From Bench to Bedside: Understanding Antimicrobial Stewardship, Reporting, and Resistance

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Northeast Association for Clinical Microbiology and Infectious Disease
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Disclosures

- None

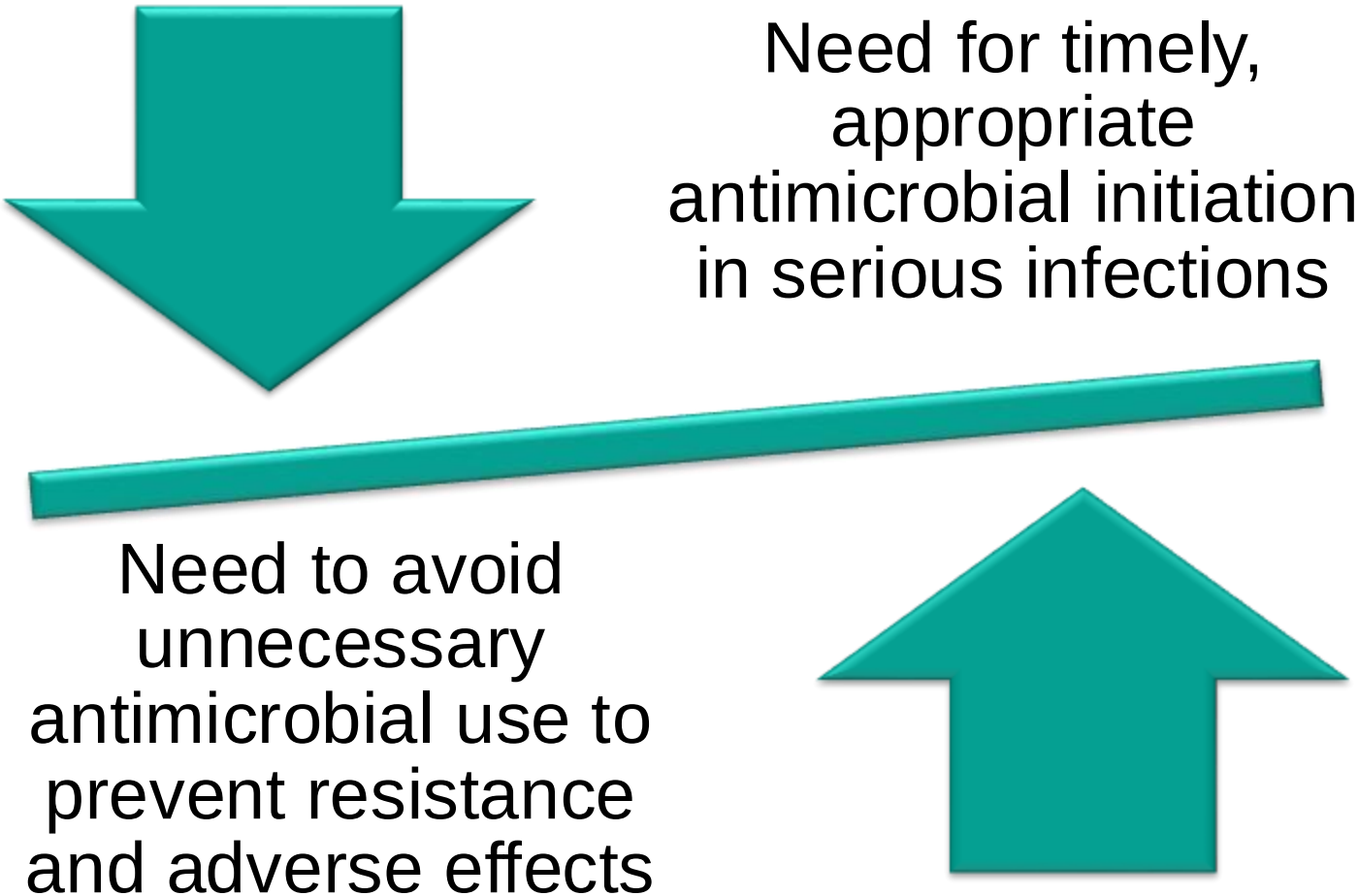
Outline

1. Define and describe the impact of antimicrobial stewardship programs

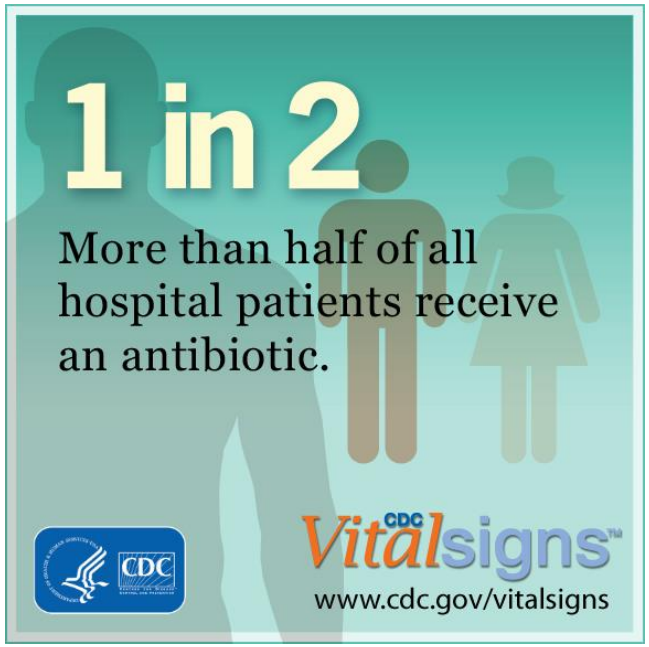
2. Discuss the role of clinical microbiologists in antimicrobial stewardship

3. Identify emerging drug resistance and novel antibacterials

Competing Tensions in Antimicrobial Use



Antimicrobial Use



Up to 50% of antibiotics prescribed are inappropriate.

Fridkin S, et al. Morbidity and Mortality Weekly Report. United States Center for Disease Control and Prevention (CDC). 2014;63(09):194-200.

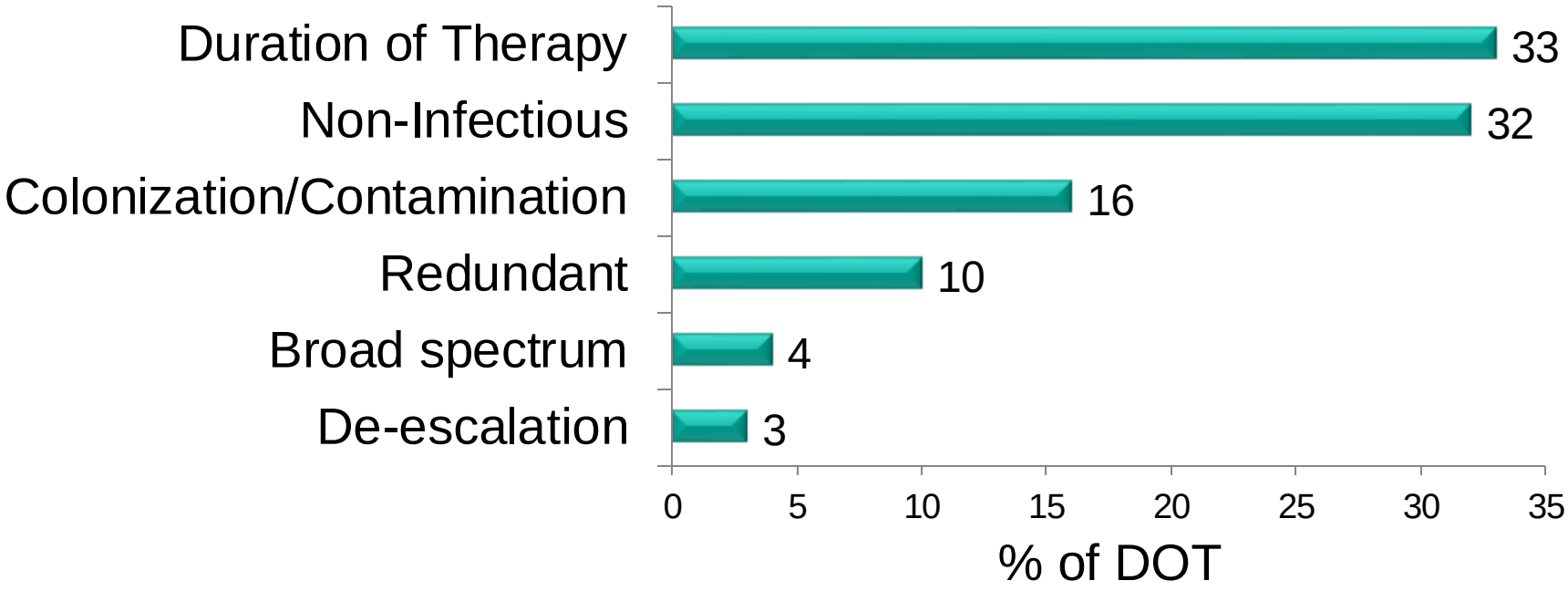
Common Misuses of Antibiotics

- Empiric antimicrobial treatment with broad-spectrum antibiotics without clear evidence of bacterial infection
- Treatment of a positive clinical culture in the absence of disease
- Failure to narrow antibiotic therapy when a causative organism is identified
- Prolonged prophylactic therapy
- Excessive durations of therapy

Leekha S, et al. *Mayo Clin Proc.* 2011;86(2):156-167.

Antibiotic Misuse

Reasons for unnecessary DOT in non-ICU patients over 2 weeks



~30% of all antibiotic days of therapy were unnecessary

DOT=days of therapy; ICU=intensive care unit
Hecker MT, et al. *Arch Intern Med.* 2003;163:972-978.

What are the consequences of antibiotic misuse?

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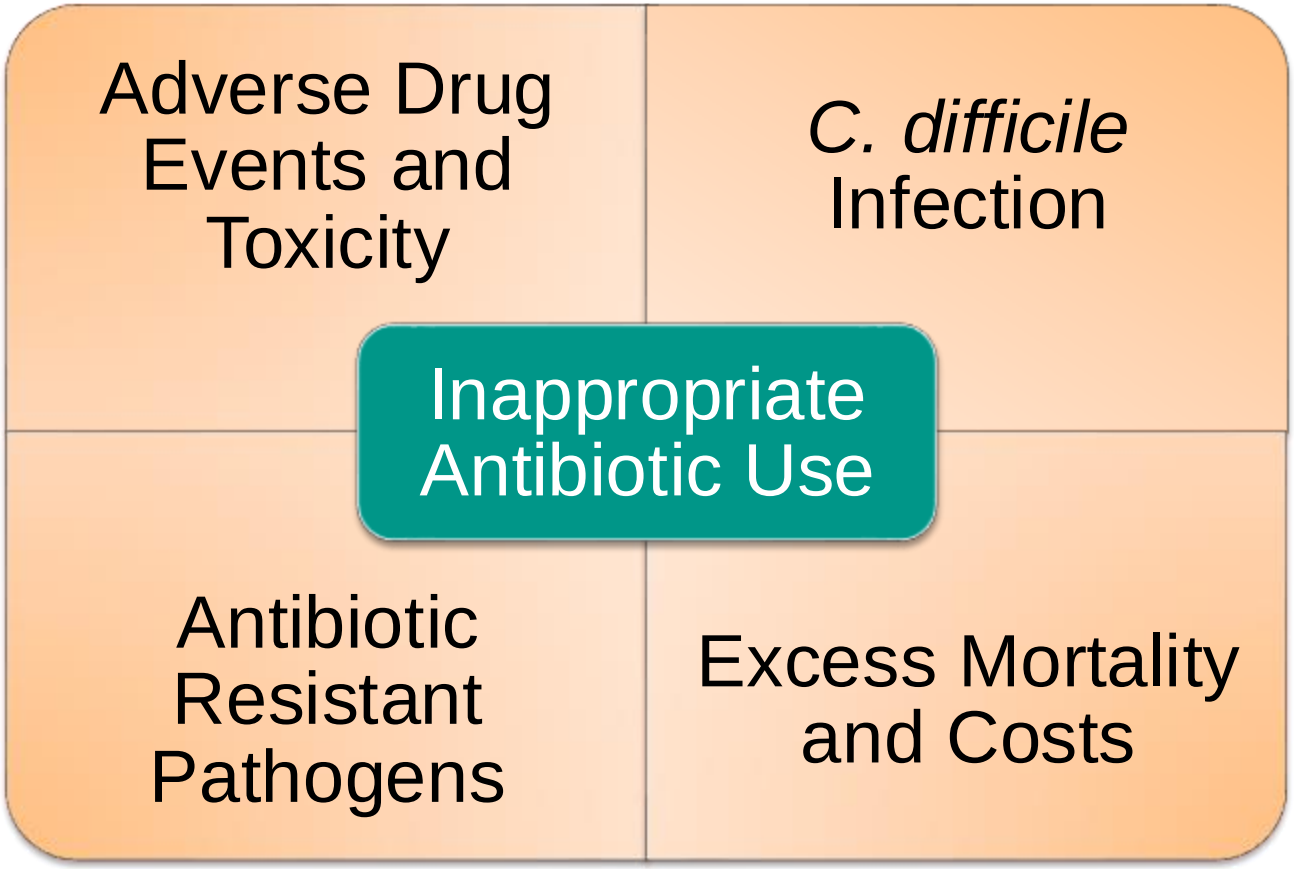
Consequences of Antibiotic Misuse



Dellit TH, et al. *Clin Infect Dis*. 2007;44:159-77.

