

Antimicrobial Resistance Series | Part 1 of 3

Mechanisms of Carbapenem Resistance in Gram-Negative Pathogens

CARBAPENEM-RESISTANT GRAM-NEGATIVE BACTERIAL PATHOGENS — A CONTINUED CRITICAL PRIORITY

- Carbapenem-resistant Gram-negative infections represent a persistent and significant global and domestic health threat, and continue to be featured on the WHO Priority Pathogens List and in the CDC Antibiotic Resistance Threats Report^{1,2}
- These pathogens represent critical priorities based on their:^{1,2}
 - Opportunistic predilection for at-risk individuals
 - Rapid colonization and nosocomial spread
 - Association with high morbidity and mortality
 - Rapid development of resistance through multiple mechanisms
 - Limited availability of treatment options

Carbapenem-resistant Gram-negative organisms on the WHO Bacterial Priority Pathogens List, 2024¹

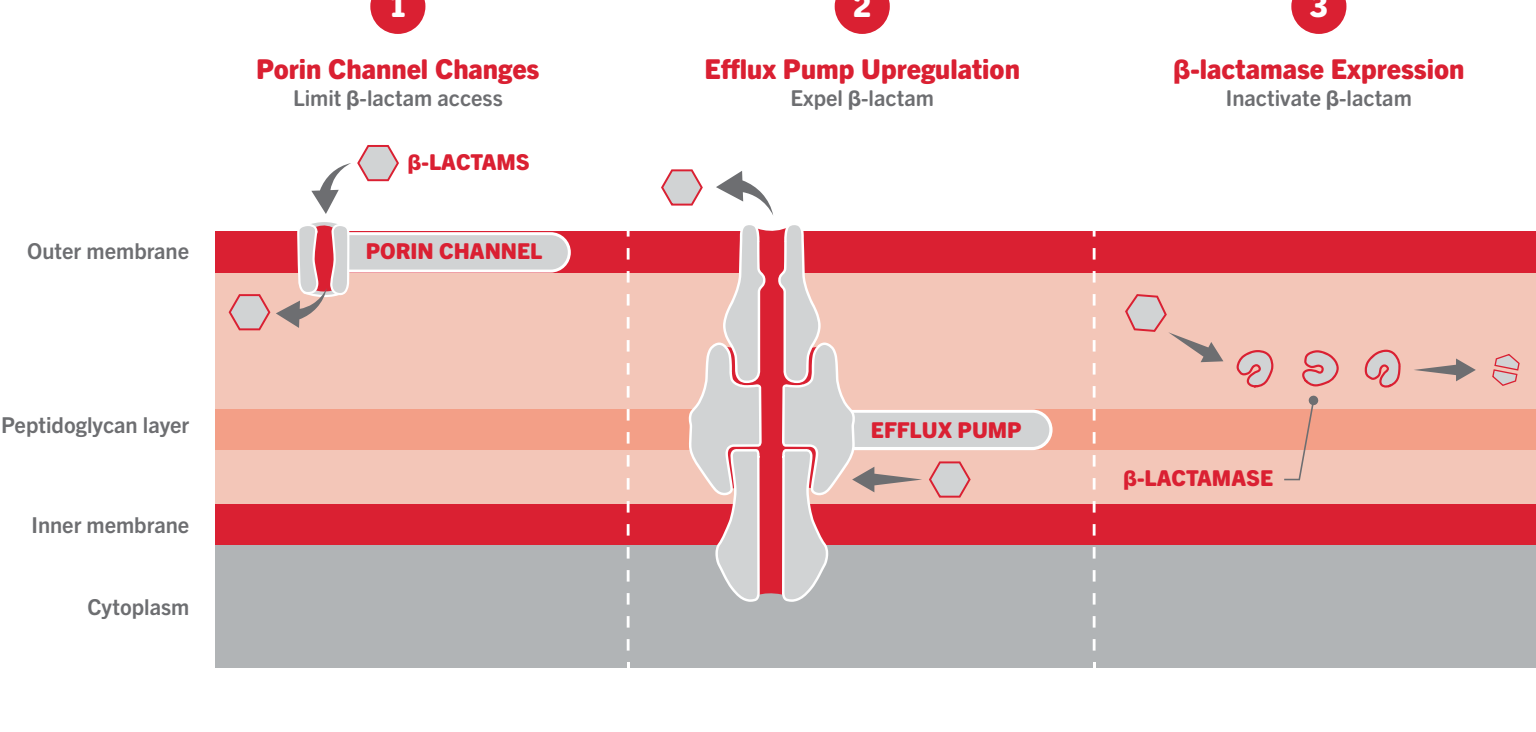
Critical Group	High Group
 Enterobacteriales carbapenem-resistant	 <i>Pseudomonas aeruginosa</i> carbapenem-resistant
 <i>Acinetobacter baumannii</i> carbapenem-resistant	

