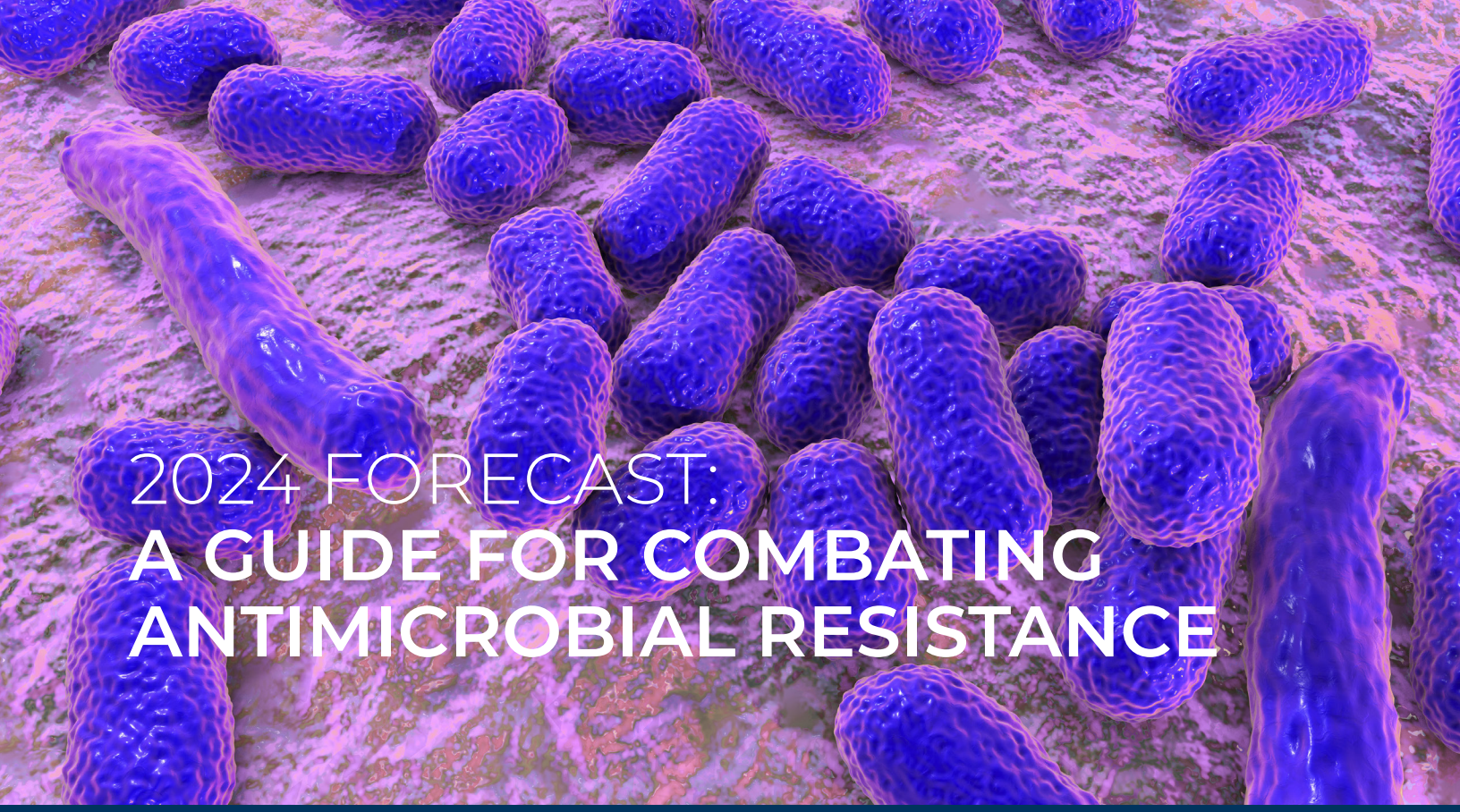

2024 FORECAST: A GUIDE FOR COMBATING ANTIMICROBIAL RESISTANCE

New Antimicrobials: What you need to know

When new antimicrobials come to market, microbiology lab personnel need to know when these drugs might be used and when resistance to the drug might be expected. Several new antimicrobials have come to market recently and this document will help labs sort through these important issues.

For some MDRO infections, like CRE-NDM infections, there are few treatment options. Especially for these infections, it is important to get a preview of what therapies are in the development pipeline. This document highlights how some old drugs are used in new ways. With increasing frequency, ESßL-producing Enterobacterales (formerly Enterobacteriaceae) are causes of community-associated urinary tract infections (UTI). These infections may need treatment with drugs that were rarely used for outpatient UTI treatment, (e.g., ertapenem).

Beckman Coulter is committed to partnering with healthcare professionals to combat antimicrobial resistance. We can best address this growing global-health crisis together.

In that spirit, we updated our previous forecast of antimicrobial-resistance profiles and combination-therapy options to advance new considerations for treating evolving infections. We hope this guide supports your efforts as you explore new agents to fight multidrug-resistant organisms.