Clostridioides difficile Infection (CDI)

- Antibiotic exposure is the single most important risk factor for the development of CDI
- Patients who receive broad-spectrum antibiotics during hospitalization are at 3 times greater risk to develop CDI

CDC. Antibiotic Resistance Threats in the United States, 2019. https://www.cdc.gov/drugresistance/pdf/threats-report/2019-ar-threats-report-508.pdf.
Fridkin S, et al. Morbidity and Mortality Weekly Report. CDC. 2014;63(09):194-200.

COVID-19 Impact on Antimicrobial Resistance

	Threat	Change in Rates or Number of Infections***			
		2020 vs. 2019	2021 vs. 2020	2022 vs. 2021	2022 vs. 2019
URGENT*	Hospital-onset CRE	▲ Increase	▲ Increase	— Stable	▲ Increase
URGENT*	Hospital-onset Carbapenem-resistant *Acinetobacter*	— Stable	— Stable	— Stable	▲ Increase**
URGENT*	Clinical Cases of *C. auris*	▲ Increase	▲ Increase	▲ Increase	▲ Increase
SERIOUS*	Hospital-onset MRSA	▲ Increase	— Stable	▼ Decrease	— Stable
SERIOUS*	Hospital-onset VRE	▲ Increase	▲ Increase	— Stable	▲ Increase
SERIOUS*	Hospital-onset ESBL-producing Enterobacterales	▲ Increase	— Stable	— Stable	▲ Increase
SERIOUS*	Hospital-onset MDR *Pseudomonas aeruginosa*	▲ Increase	▲ Increase	— Stable	▲ Increase

* Threat level for each pathogen, as categorized in CDC's *Antibiotic Resistance Threats in the United States, 2019.*
** There was no statistically significant difference in rate of hospital-onset carbapenem-resistant *Acinetobacter* in 2020, 2021, and 2022 when compared to the previous year. However, there was a statistically significant increase in rate of hospital-onset carbapenem-resistant *Acinetobacter* in 2022 when compared to 2019.
*** Hospital-onset rates were described using multivariable models for all threats except *C. auris*. Please note that in above table, stable indicates there was no statistically significant increase or decrease, decrease indicates a statistically significant decrease where $p<0.05$, and increase indicates a statistically significant increase where $p<0.05$, for all threats except for *C. auris*. Increases or decreases in *C. auris* were indicated by changes in the number of clinical cases reported nationally without hypothesis testing.

CRE=carbapenem-resistant Enterobacterales; MRSA=methicillin-resistant *Staphylococcus aureus*; VRE=vancomycin-resistant Enterococcus; ESBL=extended spectrum beta-lactamase; MDR=multidrug-resistant

CDC. Antibiotic Resistance Threats in the United States, 2021-2022. https://www.cdc.gov/antimicrobial-resistance/media/pdfs/antimicrobial-resistance-threats-update-2022-508.pdf.

How do we improve antimicrobial use and minimize resistance?

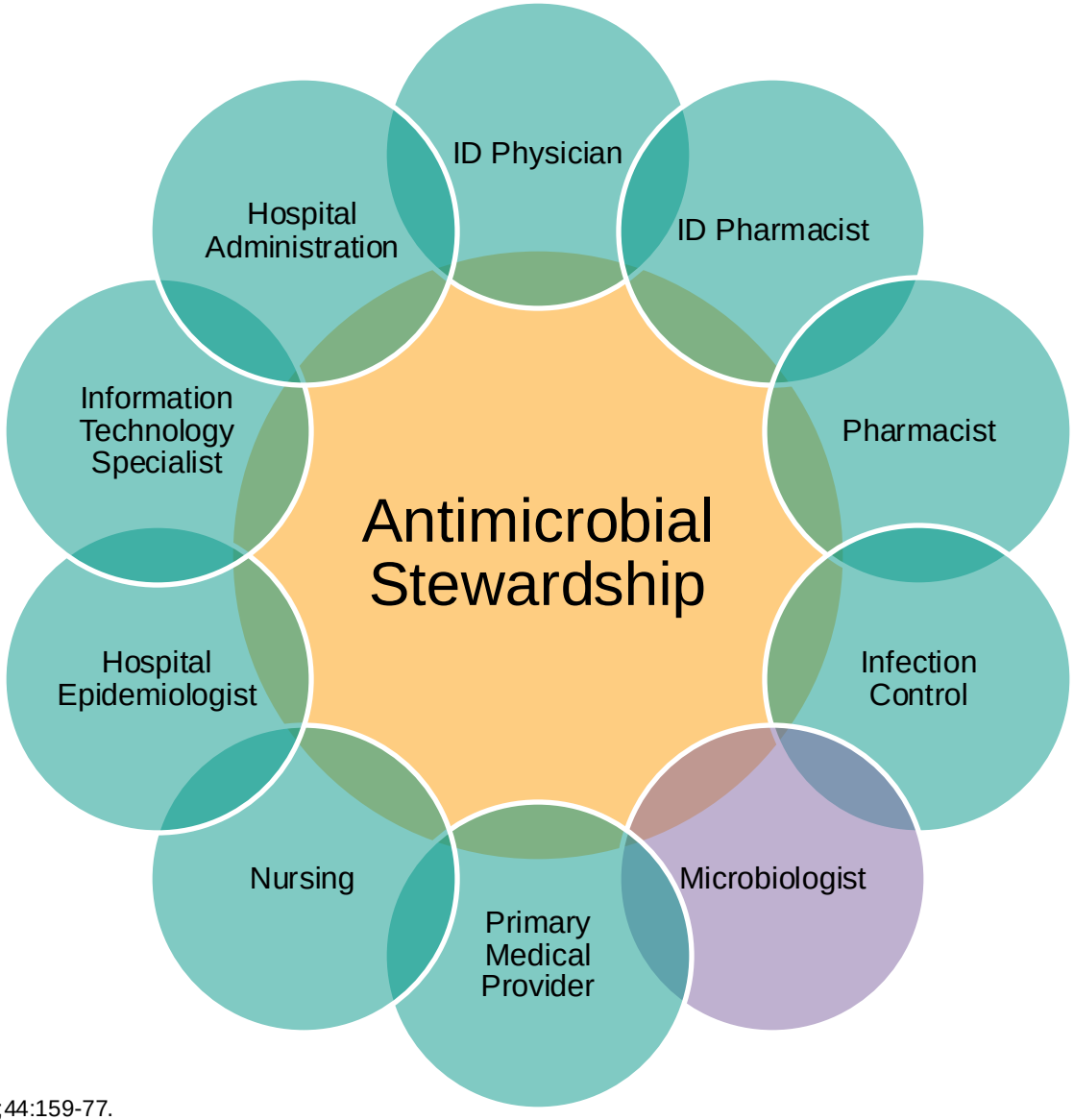
Antimicrobial Stewardship (AMS)

- Multidisciplinary approach to optimizing antimicrobials to maximize patient outcomes and decrease antimicrobial resistance

- Ensuring patients are:
  - ✓ On the right antibiotic
  - ✓ At the right dose, route, and duration
  - ✓ For the right indication

Dellit TH, et al. *Clin Infect Dis*. 2007;44:159-77.

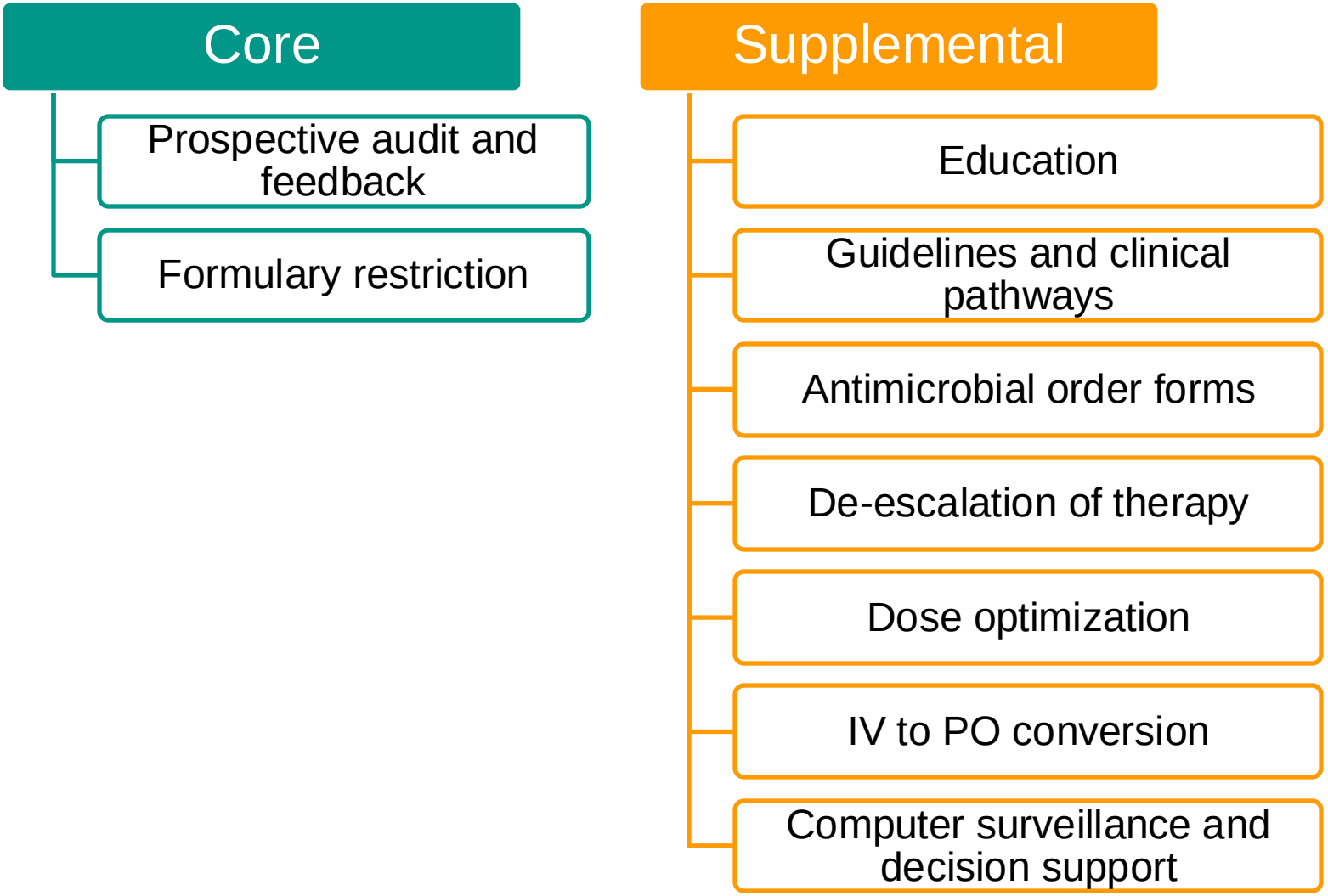
Multidisciplinary Approach



ID=infectious diseases

Dellit TH, et al. *Clin Infect Dis*. 2007;44:159-77.

