BECKMAN COULTER

2025 FORECAST

A Guide for Combating Antimicrobial Resistance

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. This document will help labs sort through these important issues.

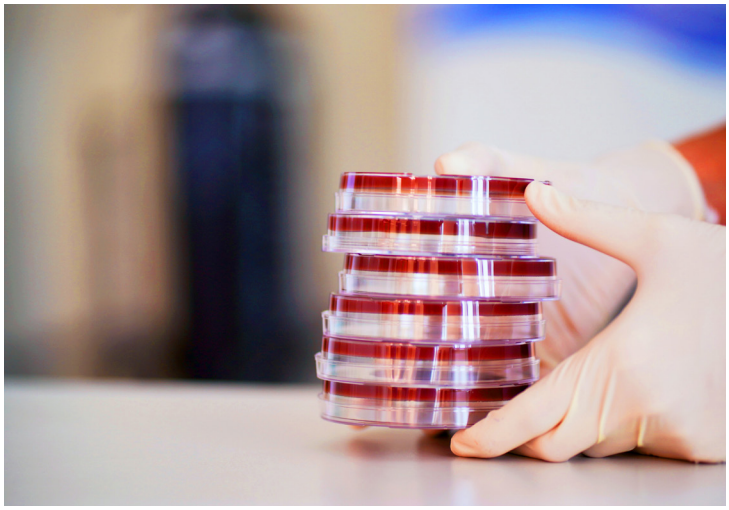
According to recent data published in the Lancet[1], antimicrobial resistance is a global public health threat that is forecasted to increase deaths associated with or attributable to AMR by 67% and 69.6%, respectively, by the year 2050. Global changes like the COVID pandemic are impacting this threat. Although rates of AMR infections decreased slightly during the COVID pandemic, this is believed to be a temporary dip caused by restrictions in travel and a reduction in antimicrobial prescribing in high income countries. These travel restrictions are gone and the World Health Organization warns that regional increases in COVID infections may drive unnecessary antimicrobial use when diagnostics are not available or not used.[2]

Diagnostics have the potential to significantly impact antimicrobial use. The CDC identified high rates of inappropriate antimicrobial use for community-associated infections and urinary tract infections.[3] For each of these, the limited use of diagnostics and the unavailability of effective diagnostics are a significant contributor to the problem.

Compounding this era of increasing AMR, microbiology laboratories are often challenged with insufficient staff to perform testing and interpret complex results. Tests that are faster, accurate, updated, and automated are essential for meeting our growing AMR threat. This is especially true for culture, identification, and antimicrobial susceptibility tests—the most important tests for picking the right antimicrobial agent.

New drugs are coming to market, and two notables are cefepime-enmetazobactam and aztreonam-avibactam. Both drugs are beta-lactam/beta-lactamase inhibitor combinations. Most drugs in the WHO pipeline fall into this class of traditional antimicrobial.[4]

Cefepime-enmetazobactam was compared to piperacillin-tazobactam in a clinical trial for treatment of complicated UTI and pyelonephritis.[5] Cefepime-enmetazobactam demonstrated a 20% improvement in efficacy for primary complicated UTI (79.1% vs. 58.9%). Aztreonam-avibactam is approved by EMEA for use in the European Union (EU) and FDA approval is expected in 2025. This is a drug that is active for most MDRO Enterobacterales isolates including metallo-beta-lactamase producing isolates. Resistance does occur, but it is uncommon. This will be an important drug in an era of increasing antimicrobial infections.



New Antimicrobials: What You Need to Know

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 › Cefepime-enmetazobactam	› Tebipenem › Sulopenem	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, imipenem-relebactam, and cefepime-enmetazobactam 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 Resistance 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	› Ceftazidime-avibactam › Meropenem-vaborbactam › Imipenem-relebactam › Plazomycin › Aztreonam-avibactam (EU)	› Cefepime-taniborbactam › Aztreonam-avibactam (USA)	The most common class A carbapenemase
CRE-OXA 48-like carbapenemase	› Ceftazidime-avibactam › Imipenem-relebactam › Plazomycin › Cefiderocol › Aztreonam-avibactam (EU)	› Cefepime-taniborbactam › Aztreonam-avibactam (USA)	The most common class D carbapenemase
CRE-NDM	› Plazomycin‡ › Cefiderocol › Aztreonam-avibactam (EU)	› Cefepime-taniborbactam › Aztreonam-avibactam (USA)	The most common class B carbapenemase. With increasing frequency, CRE-NDM isolates also carry a 16S rRNA methylase that confers resistance to all aminoglycosides including plazomicin.
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

Antimicrobial	Target Organisms	Resistance	Other Comments
Aztreonam-avibactam (EU)	› Enterobacterales	Resistance rates are very low. Resistance can occur if a beta-lactamase enzyme is not inhibited by avibactam or by decreased permeability of the outer membrane or increased efflux activity.	N/A
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
Cefepime-enmetazobactam	› Enterobacterales › *Pseudomonas aeruginosa*	Resistance to this drug is common among isolates that produce a carbapenemases or isolates that carry multiple beta-lactamase enzymes. Permeability changes and efflux-mediate resistance can also result in resistance.	N/A
Cefiderocol	› Enterobacterales › *Pseudomonas aeruginosa* › *Acinetobacter* spp.	Isolates with NDM carbapenemases and PER ESBLs 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-β-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*	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*.
	› *Staphylococcus aureus* › *Enterococcus* spp. › *Streptococcus anginosus* group		
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).