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New Antimicrobials: What you need to know

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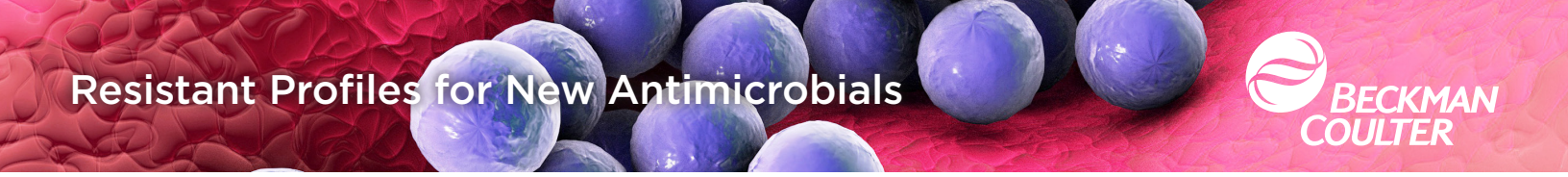
Hard-to-treat Bacterial Infections	Recently Approved Antimicrobials or Recent Recommendations*	Promising Antimicrobials in Late-phase Development	What else do you need to know?
URINARY TRACT INFECTIONS CAUSED BY:			
ESßL-producing Enterobacterales†	These drugs are not new, but were uncommonly used for UTI treatment: Uncomplicated UTI: › Oral Fosfomycin (*E. coli* only) Complicated UTI: › Ertapenem › Imipenem › Meropenem	› Tebipenem › Sulopenem › Cefepime-enmetazobactam	With increasing frequency, UTIs caused by ESßL-producing Enterobacterales are seen in outpatients with no previous healthcare exposures. Including drugs that are active against ESßL-producing bacteria on a UTI AST panel will be important. New drugs like ceftolozane-tazobactam, ceftazidime-avibactam, meropenem-vaborbactam, and imipenem-relebactam may be active for these infections, but these drugs may be reserved for serious infections with limited treatment options.
SERIOUS INFECTIONS CAUSED BY:			
MRSA	› Eravacycline › Omadacycline › Lefamulin	› Ceftobiprole › Contezolid › Gepotidacin	See Resistant Profile table for more information.
VRE	› Eravacycline › Omadacycline	› Contezolid	CLSI revised daptomycin breakpoints in 2019 to account for high-dose daptomycin treatment of VR-*E. faecium* infections. *E. faecium* are the most common VRE species.
CRE-KPC (most common class A carbapenemase)	› Ceftazidime-avibactam › Meropenem-vaborbactam › Imipenem-relebactam › Plazomycin	› Cefepime-taniborbactam › Aztreonam-avibactam	N/A
CRE-OXA 48-like carbapenemase (most common class D carbapenemase)	› Ceftazidime-avibactam › Imipenem-relebactam › Plazomycin › Cefiderocol	› Cefepime-taniborbactam › Aztreonam-avibactam	N/A
CRE-NDM (most common class B carbapenemase)	› Plazomycin‡ › Cefiderocol	› Cefepime-taniborbactam › Aztreonam-avibactam	‡With increasing frequency, CRE-NDM isolates also carry a 16S rRNA methylase which confers resistance to all aminoglycosides including plazomycin.
CR-*Pseudomonas aeruginosa*	› Ceftolozane-tazobactam › Cefiderocol	› Cefepime-taniborbactam	Most CR-*P. aeruginosa* do not produce a carbapenemase, but with increasing frequency VIM-producing CR-*P. aeruginosa* are causes of outbreaks in healthcare facilities. VIM is a class B carbapenemase and, like NDM, is not inhibited by most ß-lactamase inhibitors.
CR-*Acinetobacter* spp.	› Cefiderocol › Sulbactam-durlobactam		Minocycline may be active.

*See treatment guidelines for recommended use of antimicrobials by infection type.

†The term Enterobacterales is used instead of Enterobacteriaceae because this new name was adopted by both CLSI (2020 documents) and EUCAST.