Antimicrobial Stewardship Program (ASP) Strategies



IV=intravenous; PO=oral

Dellit TH, et al. *Clin Infect Dis*. 2007;44:159-77.

Impact of Antimicrobial Stewardship

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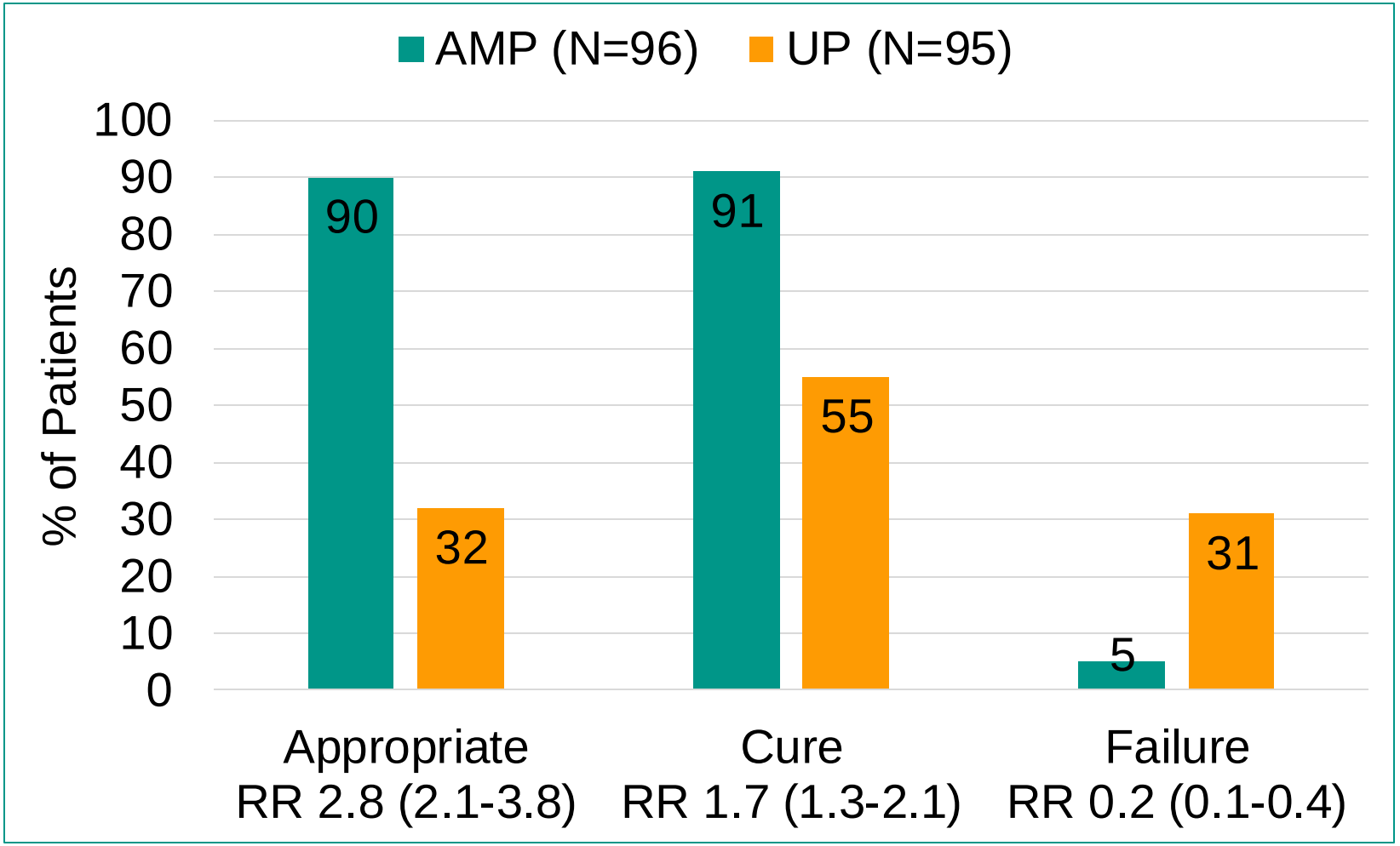
Improving Antibiotic Use Improves Infection Cure Rates

Clinical outcomes with and without antimicrobial stewardship

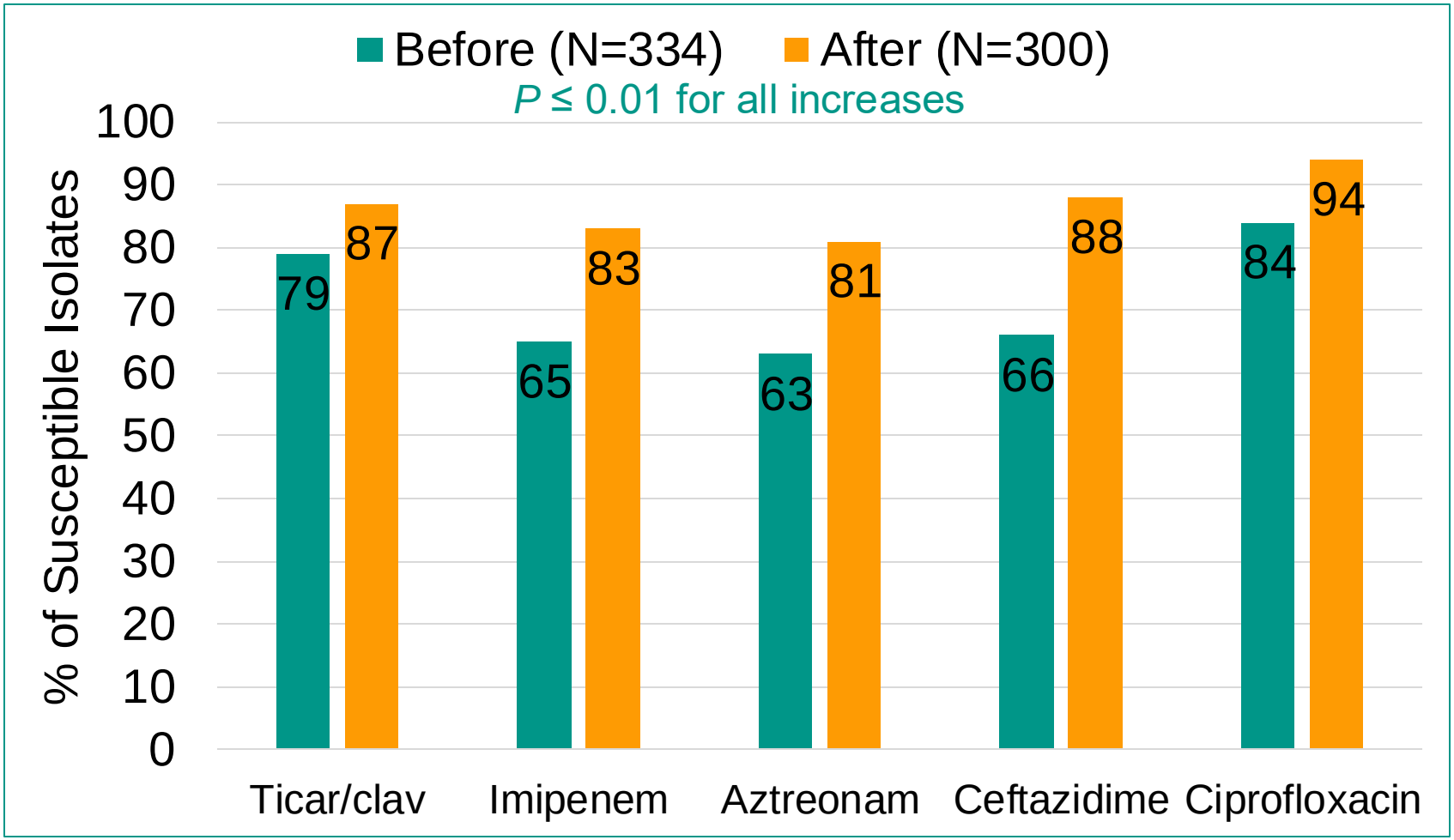


AMP=Antibiotic Management Program; UP=usual practice; RR=relative risk (95% confidence interval)

Fishman N. *Am J Med*. 2006;119(6 Suppl 1):S53-S70.

Improving Antibiotic Use Reduces Resistance

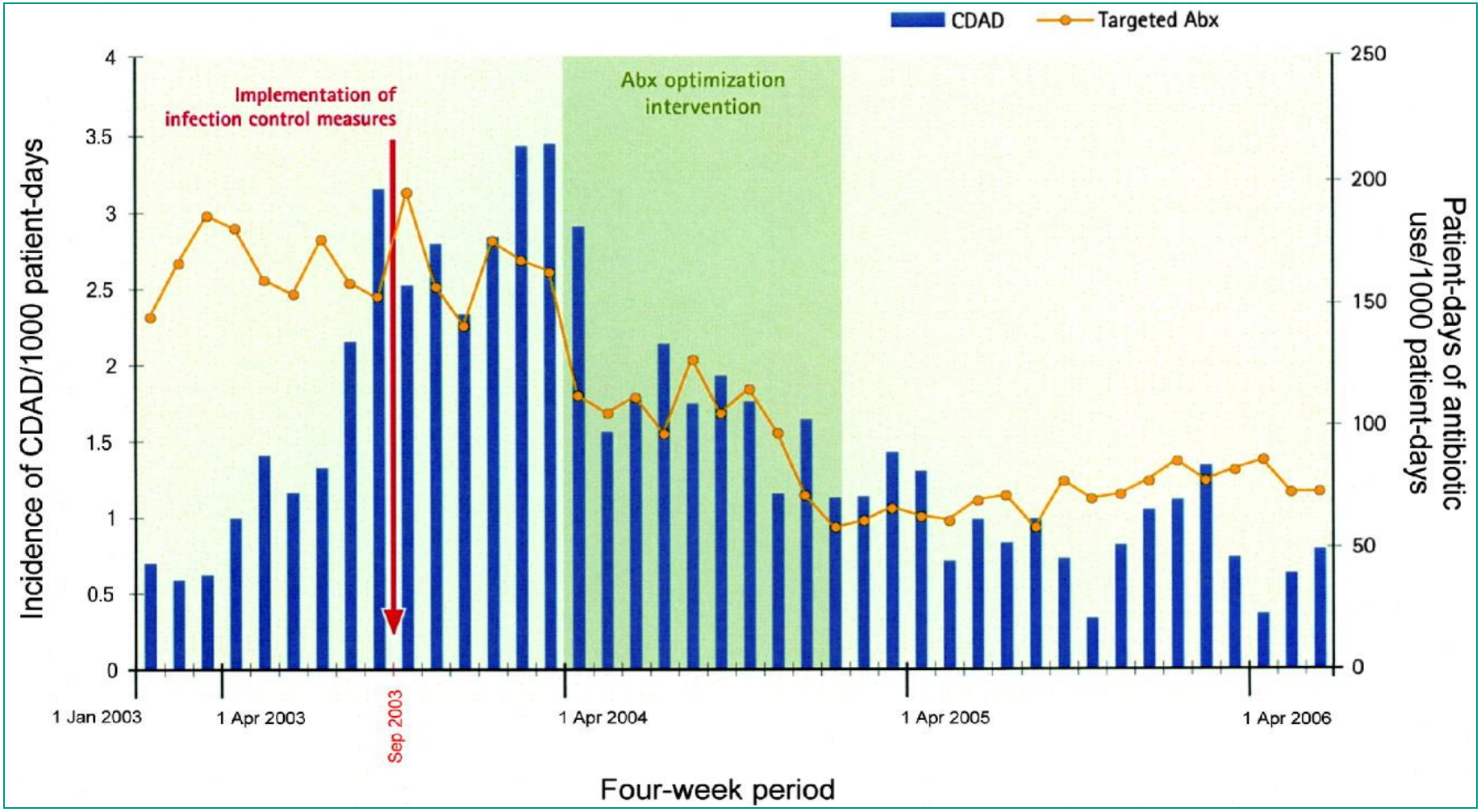
P. aeruginosa susceptibilities before and after implementation of antibiotic restrictions



Ticar/clav=ticarcillin/clavulanate

White AC Jr, et al. *Clin Infect Dis*. 1997;25(2):230-239.