Carbapenem-resistant Gram-negative organisms in the CDC Antibiotic Resistance Threats Report, 2019²

Urgent Threats	Serious Threats
 Carbapenem-resistant Enterobacteriaceae	 Multidrug-resistant <i>Pseudomonas aeruginosa</i>
 <i>Acinetobacter</i>	

MECHANISMS OF CARBAPENEM RESISTANCE

- There are three primary mechanisms by which carbapenem resistance occurs in Gram-negative pathogens: **porin channel loss**, **active drug efflux**, and **enzymatic hydrolysis**^{3,4}
- Carbapenem resistance is rarely driven by a single mechanism; when pathogens exploit multiple mechanisms simultaneously, this can result in pan-drug-resistant phenotypes with severely limited treatment options^{3,4}



- 1

Porin channel loss / downregulation
 - Deletion, downregulation, or structural mutation of outer membrane porin channels reduces β -lactam penetration^{3,4}
 - Often acts synergistically with β -lactamase expression^{3,4}
 - Examples: OprD deletion (*Pseudomonas aeruginosa*), OmpK35/OmpK36 alteration (Enterobacteriales), CarO alteration (*Acinetobacter baumannii*)⁵⁻⁹
- 2

Efflux pump upregulation
 - Overexpression of efflux pumps actively expels β -lactams before they reach their target (i.e., penicillin-binding proteins)^{3,4}
 - Confers resistance to multiple classes of antibacterials⁴
 - Examples: MexAB-OprM and MexCD-OprJ (*P. aeruginosa*), AcrAB-TolC (Enterobacteriales), AdeABC (*A. baumannii*), SmeABC and SmeDEF (*Stenotrophomonas maltophilia*)⁵⁻¹⁰
- 3

β -lactamase & carbapenemase expression
 - β -lactamases hydrolyze the β -lactam ring of β -lactam antibacterials (e.g., penicillin, cephalosporins, carbapenems, monobactams), rendering them ineffective⁴
 - β -lactamases can have different substrate specificities (e.g., penicillinases, cephalosporinases, ESBLs, carbapenemases)⁴
 - Carbapenemases are a subset of β -lactamases with the ability to hydrolyze carbapenems, typically alongside other β -lactams, thereby substantially limiting β -lactam treatment options⁴
 - Overproduction of certain non-carbapenemases, such as AmpC, can also contribute to carbapenem resistance⁴
 - Examples of carbapenemases: KPC, GES, NDM, VIM, IMP^{5,6,10-13}

DIFFERENT β -LACTAMASE CATEGORIES

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- The Ambler classification system categorizes β -lactamase enzymes into 4 groups (i.e., A, B, C, D) based on:^{4,14}
 - The central catalytic domain (serine or zinc)
 - Substrate preference
 - Carbapenemases are found in Classes A, B, and D; Class C includes cephalosporinases, some of which have weak hydrolytic activity against carbapenems (e.g., AmpC when overexpressed can contribute to carbapenem resistance)^{4,14}
 - ~7300 β -lactamase genes have been identified as of 2025¹⁵
 - The genes may be chromosomally encoded or acquired via horizontal transfer of mobile genetic elements⁶

