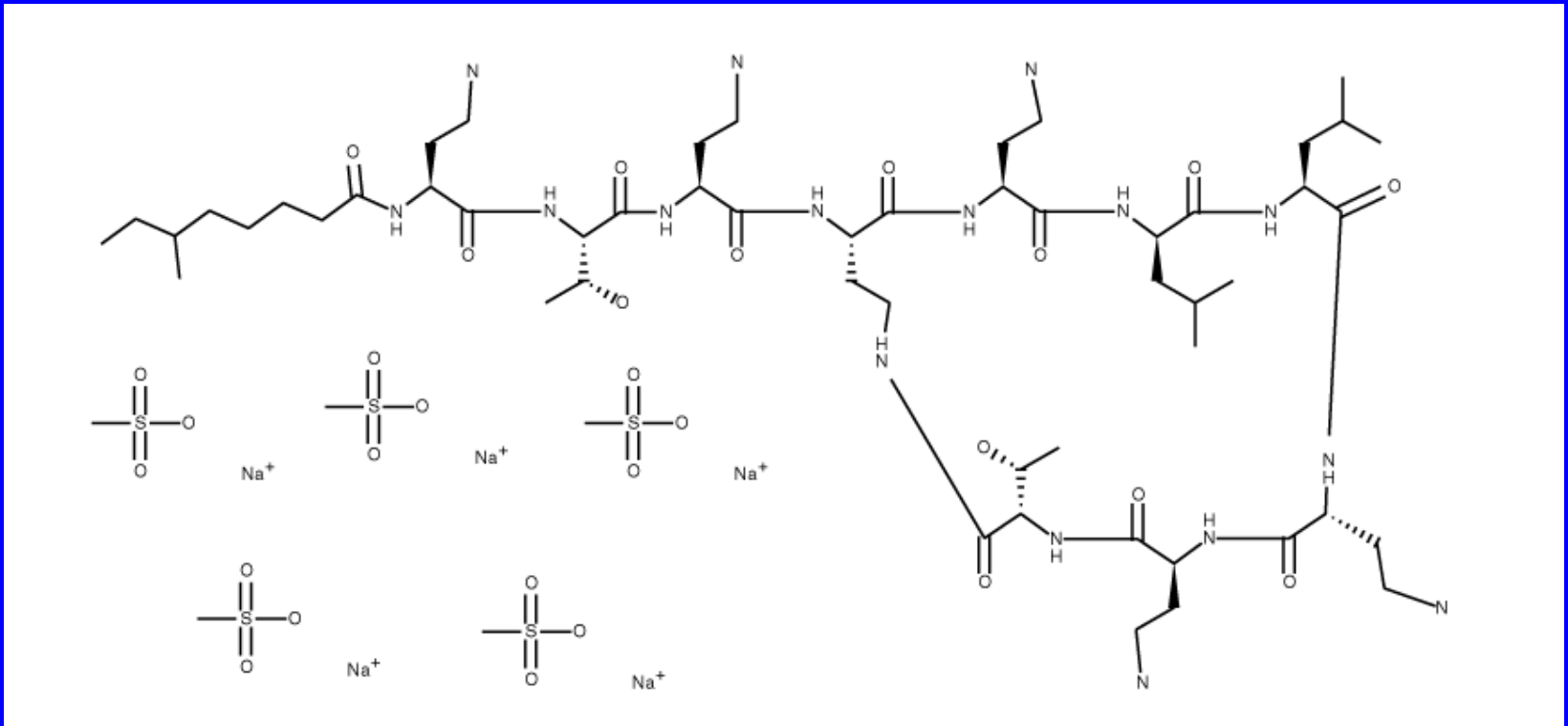


15 States Reporting NDM Carbapenemase Enzyme

Agents for Treatment of Resistant Gram-Negative Bacterial Infections

- Colistin
- Tigecycline
- Ceftolozane-Tazobactam
- Ceftazidime-Avibactam

Colistin [Polymyxin E, Colistimethate (CMS)]