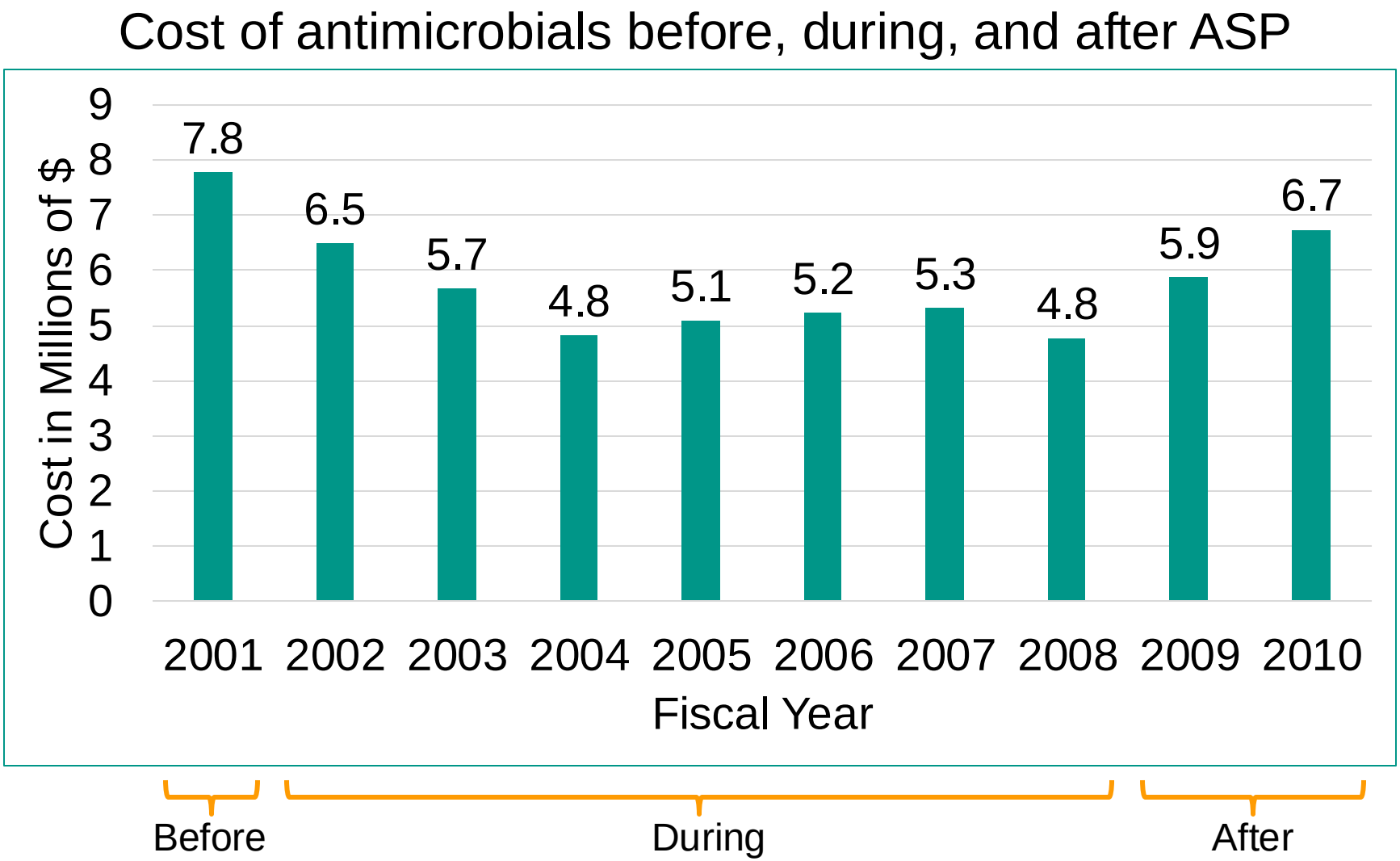
Improving Antibiotic Use Decreases *C. difficile* Rates



CDAD=*C. difficile*-associated disease

Valiquette L, et al. *Clin Infect Dis*. 2007;45 Suppl 2:S112-S121.

Improving Antibiotic Use Decreases Health Care Costs



Standiford HC, et al. *Infect Control Hosp Epidemiol*. 2012;33(4):338-345.

Clinical Microbiologists and Antimicrobial Stewardship

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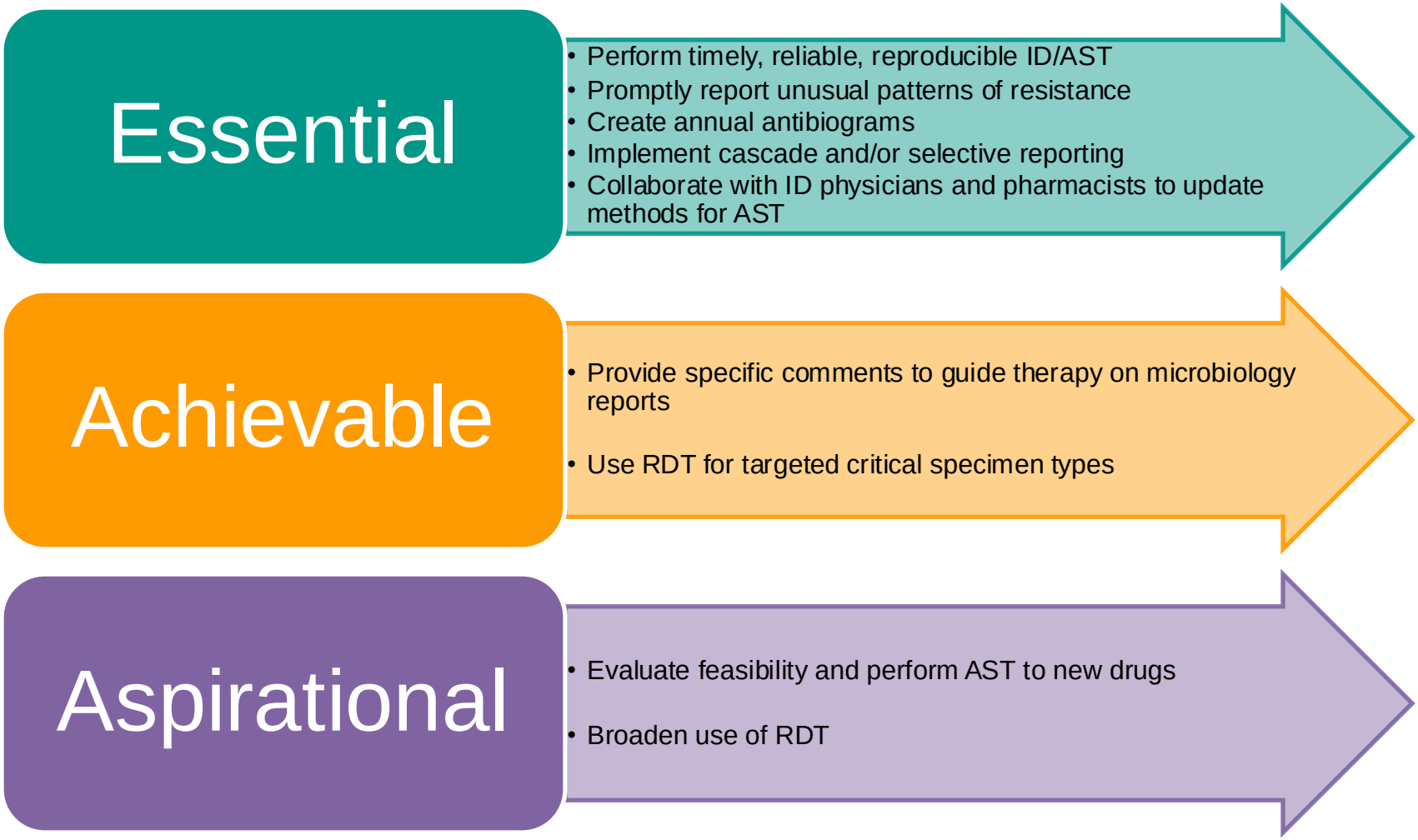
AMS Activities by Microbiologists



ID/AST=identification/antimicrobial susceptibility testing; RDT=rapid diagnostic testing

Morency-Potvin P, et al. *Clin Microbiol Rev*. 2016;30(1):381-407.

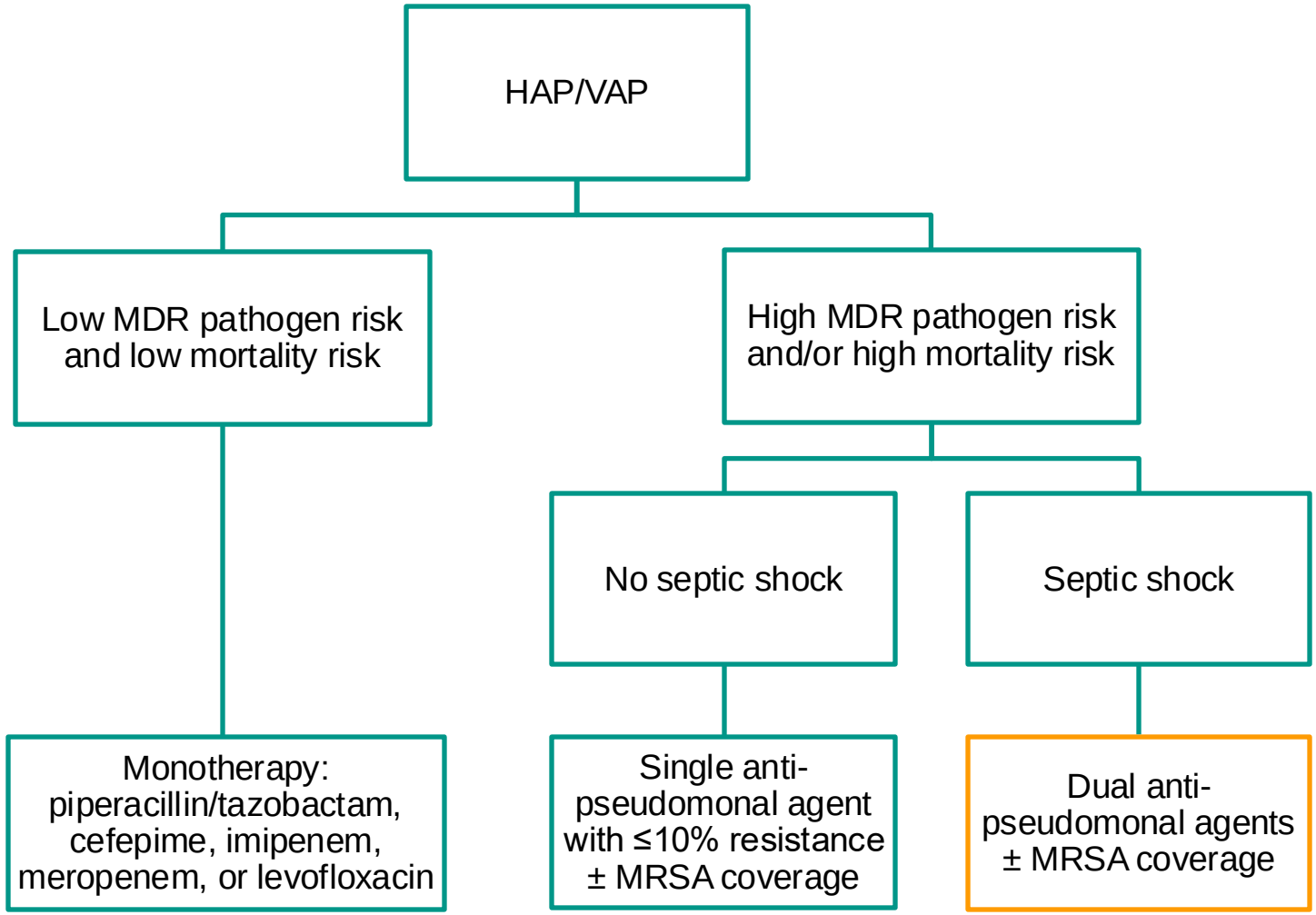
Antibiograms

Enhanced antibiograms for institutional needs:

- Patient location (e.g., ICU, outpatient)
- Syndromic: select specimen types (e.g., blood, urine)
- Patient population (e.g., surgical, pediatric)
- Rolling
- Aggregated
- Antimicrobial agent combinations
- Antimicrobial resistance markers

Morency-Potvin P, et al. *Clin Microbiol Rev*. 2016;30(1):381-407.
CLSI. *Analysis and Presentation of Cumulative Antimicrobial Susceptibility Test Data*. 5th Ed.
CLSI guideline M39. Clinical and Laboratory Standards Institute, USA, 2022.