Ambler Classification of β -lactamases^{4,5}

Class	Characteristic active site	Example carbapenemases	Example non-carbapenemases
A	Serine	KPC, SME, GES	TEM, SHV, CTX-M
B	Metallo (Zn ²⁺)	IMP, NDM, VIM	--
C	Serine	--	AmpC, CMY, GC1, DHA, FOX
D	Serine	OXA-48-like, OXA-23-like	OXA-1, OXA-2, OXA-9, OXA-10

CARBAPENEM RESISTANCE: RARELY ONE MECHANISM ACTING ALONE

- Carbapenem resistance mechanisms rarely act in isolation—porin channel loss, efflux pump upregulation, and β -lactamase/carbapenemase expression frequently co-occur within a single isolate, with additive or synergistic effects^{3,4}
- These carbapenem resistance mechanisms alter the in vitro activity of agents against isolates and can also lead to MDR, XDR, and DTR phenotypes, each representing a phenotype with progressively more limited treatment options^{16,17}

Awareness of the in vitro activity profiles of available agents against carbapenem-resistant Gram-negative pathogens expressing different resistance mechanisms can help inform clinical decision-making

See Parts 2 and 3 for more information

AmpC=ampicillin chromosomal cephalosporinase; CDC=Centers for Disease Control and Prevention; CMY=cephamycin-hydrolyzing β -lactamase; CTX-M=cefotaxime-hydrolyzing β -lactamase—Munich; DHA= β -lactamase named after Dhahran Hospital, Saudi Arabia; DTR=difficult-to-treat resistance; ESBL=extended-spectrum β -lactamase; FOX=plasmid-mediated class C β -lactamase; GC1=Global Clone 1; GES=Guiana extended-spectrum β -lactamase; IMP=imipenemase; KPC=*Klebsiella pneumoniae* carbapenemase; MDR=multidrug-resistant; NDM=New Delhi metallo- β -lactamase; OXA=oxacillinase; SHV=sulthidryl variant of the TEM enzyme; SME=*Serratia marcescens* enzyme; TEM=Temoneira class A extended-spectrum β -lactamase; VIM=Verona integron-encoded metallo- β -lactamase; WHO=World Health Organization; XDR=extensively drug-resistant.

References
1. WHO. WHO bacterial priority pathogens list, 2024. <https://iris.who.int/server/api/core/bitstreams/1a41ef7e-dd24-4ce6-a9a6-1573562e7f37/content>. Accessed June 3, 2026. 2. CDC. Antibiotic resistance threats in the United States, 2019. <https://www.cdc.gov/antimicrobial-resistance/media/pdfs/2019-ar-threats-report-508.pdf>. Accessed June 3, 2026. 3. Fernández L, Hancock REW. *Clin Microbiol Rev*. 2012;25(4):661-681. 4. Bush K. *Antimicrob Agents Chemother*. 2018;62:e01076-18. 5. Glen KA, Lamont IL. *Pathogens*. 2021;10:1638. 6. Ruppé E, et al. *Ann Intensive Care*. 2015;5:21. 7. Kakoullis L, et al. *Antibiotics*. 2021;10:415. 8. Suay-García B, Pérez-Gracia MT. *Antibiotics*. 2019;8:122. 9. Nguyen M, Joshi SG. *J Appl Microbiol*. 2021;131:2715-2738. 10. Lister PD, et al. *Clin Microbiol Rev*. 2009;22:582-610. 11. Zhao W-H, Hu Z-Q. *Crit Rev Microbiol*. 2010;36(3):245-258. 12. van Duin D, Doi Y. *Virulence*. 2017;8(4):379-382. 13. Breijyeh Z, et al. *Molecules*. 2020;25:1340. 14. Nordmann P, Poirel L. *Clin Infect Dis*. 2019;69(suppl7):S521-S528. 15. Mlynarcik P, et al. *Antibiotics (Basel)*. 2025;14(11):1174. 16. Magiorakos AP, et al. *Clin Microbiol Infect*. 2012;18(3):268-281. 17. Kadri SS, et al. *Clin Infect Dis*. 2018;67(12):1803-1814.