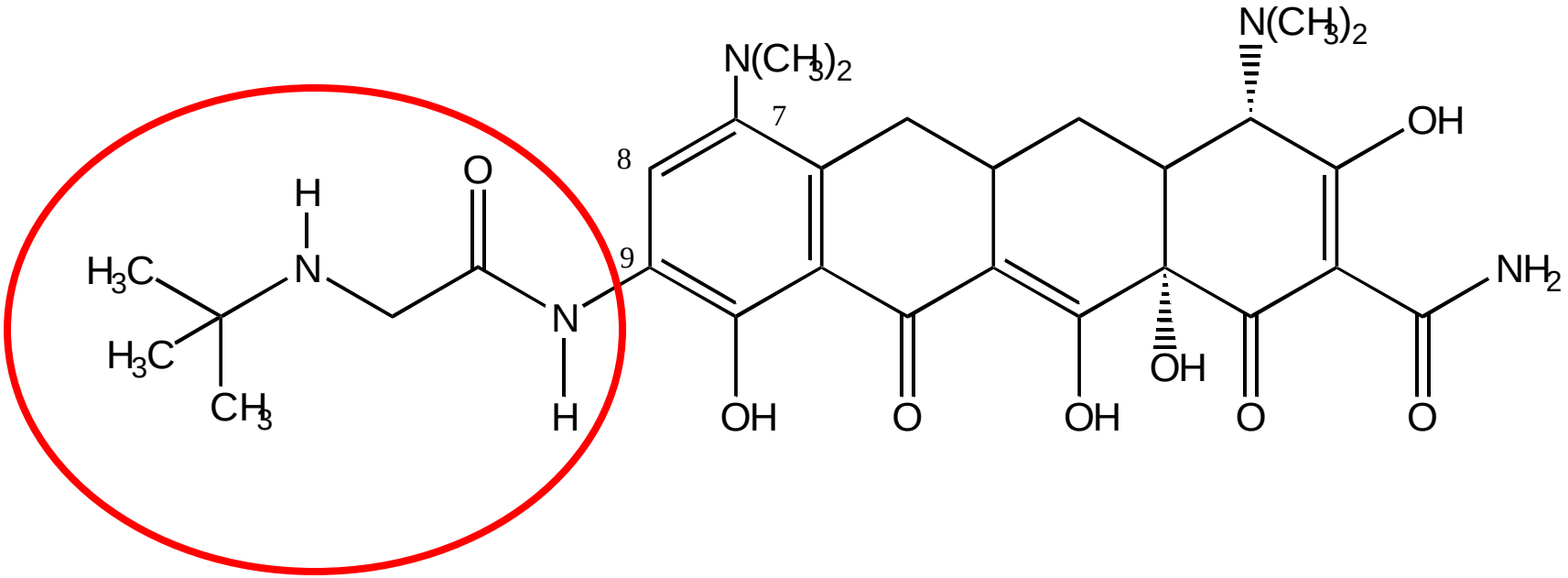
Colistin
Mechanism and Resistance

- Interacts with membrane phospholipids and lipopolysaccharide
- Bactericidal detergent-like action
- Spectrum of activity (MICs 1-2 μg/ml)
  - *Pseudomonas aeruginosa*
  - *Acinetobacter baumanii*
  - Other gram-negative bacteria except *Proteus*, *Providencia*, *Serratia*, *Burkholderia*
- Resistance
  - Rates vary, and resistance can emerge on therapy
  - *pmrAB* and *parRS* regulatory gene mutations reduce membrane negative charge and binding of positively charged colistin

Zavascki AP et al. J Antimicrob Chemother. 2007; 60:1206
Cruz DN et al. JAMA 2009; 301:2445