Empiric Combination Therapy for Pneumonia



HAP=hospital-acquired pneumonia; VAP=ventilator-associated pneumonia

Kalil AC, et al. *Clin Infect Dis*. 2016;63(5):e61-e111.

Combination Antibiogram to Evaluate Cross-Resistance

Combination antibiogram for *P. aeruginosa* isolates (% susceptible)

Antibiotic	Monotherapy	In Combination With			
		Gentamicin	Amikacin	Ciprofloxacin	Levofloxacin
Ceftazidime	84	94	99	95	94
Imipenem	84	94	99	94	92
Cefepime	90	96	99	95	94
Meropenem	89	96	99	95	94
Piperacillin-tazobactam	83	95	99	95	93

Ai MY, et al. *J Microbiol Immunol Infect*. 2023;56(2):344-350.

Antibiogram with Resistance Markers for Therapy Optimization

Antibiograms as a function of resistance markers

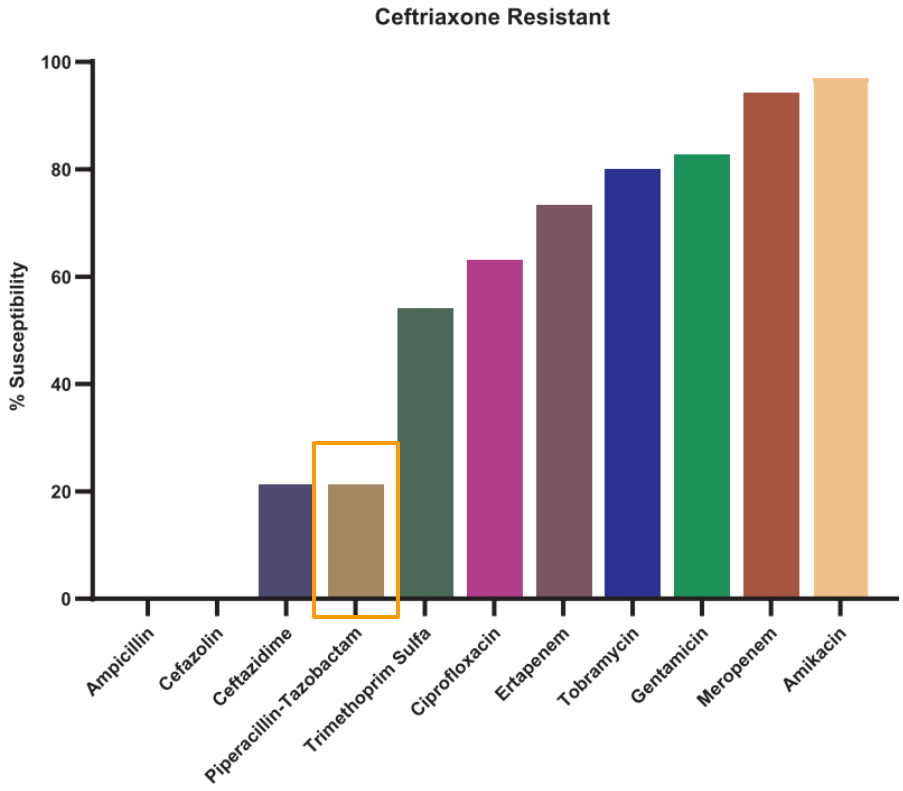
Organism	Resistance marker	*n*	% susceptible isolates											
			SAM	TZP	CZO	CRO	FEP	ETP	MEM	IMI	GEN	TOB	CIP	LVX	ATM
Detroit Medical Center															
E. coli	CTX-M	58	5	84	0	3	22	100	100		48	26	5		10
	None	326	52	99	75	98	99	100	100		92	92	82		99
K. pneumoniae	CTX-M	28	0	57	0	4	4	96	100		46	25	36		25
	KPC	6	0	0	0	0	33	0	0		17	0	17		17
	None	106	83	97	84	94	99	100	100		94	95	94		93
K. oxytoca	KPC	1	0	0	0	0	0	0	0		100	100	0		0
	None	22	41	91	32	95	100	100	100		100	100	100		100
Proteus spp.	CTX -M	4	25	100	0	0	50	100	100		25	50	0		100
	None	53	79	96	11	94	100	100	100		96	96	64		100
Enterobacter spp.	CTX-M	1	R	100	R	R	0	100	100		0	0	0		0
	None	60	R	87	R	R	97	98	98		95	95	93		87
Citrobacter spp.	None	10		100	R	R	100	100	100		100	100	100		100
Acinetobacter spp.	OXA	10	20		R	R	20	R	20		10	10	0		
	None	29	86		R	R	79	R	93		29	83	76		
P. aeruginosa	None	51		82	R	R	88	R	86		86	96	84		75
University of Maryland Medical Center															
E. coli	CTX-M	14	21	93	0	0	0	99	100		29			21	0
	None	91	44	88	82	98	98	100	100		83			70	100
K. pneumoniae	CTX-M	7	0	43	0	0	14	100	100		57			43	0
	KPC	5	0	0	0	0	20	0	0		60			80	0
	None	45	80	93	85	91	100	100	100		98			100	95
K. oxytoca	None	9	67	100	89	100	100	100	100		100			100	100
Proteus spp.	None	11	82	100	82	100	100	100	100		100			64	100
Enterobacter spp.	CTX-M	3	R	67	R	R	33	100	100		33			67	33
	None	31	R	65	R	R	80	100	100		93			97	63
Citrobacter spp.	None	6		83	R	R	100	100	100		83			83	83
Acinetobacter spp.	OXA	5	60		R	R	0	R		0	40		78		
	None	9	89		R	R	89	R		89	89		89		
P. aeruginosa	None	43		65	R	R	86	R	67	56	86		58		51

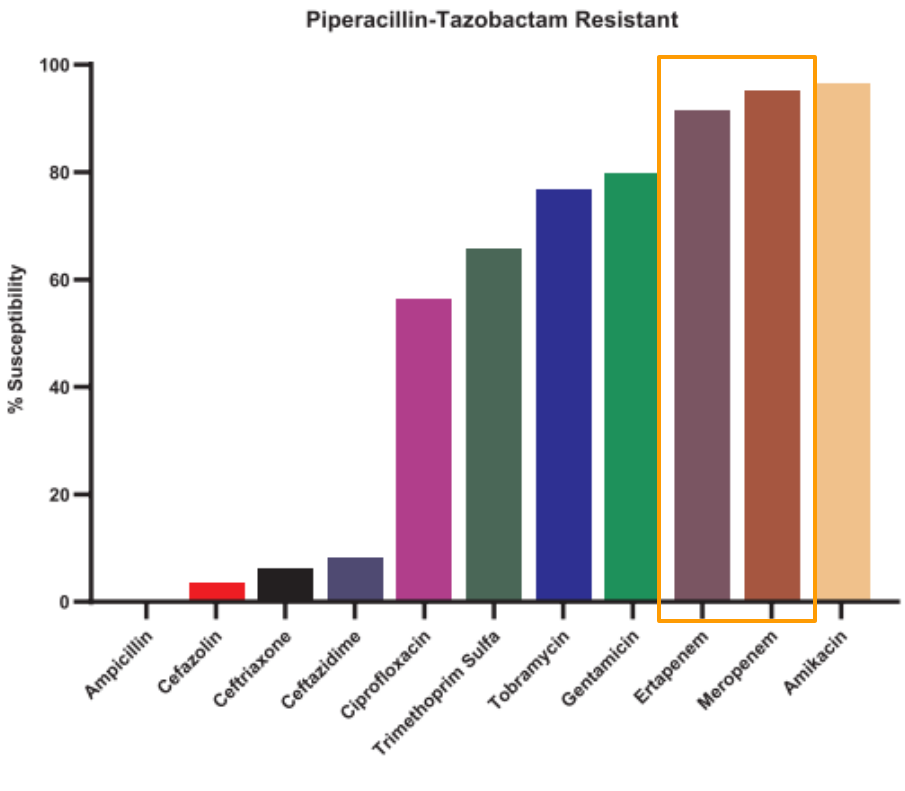
SAM=ampicillin-sulbactam; TZP=piperacillin-tazobactam; CZO=cefazolin; CRO=ceftriaxone; FEP=cefepime; ETP=ertapenem; MEM=meropenem; IMI=imipenem; GEN=gentamicin; TOB=tobramycin; CIP=ciprofloxacin; LVX=levofloxacin; ATM=aztreonam; CTX-M=cefotaxime-Munich; KPC=*K. pneumoniae* carbapenemase; R=intrinsic resistance

Pogue JM, et al. *Antimicrob Agents Chemother*. 2018;62(5):e02538-17.

Escalation Antibiogram for Nonresponding Patients

Antibiograms as a function of antimicrobial resistance

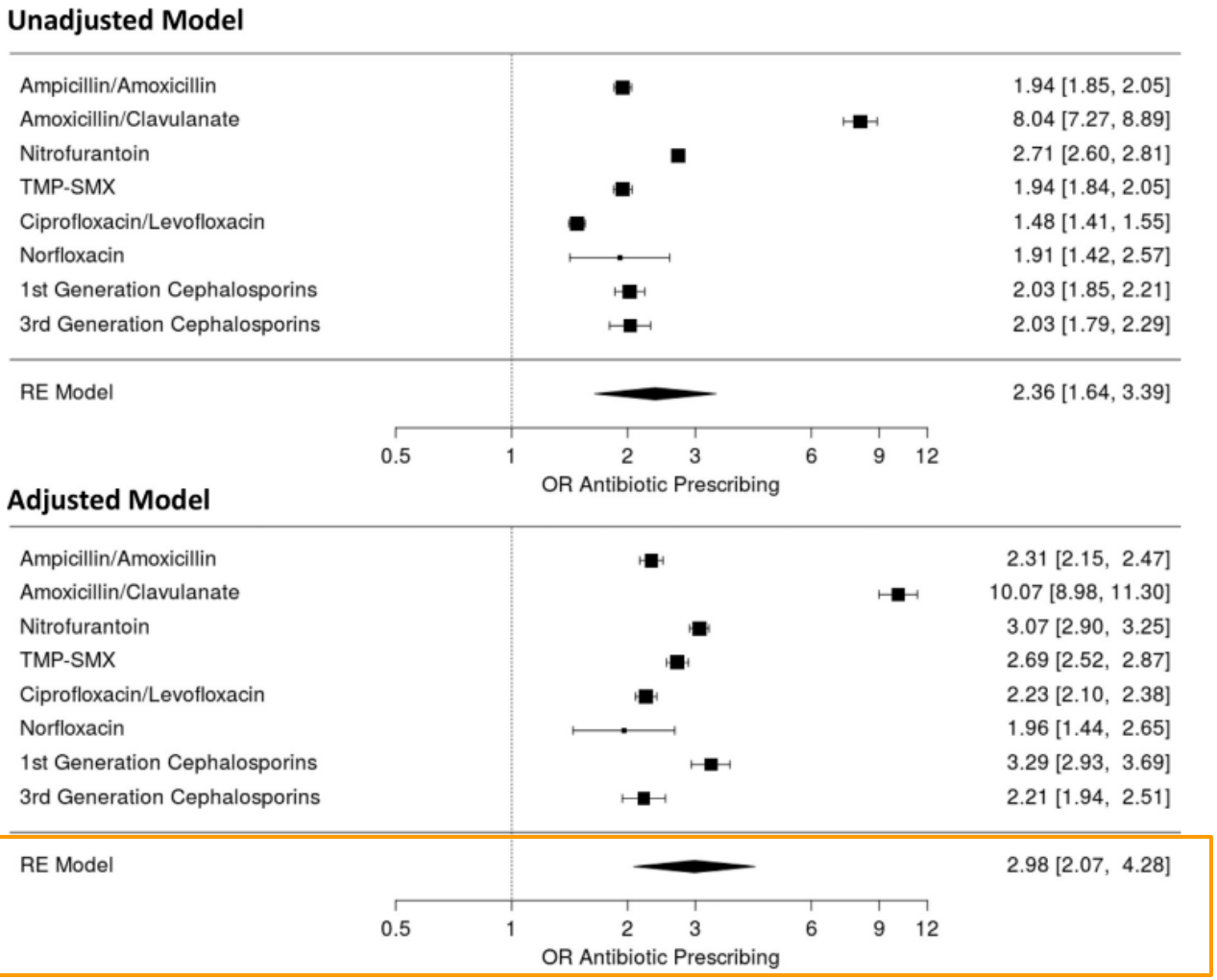




Teitelbaum D, et al. *Clin Infect Dis*. 2022;75(10):1763-1771.