Resistant Profiles for New Antimicrobials

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Antimicrobial	Target Organisms	Resistance	Other comments
Cefepime-taniborbactam	› Enterobacterales › *Pseudomonas aeruginosa*	Resistance may occur through multiple mechanisms, including expression of IMP, some alterations in PBP3, and permeability (porin) changes.	N/A
Cefiderocol	› Enterobacterales › *Pseudomonas aeruginosa* › *Acinetobacter* spp.	Isolates with NDM carbapenemases and PER ESßLs can test resistant, but the enzyme alone is not sufficient for resistance. Other factors likely contribute to the elevated cefiderocol MIC.	The PER ESßL is relatively uncommon. It is found in *P. aeruginosa* and *Acinetobacter* spp.
Ceftazidime-avibactam§	› Enterobacterales	Mutations can occur in the KPC gene that confer resistance to ceftazidime-avibactam.	Ceftazidime-avibactam is not active against Gram-negative bacteria producing class B carbapenemases. These are the metallo-ß-lactamases like NDM, IMP, and VIM.
Delafloxacin	› Enterobacterales › *Pseudomonas aeruginosa*	Like other fluoroquinolones, delafloxacin resistance is common among Gram-negative bacteria.	N/A
	› *Staphylococcus spp.* › *Streptococcus spp.* › *Enterococcus spp.*	Requires double mutations in both *gyrA* and *parC* for resistance. The other fluoroquinolones are resistant after one mutation in each gene.	Because the number of mutations required for resistance differs among fluoroquinolones, isolates may test resistant to drugs like ciprofloxacin and levofloxacin but test susceptible to delafloxacin.
Eravacycline§	› Enterobacterales › *Staphylococcus aureus* › *Enterococcus* spp. › *Streptococcus anginosus* group	Resistance to eravacycline occurs in isolates of Enterobacterales, *S. aureus* and *Enterococcus* spp.	Cross-resistance occurs between tigecycline and eravacycline in Enterobacterales, *Staphylococcus* and *Enterococcus*.
Imipenem-relebactam	› Enterobacterales	Imipenem-relebactam is most active against CRE with class A enzymes (e.g., KPC).	Imipenem-relebactam has reduced activity for isolates producing class D carbapenemases (e.g., OXA-48 like), and CRE producing class B carbapenemases (e.g., NDM, IMP, and VIM).
Lefamulin	› *Staphylococcus aureus* (methicillin-susceptible isolates) › *Streptococcus pneumoniae*	Resistance to lefamulin occurs in Gram-positive bacteria but is uncommon and more likely to occur in isolates of animal origin than isolates of human origin.	N/A
Meropenem-vaborbactam§	› Enterobacterales	Meropenem-vaborbactam is active against CRE producing class A carbapenemases like KPC. No resistance reported.	Meropenem-vaborbactam is not active against CRE producing class D (e.g., OXA-48-like) or class B (e.g., NDM, IMP and VIM) carbapenemases.
Omadacycline	› Enterobacterales › *Staphylococcus spp.* › *Enterococcus spp.* › *Streptococcus spp.*	Some, but not all, mechanisms of tetracycline resistance can also confer resistance to omadacycline.	Tetracycline-resistant Gram-positive isolates can test susceptible to omadacycline. Tetracycline-resistant Enterbacterales are more likely to test resistant to omadacycline.
Plazomycin	› Enterobacterales	Resistance occurs in isolates carrying plasmid-mediated genes encoding 16S methylases. These genes also confer resistance to all aminoglycosides.	The 16S methylase genes are most commonly found in CRE-NDM isolates and only rarely in other types of CRE.
Sulbactam-durlobactam	› *Acinetobacter* spp.	Increased expression of TEM-1, ADC-30, and metallo-ß-lactamases can cause resistance in *Acinetobacter* species	N/A

§Drugs on MicroScan panels.

Acronyms

ESßL	Extended-spectrum ß-lactamase	**NDM**	New Delhi Metallo-ß-lactamase
CR	Carbapenem-resistant	**OXA**	Oxacillinase
CRE	Carbapenem-resistant Enterobacterales	**PER**	*Pseudomonas* extended resistance
CRPA	Carbapenem-resistant *Pseudomonas aeruginosa*	**UTI**	Urinary tract infection
KPC	*Klebsiella pneumoniae* carbapenemase	**VIM**	Verona Integron-Borne Metallo-ß-lactamase
MDRO	Multidrug-resistant organism	**VRE**	Vancomycin-resistant *Enterococcus*
MRSA	Methicillin-resistant *Staphylococcus aureus*		

Acquired Carbapenemases in Enterobacterales

Molecular Class	Example Types	Activity
A	**KPCs** Also others, but not common	Largest number, usually on plasmid, most inactivated by clavulanic acid
B	**NDM, VIM, IMP** Enterobacterales, *P. aeruginosa*, *Acinetobacter*	Metallo ß-lactamases (MBL): Resistant to many drugs, including carbapenems › Enzyme does not hydrolyze aztreonam › May require zinc for expression
C	—	None here
D	**OXA enzymes**	***K. pneumoniae* (OXA-48)** OXA-23, -40, -51, -58 in *Acinetobacter* Others in *Pseudomonas* and other non-Enterobacterales

References & Resources

Breakpoints (i.e., Interpretive Criteria)

CLSI M100: https://clsi.org/standards/products/free-resources/access-our-free-resources/

EUCAST Clinical Breakpoints: https://www.eucast.org/fileadmin/src/media/PDFs/EUCAST_files/Breakpoint_tables/v_13.0_Breakpoint_Tables.pdf

FDA Antibacterial Susceptibility Test Interpretive Criteria: https://www.fda.gov/drugs/development-resources/antibacterial-susceptibility-test-interpretive-criteria

Antimicrobial Developmental Pipeline

The Antibiotic Pipeline: https://www.pewtrusts.org/en/research-and-analysis/data-visualizations/2014/antibiotics-currently-in-clinical-development

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