Tigecycline

9-*t*-butylglycylamido-minocycline

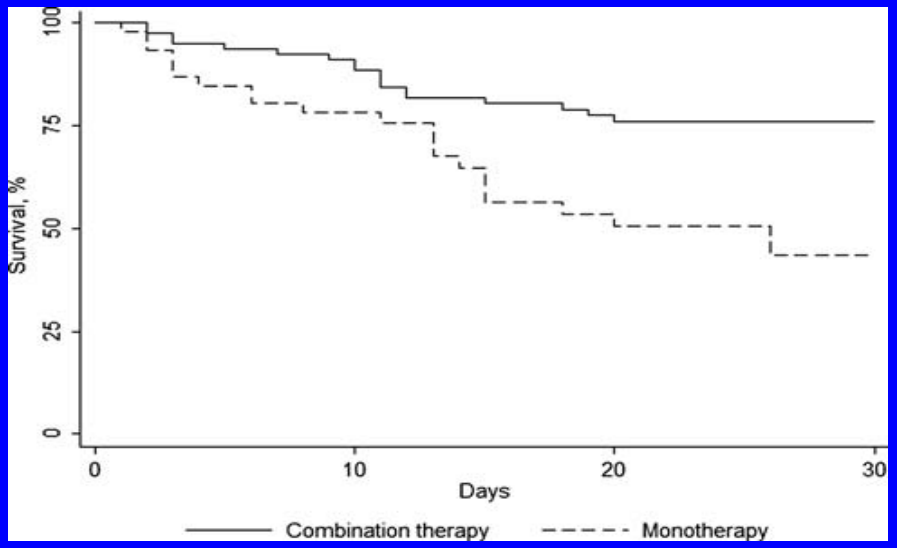


Tigecycline
Spectrum of Activity

- Staphylococci (including methicillin-resistant)
- Streptococci (including *S. pneumoniae*)
- Enterococci (including vancomycin-resistant)
- *Enterobacteriaceae*
  - Not *Proteus*, *Serratia*
- Non-enteric gram-negative bacilli
  - *Acinetobacter* and *Stenotrophomonas*
  - Not *Pseudomonas aeruginosa*
- Anaerobes (including *Bacteroides*)

Combination Therapy for Carbapenemase-Producing *K. pneumoniae* Bacteremia

Multicenter retrospective cohort study
n = 125 patients

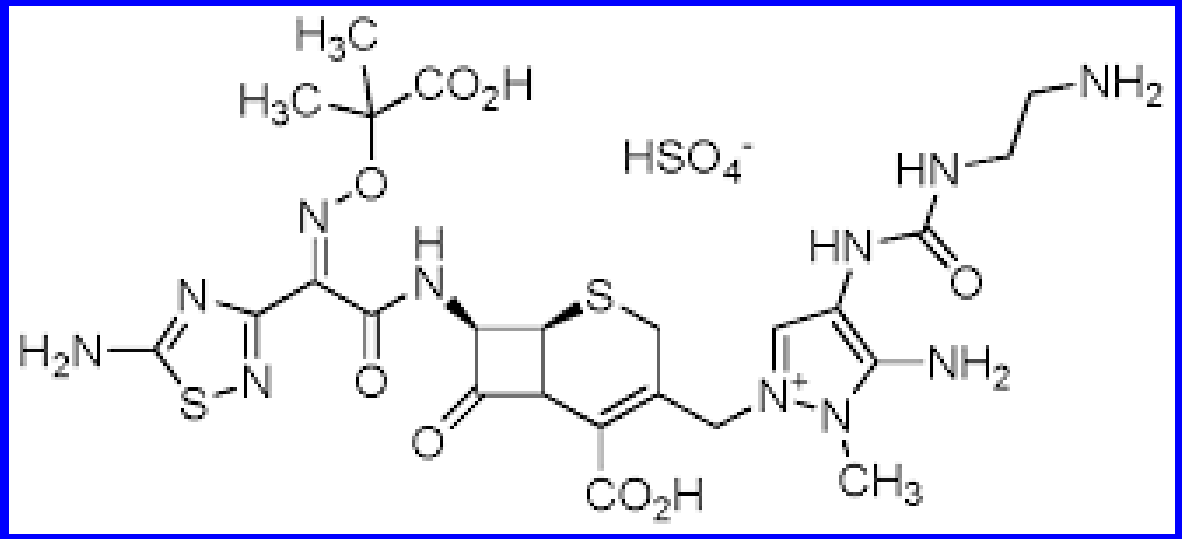


Multivariate Analysis of Mortality Risk Factors:

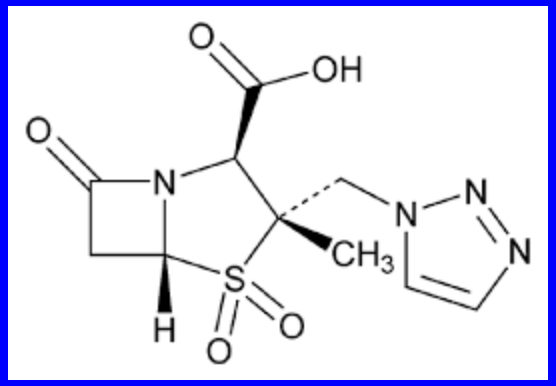
Variable	P Value	OR (95% CI)
Presentation with septic shock	0.008	7.17 (1.65-31.0)
Inadequate initial treatment	0.003	4.17 (1.61-10.8)
High APACHE III score	<0.001	1.04 (1.02-1.07)
Postantibiogram therapy with: tigecycline + colistin + meropenem	0.01	0.11 (0.02-0.69)