Reporting is Associated with Prescribing

Patient-level antibiotic susceptibility reporting and association with directed antibiotic prescribing



TMP-SMX=trimethoprim-sulfamethoxazole; OR=odds ratio

Langford BJ, et al. *Clin Microbiol Infect*. 2021;27(4):568-575.

Cascade and Selective Reporting

Table 1A-1. Enterobacterales (excluding *Salmonella/Shigella*)[a]

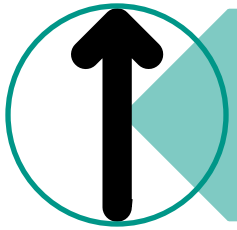
Tier 1: Antimicrobial agents that are appropriate for routine, primary testing and reporting	Tier 2: Antimicrobial agents that are appropriate for routine, primary testing but may be reported following cascade reporting rules established at each institution	Tier 3: Antimicrobial agents that are appropriate for routine, primary testing in institutions that serve patients at high risk for MDROs but should only be reported following cascade reporting rules established at each institution	Tier 4: Antimicrobial agents that may warrant testing and reporting by clinician request if antimicrobial agents in other tiers are not optimal because of various factors
Ampicillin			
Cefazolin	Cefuroxime		
Cefotaxime or ceftriaxone[b]	Cefepime[c]		
	Ertapenem Imipenem Meropenem	Cefiderocol	
		Ceftazidime-avibactam	
		Imipenem-relebactam	
		Meropenem-vaborbactam	
Amoxicillin-clavulanate Ampicillin-sulbactam			
Piperacillin-tazobactam			
Gentamicin	Tobramycin	Plazomicin	
	Amikacin		
Ciprofloxacin Levofloxacin			
Trimethoprim-sulfamethoxazole			
	Cefotetan Cefoxitin		
	Tetracycline[d]		
			Aztreonam
			Ceftaroline[b]
			Ceftazidime[b]
			Ceftolozane-tazobactam
Urine Only			
Cefazolin (surrogate for uncomplicated UTI)[e]			
Nitrofurantoin			
		Fosfomycin[f] (*Escherichia coli*)	

CLSI. *Performance Standards for Antimicrobial Susceptibility Testing*. 34th ed. CLSI supplement M100. CLSI, USA 2024.

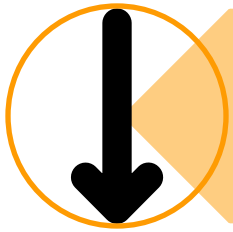
Comment Nudges

Commensal respiratory flora

Commensal respiratory flora only: No *S. aureus*/MRSA or *P. aeruginosa*

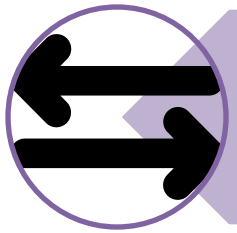


De-escalation from anti-MRSA or anti-pseudomonal therapy



Duration of anti-MRSA and anti-pseudomonal therapy

Acute kidney injury



ICU and hospital length of stay

All-cause mortality

Musgrove MA, et al. *Open Forum Infect Dis*. 2018;5(7):ofy162.

Interpretation Guideline Changes

Aminoglycoside breakpoint revisions from CLSI M100-Ed33

	Enterobacterales	*P. aeruginosa*
Gentamicin	Lowered	Deleted
Tobramycin	Lowered	Lowered
Amikacin	Lowered	Urine only

Table 1. Comparisons of unit-specific combination antibiograms for Gram-negative respiratory isolates by using 2022 vs. 2023 breakpoints and subgroup results for isolates with *P. aeruginosa* and non-*P. aeruginosa*

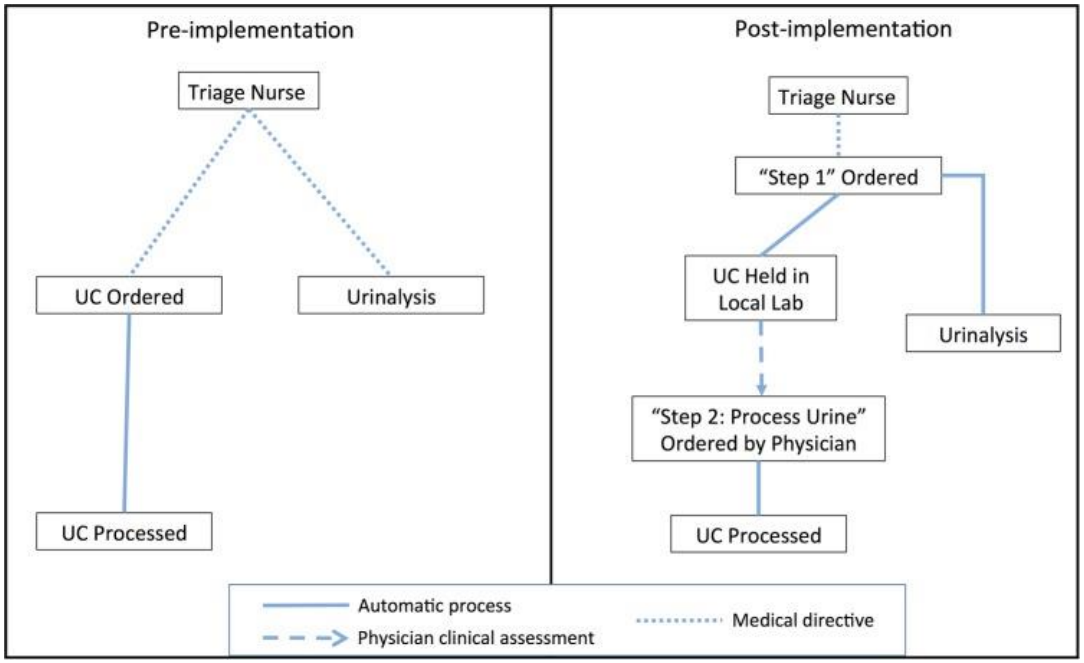
Isolates, agent	Isolates susceptible, % by agent											
	Monotherapy		Amikacin		Gentamicin		Tobramycin		Levofloxacin		Ciprofloxacin	
CLSI	2022	2023	2022	2023	2022	2023	2022	2023	2022	2023	2022	2023
All isolates (221 isolates)												
Cefepime	75.1	75.1	88.7	79.6	86.0	79.2	86.4	85.1	89.6	89.6	80.5	80.5
Meropenem	80.1	80.1	86.9	81.4	85.5	81.4	86.0	84.6	94.1	94.1	82.8	82.8
Piperacillin-tazobactam	62.9	62.9	85.5	74.7	83.3	74.2	84.2	81.9	88.7	88.7	77.4	77.4
Levofloxacin	82.4	82.4										
Ciprofloxacin	71.5	71.5										
Amikacin	85.1	58.8										
Gentamicin	81.0	56.6										
Tobramycin	82.8	79.2										

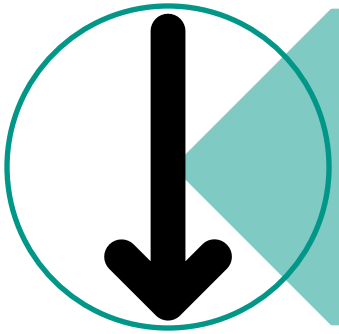
Isolates, agent	Isolates susceptible, % by agent											
	Monotherapy		Amikacin		Gentamicin		Tobramycin		Levofloxacin		Ciprofloxacin	
CLSI	2022	2023	2022	2023	2022	2023	2022	2023	2022	2023	2022	2023
***P. aeruginosa* isolates (58 isolates)**												
Cefepime	67.2	67.2	94.8	67.2	93.1	67.2	98.3	94.8	81.0	81.0	81.0	81.0
Meropenem	81.0	81.0	98.3	81.0	96.6	81.0	100.0	96.6	89.7	89.7	89.7	89.7
Piperacillin-tazobactam	60.3	60.3	94.8	60.3	93.1	60.3	98.3	94.8	81.0	81.0	81.0	81.0
Levofloxacin	75.9	75.9										
Ciprofloxacin	75.9	75.9										
Amikacin	93.1	0.0										
Gentamicin	91.4	0.0										
Tobramycin	98.3	93.1										

Humphries RM. AST News Update June 2023: New! CLSI M100-Ed33: Updated Aminoglycoside Breakpoints for Enterobacterales and *Pseudomonas aeruginosa*. https://clsi.org/about/blog/ast-news-update-june-2023-new-clsi-m100-ed33-updated-aminoglycoside-breakpoints-for-enterobacterales-and-pseudomonas-aeruginosa/.
Wangchinda W, et al. *Open Forum Infect Dis*. 2023;10(Suppl 2):ofad500.427.

Preanalytical Guidance

ED UC ordering before and after intervention





Weekly ED UC %

Patients admitted with UC

Antibiotics prescribed for urinary indication

ED=emergency department; UC=urine culture

Stagg A, et al. *BMJ Qual Saf.* 2018;27(2):140-147.

RDT and ASP

Timbrook TT, et al. *Clin Infect Dis.* 2017;64(1):15-23.

RDT and ASP at Lifespan

Pre- and post-implementation of Accelerate Pheno® with ASP intervention for GNB

Outcome	Pre (N = 102)	Post (N = 162)	*P* Value
Length of stay, days	7 (5-11)	5 (3-8)	**<0.001**
Duration of IV therapy, days	8 (5-15)	4 (3-7)	**<0.001**
Total duration of antibiotic therapy, days	15 (14-17)	13 (8-15)	**<0.001**
IV to PO conversion, n (%)	62 (61%)	126 (78%)	**0.003**
Time to optimal therapy, hours	64 (52-91)	20 (12-31)	**<0.001**
Time to discontinuation of anti-MRSA therapy, days	2 (1-3)	1 (1-2)	**0.002**
Time to discontinuation of anti-pseudomonal beta-lactam, days	3 (3-5)	2 (1-2)	**<0.001**

Data presented in median (interquartile range) unless otherwise noted
GNB=Gram negative bacteremia; Anti-pseudomonal beta-lactam=cefepime, piperacillin-tazobactam, meropenem
Ventres J, et al. Poster presented at: ESCMID Global; 2024; Barcelona, Spain.