§Drugs on MicroScan panels.

Resistant Profiles for New Antimicrobials

Antimicrobial	Target Organisms	Resistance	Other Comments
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

New Recommendations for the Detection of Resistance Mechanisms

Authority	Recommendation
Clinical and Laboratory Standards Institute, M100[7]	*"Enterobacterales that harbor OXA-48-family enzymes may test susceptible to meropenem-vaborbactam but may not respond to this therapy in vivo. If OXA-48 is detected, suppress or report as resistant"* *"Cefepime S/SDD results should be suppressed or reported as R for isolates that demonstrate carbapenemase production".*
Infectious Disease Society of America (IDSA)[8]	IDSA Guidelines for treatment of antimicrobial resistant infections includes recommendations for knowing beta-lactamase-mediated mechanisms in order to choose an active therapeutic agents (IDSA 2024 Guidance on the Treatment of Antimicrobial Resistant Gram-Negative Infections (idsociety.org)).

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Surveillance Data for Resistance Profiles

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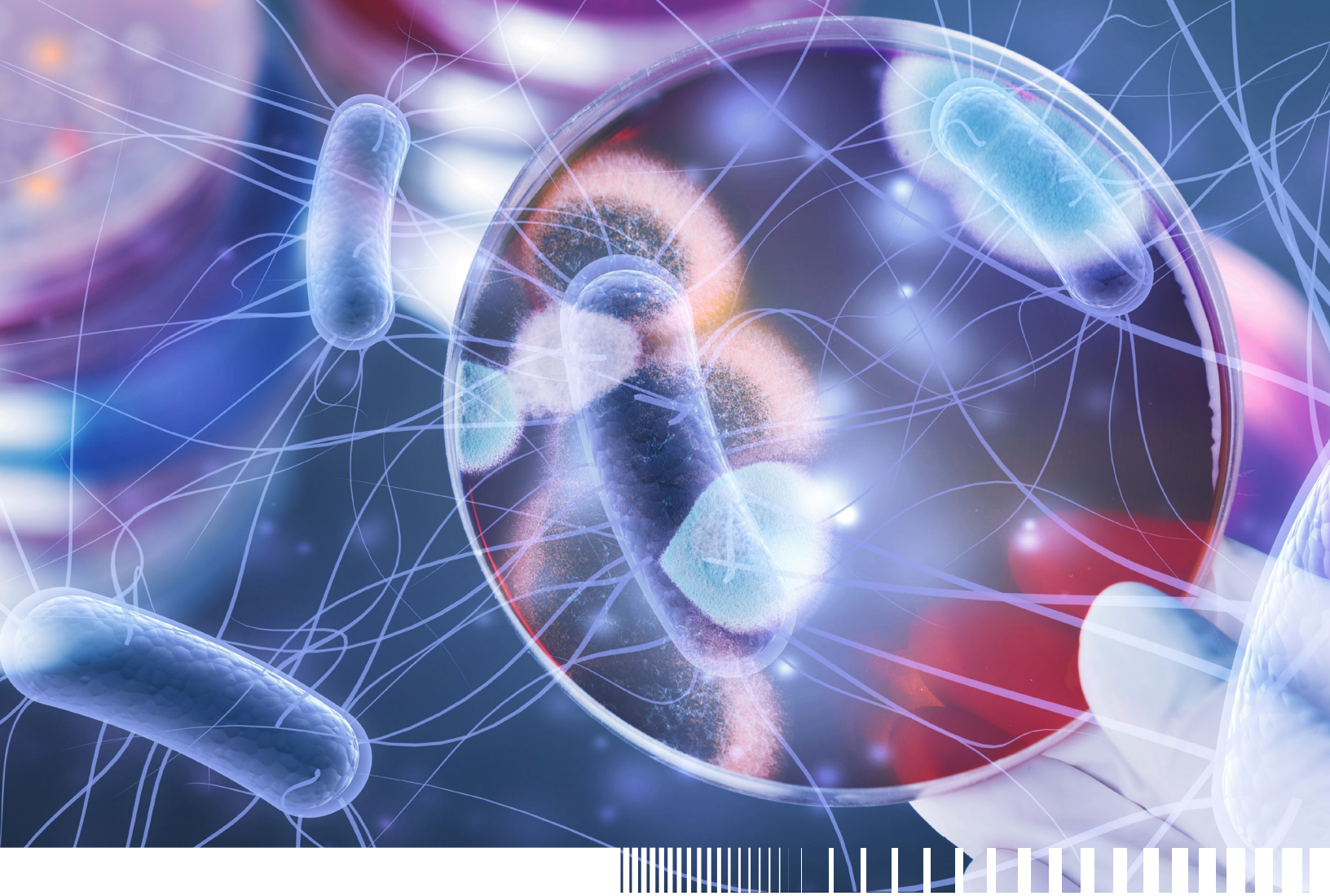

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