Tumbarello M et al. Clin Infect Dis. 2012; 55:943

Ceftolozane-Tazobactam Structure



Ceftolozane



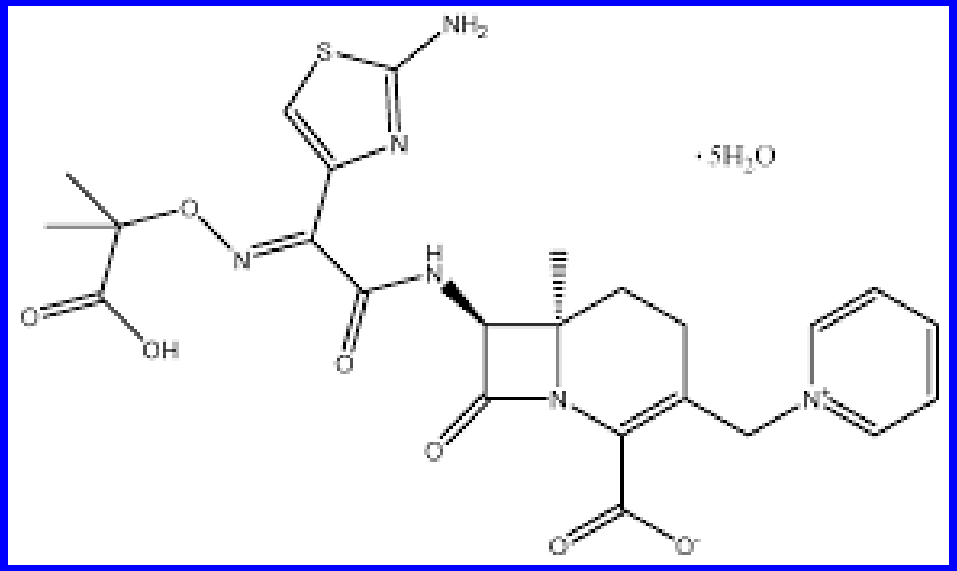
Tazobactam

Ceftolozane-Tazobactam

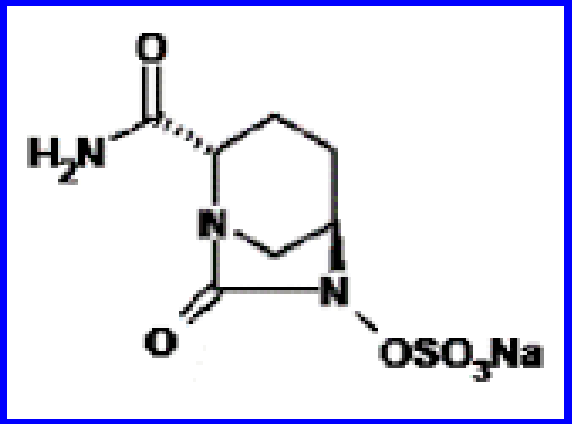
- FDA approved December 2014 for:
  - Complicated urinary tract infections
  - Complicated intraabdominal infections
- Spectrum of activity
  - Ceftolozane - increased potency against *P. aeruginosa*, including AmpC-overexpressing, and efflux pump resistant mutants; active against other enteric Gram-negative bacteria
  - Tazobactam – inhibits many β-lactamases, adding activity against some ESBL-producing enteric bacteria and *Bacteroides fragilis*; not active against carbapenemases
  - Not active against some ceftazidime-resistant enteric bacteria, *Acinetobacter*, *Stenotrophomonas*, staphylococci, or enterococci

Walkty A et al. Antimicrob Agents Chemother 2013; 57:5707

Ceftazidime-Avibactam Structure



Ceftazidime



Avibactam

Ceftazidime-Avibactam

- FDA approved February 2015 (based on Phase II data) for:
  - Complicated urinary tract infections (cUTI), including pyelonephritis
  - Complicated intraabdominal infections (cIAI)
- Spectrum of activity
  - Ceftazidime
    - Third-generation cephalosporin with activity against *P. aeruginosa*
    - Poor activity against *Acinetobacter* and *Burkholderia*
    - Poor activity against anaerobes, Gram-positive bacteria
  - Avibactam – synthetic β-lactamase inhibitor inhibiting: ESBLs, AmpC, and KPC carbapenemases
    - Inhibitor resistance from mutations in sensitive β-lactamases rare
    - Does not inhibit metallo- β-lactamases (VIM, NDM-1)