Emerging Drug Resistance and Novel Antibacterials

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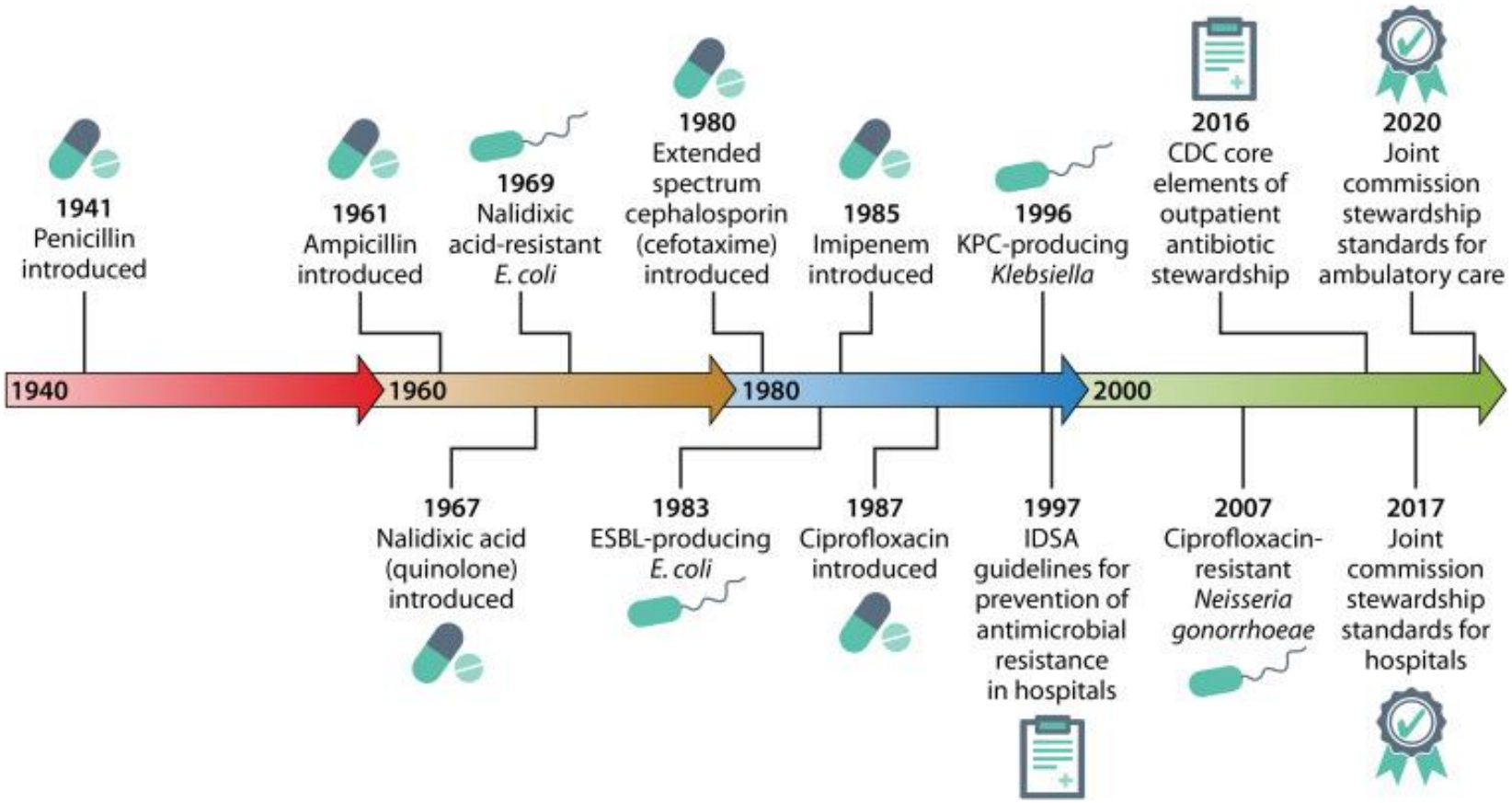
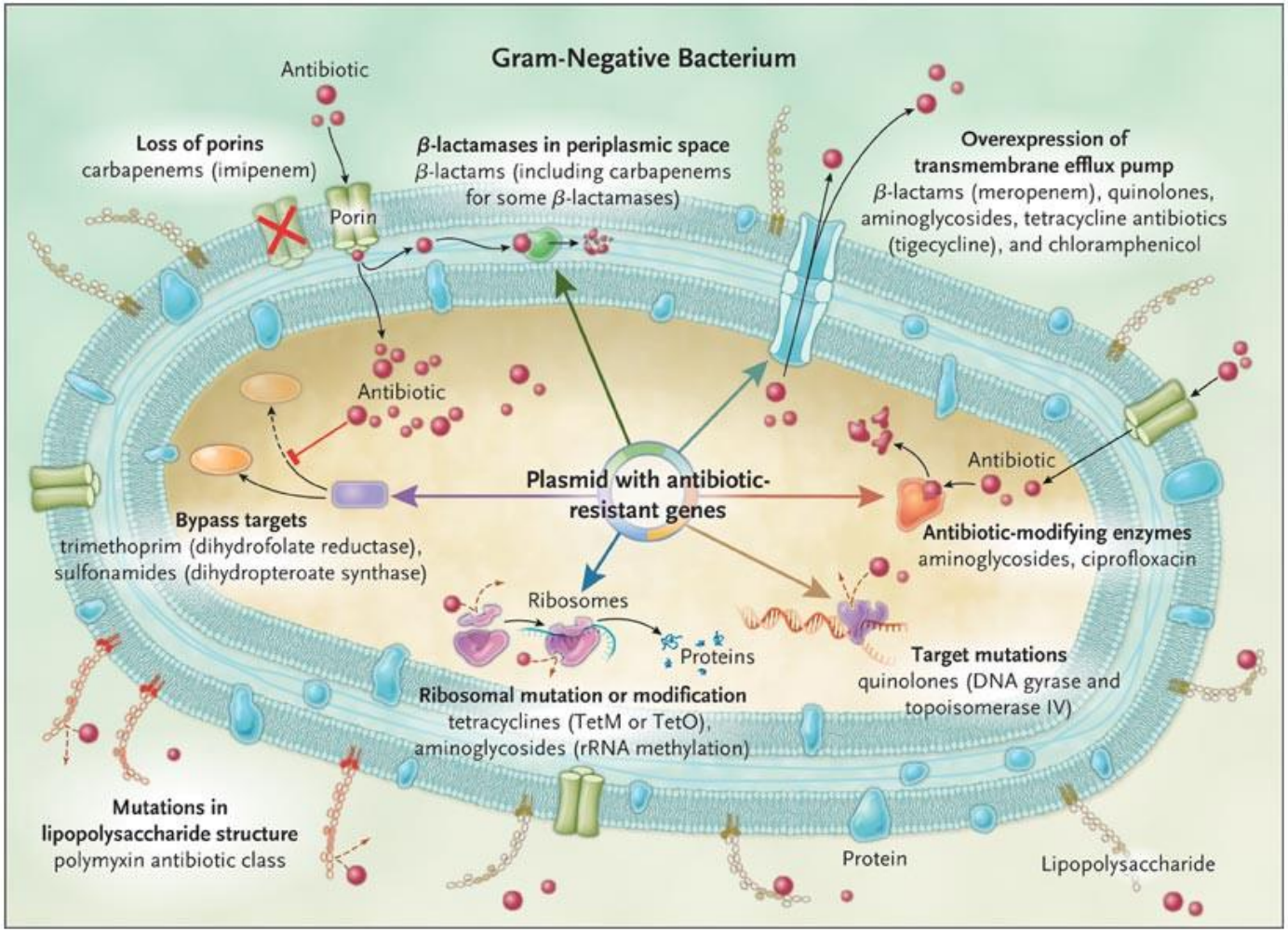
Timeline of Antibiotic Development, Resistance, and Stewardship



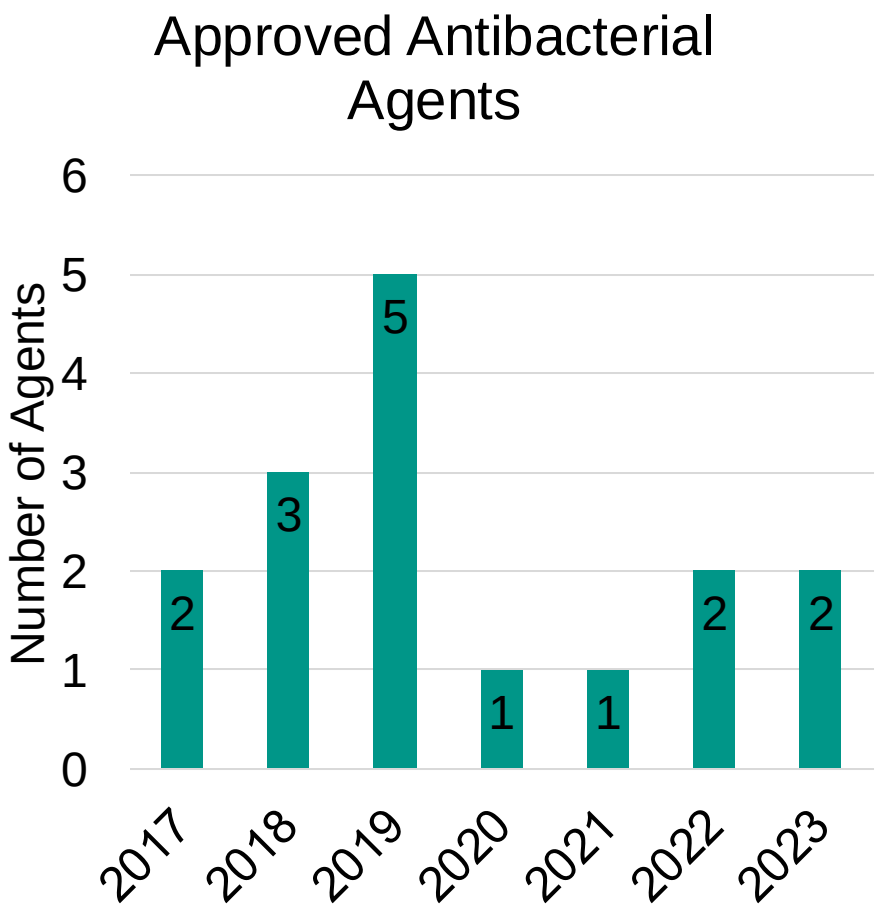
Goebel MC, et al. *Clin Microbiol Rev*. 2021;34(4):e0000320.
2023 Antibacterial agents in clinical and preclinical development: an overview and analysis. Geneva: World Health Organization (WHO); 2024.

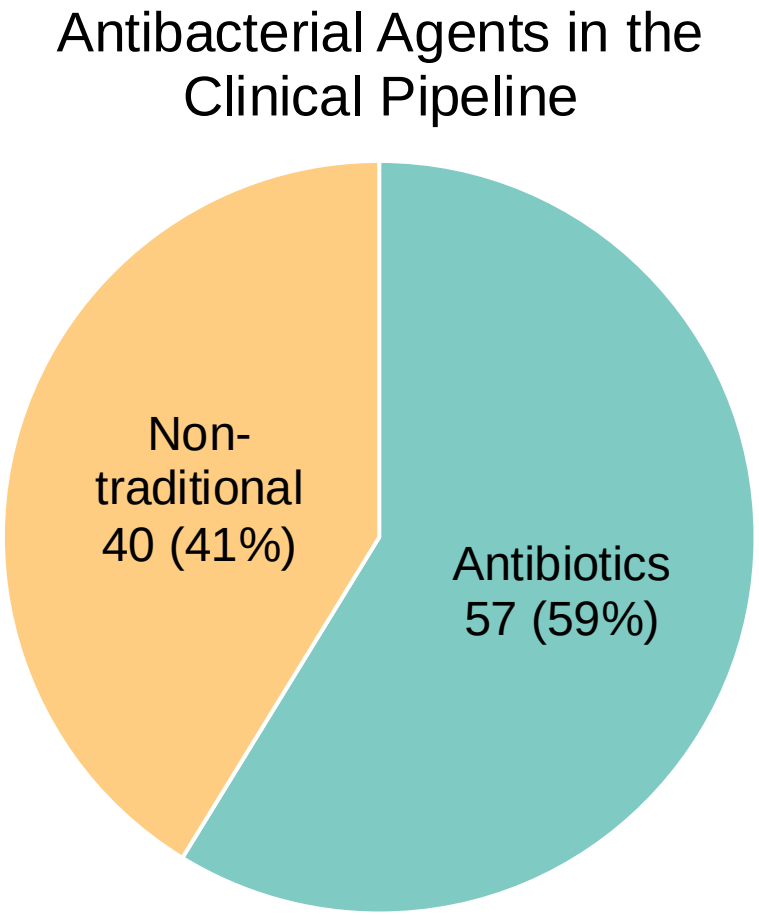
Mechanisms of Antimicrobial Resistance



Peleg AY, et al. *N Engl J Med*. 2010;362(19):1804-1813.