Zhanel GG et al. Drugs 2013; 73:159

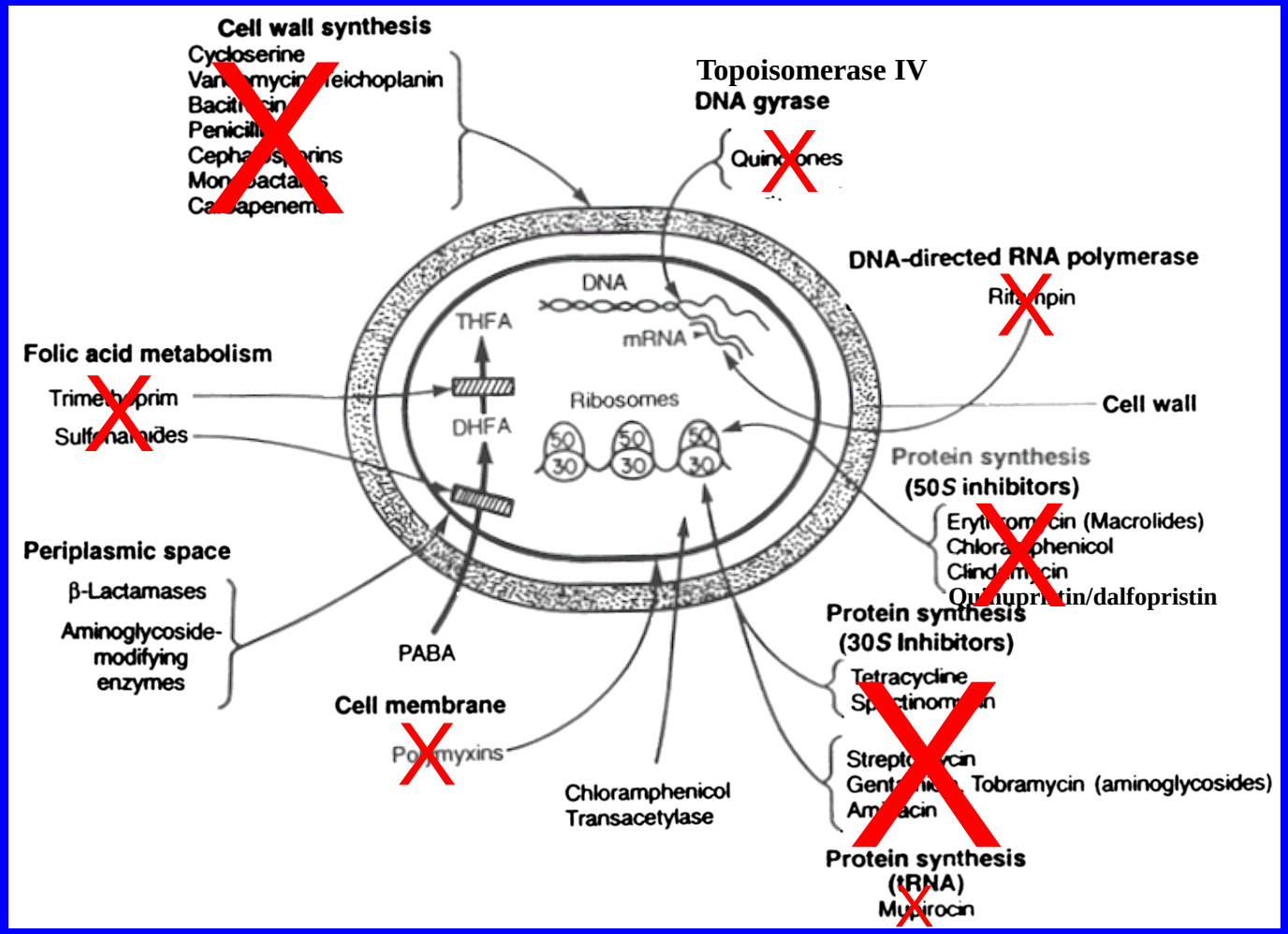
Costs of Antimicrobials

Drug	Dose	Daily Cost
Ceftriaxone	1000 mg IV Q24h	$46
Ceftazidime	1000 mg IV Q8h	$14
Cefepime	1000 mg IV Q8h	$61
Ceftaroline	600 mg IV Q12h	$303
Colistin	2.5 mg/kg Q12h	$101[a]
Tigecycline	50 mg IV Q12h	$272
Ceftolozane-tazobactam	1500 mg IV Q8h	$299
Ceftazidime-avibactam	2500 mg IV Q8h	$1,026

[a] based on 70 kg person

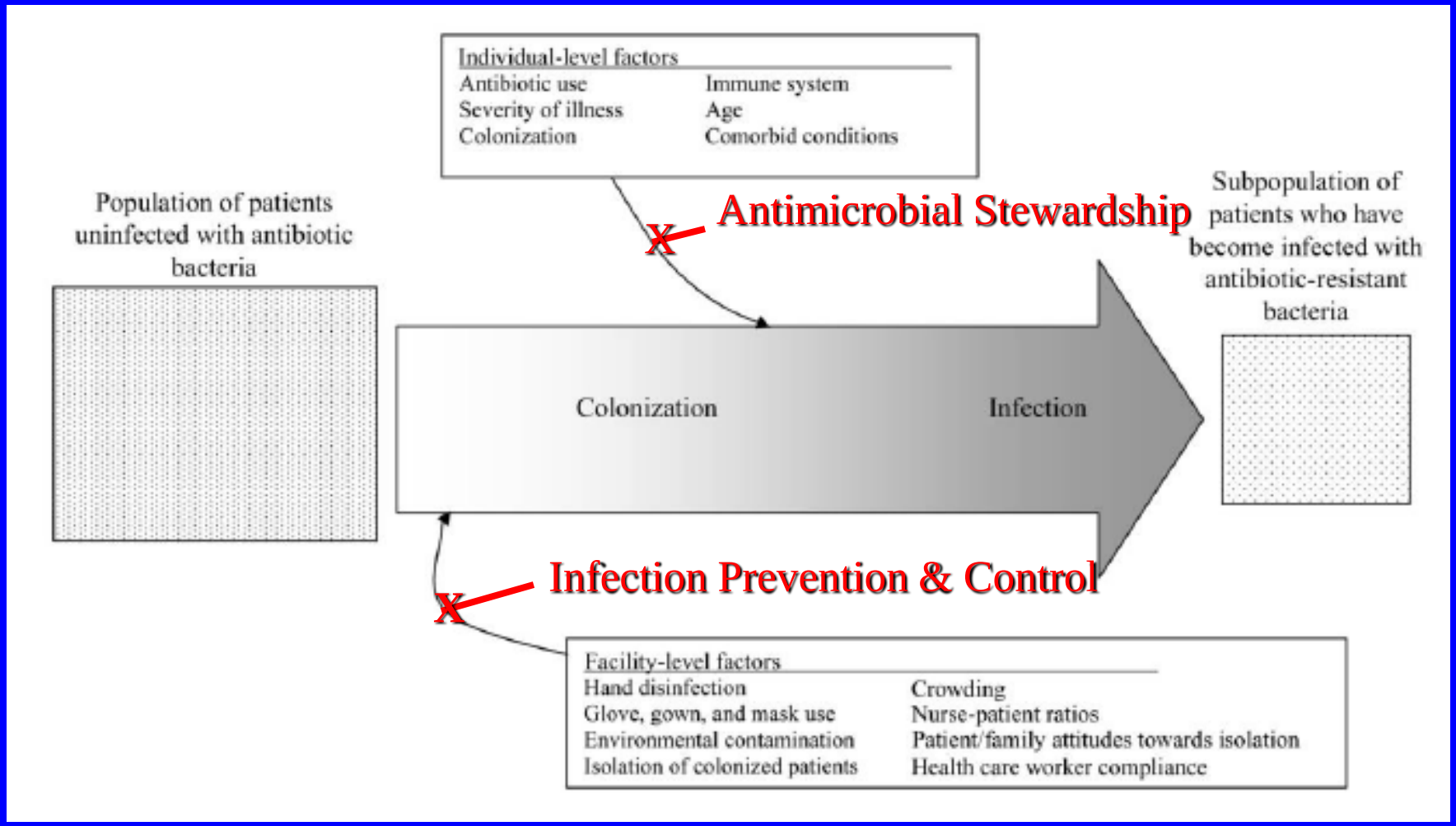
Average Wholesale Price March 2015

The Future?



Neu HC. Science 1992; 257:1064-73

Factors Affecting Acquisition of Healthcare-Associated Antibiotic-Resistant Bacterial Infections



Harris AD. Clin Infect Dis 2008; 46:686