Antibacterial Clinical Pipeline 7/2017 to 12/2023

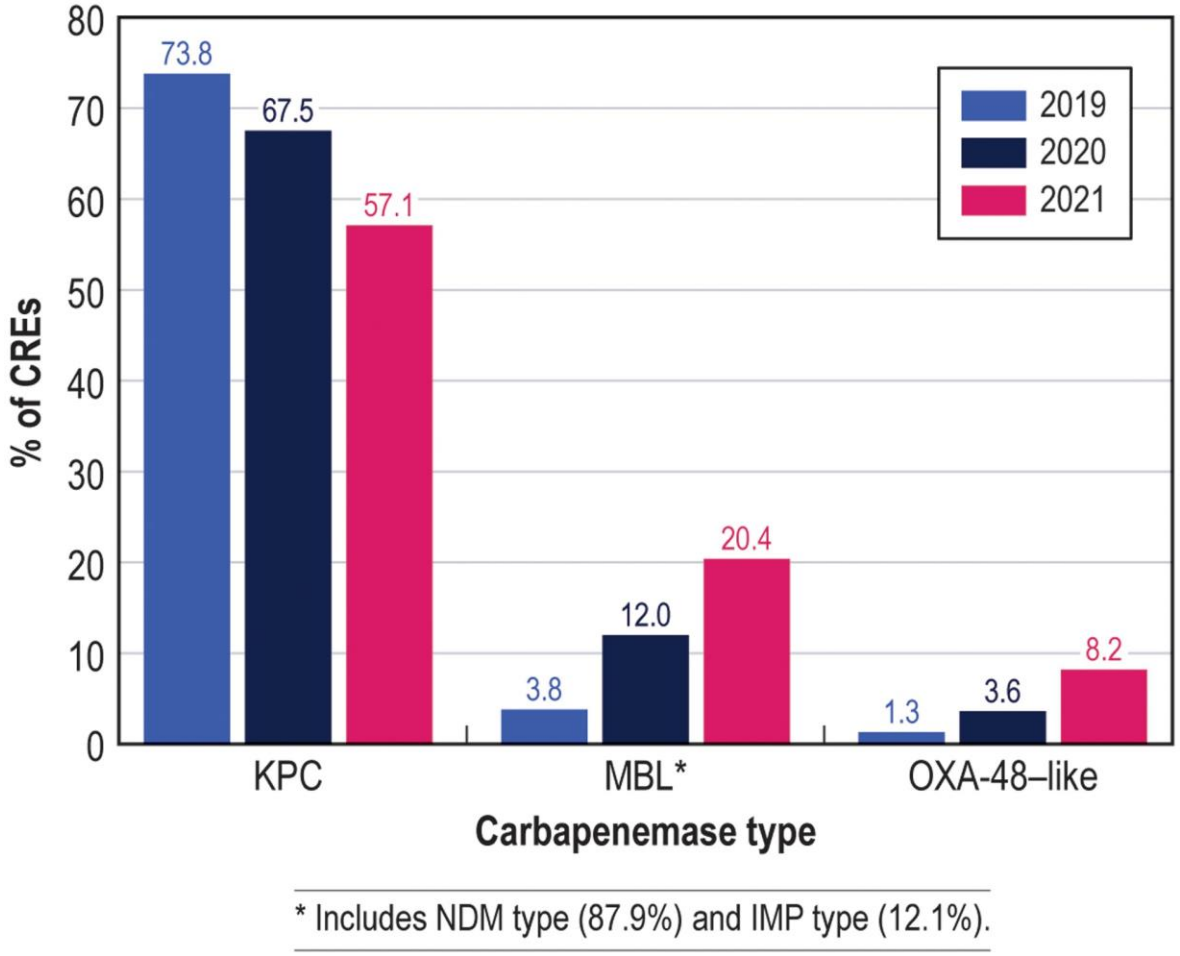




2023 Antibacterial agents in clinical and preclinical development: an overview and analysis. Geneva: WHO; 2024.

Changing Carbapenemase Epidemiology

Carbapenemase trends in the US from 2019 to 2021



CRE=carbapenem-resistant Enterobacterales; MBL=metallo-β-lactamase; OXA=oxacillinase; NDM=New Delhi MBL; IMP=imipenemase

Sader HS, et al. *Open Forum Infect Dis*. 2023;10(2):ofad046.

CRE Activity of Novel β-Lactams

Antibiotic	Class	KPC	MBL	OXA-48
Cefiderocol	Siderophore cephalosporin	Yes	Yes	Yes
Ceftazidime-avibactam	3rd generation cephalosporin, DBO β-lactamase inhibitor	Yes	No	Yes
Ceftazidime-avibactam + aztreonam	3rd generation cephalosporin, DBO β-lactamase inhibitor, monobactam		Yes	
Imipenem-cilastatin-relebactam	Carbapenem, degradation inhibitor, DBO β-lactamase inhibitor	Yes	No	No
Meropenem-vaborbactam	Carbapenem, boronate β-lactamase inhibitor	Yes	No	No

DBO=diazabicyclooctane

Tamma PD, et al. *Clin Infect Dis*. 2024.
2023 Antibacterial agents in clinical and preclinical development: an overview and analysis. Geneva: WHO; 2024.

CRE Testing and Reporting

Carbapenemase	CAZ-AVI	IMI-REL	MEM-VAB	Other
KPC alone	Test and report	Test and report	Test and report	
OXA-48 alone	Test and report	Suppress or report as R or do not test	Suppress or report as R or do not test	
KPC + OXA-48	Test and report	Suppress or report as R or do not test	Suppress or report as R or do not test	
MBL ± serine β-lactamase	Suppress or report as R or do not test	Suppress or report as R or do not test	Suppress or report as R or do not test	Test and report cefiderocol or CAZ-AVI + aztreonam
Carbapenem-R but negative for carbapenemases	Test and report	Test and report	Test and report	

CAZ-AVI=ceftazidime-avibactam; IMI-REL=imipenem-cilastatin-relebactam; MEM-VAB=meropenem-vaborbactam; R=resistant

Tamma PD, et al. *Clin Infect Dis*. 2024.
CLSI. *Performance Standards for Antimicrobial Susceptibility Testing*. 34th ed. CLSI supplement M100. CLSI, USA 2024.
Narayanan N, et al. Breaking Bad Bacteria: Mastering the 2024 CLSI M100 Updates Together. https://sidp.mapleIms.com/mod/resource/view.php?id=996.

Ceftazidime-Avibactam + Aztreonam

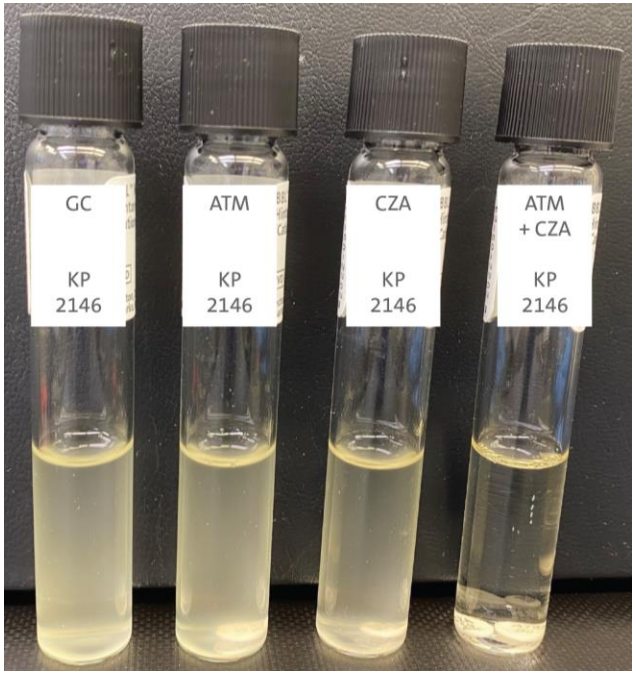
CDC's Antimicrobial Resistance Laboratory Network Expanded AST Program

- Digital printer creates custom AST panels for aztreonam-avibactam MIC testing

Southeast: Tennessee Public Health Laboratory | ARLN.health@tn.gov
Mid-Atlantic: Maryland Public Health Laboratory | MDPHL.arln@maryland.gov
Northeast: Wadsworth Center Labs | ARLNcoreNY@health.ny.gov

Broth Disk Elution Method

- Uses disks as source of antimicrobials for broth dilution testing



MIC=minimum inhibitory concentration; GC=growth control; ATM=aztreonam; KP 2146 = *K. pneumoniae* ATCC® BAA-2146™

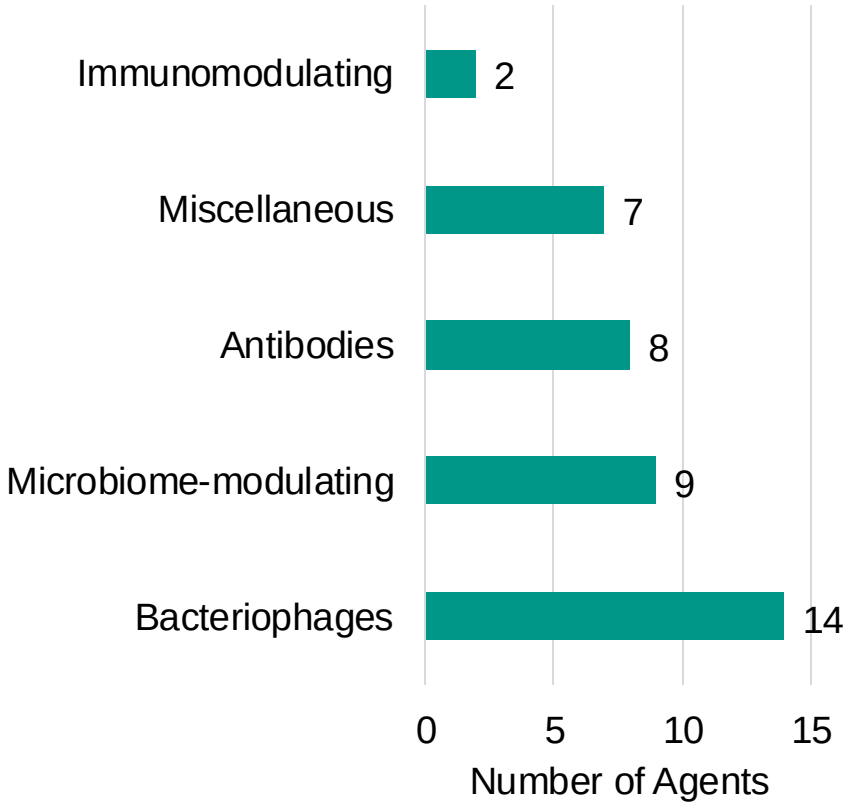
CDC. Antimicrobial Resistance Laboratory Network Testing. https://www.cdc.gov/antimicrobial-resistance-laboratory-networks/php/about/testing-services.html.
CLSI. *Performance Standards for Antimicrobial Susceptibility Testing*. 34th ed. CLSI supplement M100. CLSI, USA 2024.

Non-Traditional Antibacterial Agents

Approved Agents

Agent	Approval	Administration	Indication
SER-109 (Vowst™ fecal microbiota spores, live-brpk)	US FDA	Oral capsules	Prevention of rCDI after antibacterial treatment for rCDI
RBX2660 (Rebyota® fecal microbiota, live-jslm)	US FDA	Suspension delivered by enema	
BB128 (Biomictra™ faecal microbiota)	Australia TGA	Suspension delivered by endoscopy or enema	Restoration of gut microbiota in rCDI

Agents in the Clinical Pipeline



FDA=Food and Drug Administration; TGA=Therapeutic Goods Administration; rCDI=recurrent *Clostridioides difficile* infection

2023 Antibacterial agents in clinical and preclinical development: an overview and analysis. Geneva: WHO; 2024.

Conclusion

- ASPs use a multidisciplinary approach to optimize antimicrobials, maximize patient outcomes, and decrease antimicrobial resistance
- Clinical microbiologists are essential members of ASP
- Novel antibacterials must be used judiciously
- There is a critical need for innovative antibacterial agents

From Bench to Bedside: Understanding Antimicrobial Stewardship, Reporting, and Resistance

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Northeast Association for Clinical Microbiology and Infectious Disease
37th Annual Meeting

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