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Editorial

IDSA 2026 Guidance on the Treatment of Gram-Negative Infections: What Is New and What Should Change at the Bedside?

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1. Introduction

In 2019, bacterial antimicrobial resistance was associated with 4.95 million deaths worldwide, and forecasts indicate that the burden attributable to multidrug-resistant (MDR) Gram-negative bacteria will keep growing [1,2]. Resistance mechanisms do not stand still, and neither does their epidemiology. Diagnostics and therapeutic options have improved as well, so the management of these infections is changing quickly [3].

Recommendations now need revising whenever a drug is approved, a new mechanism emerges, breakpoints move or a comparative study is published. Many questions remain open.

A list of active drugs is not enough to deal with this. Clinicians need a framework, updated over time, that brings together microbiology read against current breakpoints (at least from a US perspective) [4], the clinical syndrome and its severity, source control, the resistance mechanism and pharmacokinetic/pharmacodynamic (PK/PD) principles. The 2026 guidance of the Infectious Diseases Society of America (IDSA) on Gram-negative infections goes a long way towards achieving such a framework [5].

As in the 2024 version, the document covers six resistance phenotypes: extended-spectrum β-lactamase-producing *Enterobacterales* (ESBL-E), AmpC β-lactamase-producing *Enterobacterales* (AmpC-E), carbapenem-resistant *Enterobacterales* (CRE), *Pseudomonas aeruginosa* with difficult-to-treat resistance (DTR *P. aeruginosa*), carbapenem-resistant *Acinetobacter baumannii* complex (CRAB) and *Stenotrophomonas maltophilia* [5]. In this editorial we summarize what has changed and discuss where the new recommendations are based on a solid foundation and where the evidence is thinner.

2. General Changes and ESBL-Producing *Enterobacterales*

Three general changes stand out compared with 2024. The first concerns urinary tract infection (UTI): the guidance now separates infection limited to the lower tract from invasive infection, in line with the IDSA definitions of complicated UTI [6]. Uncomplicated UTI (uUTI) is an infection confined to the bladder in an afebrile patient. Complicated UTI (cUTI) is any infection that extends beyond the bladder, including pyelonephritis, febrile or bacteremic UTI, catheter-associated UTI and prostatitis.

The second change is that the choice of therapy for MDR organisms increasingly depends on the resistance mechanism detected. The third is a more candid handling of un-

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certainty. Several recommendations, notably those for *S. maltophilia*, are based on microbiological, PK/PD and animal data rather than on human studies comparing clinical outcomes.

The ESBL-E section opens with a new operational definition. For *Escherichia coli*, *Klebsiella pneumoniae* and *Klebsiella oxytoca*, ESBL production is presumed when the ceftriaxone minimum inhibitory concentration (MIC) is ≥4 µg/mL, a cut-off that recent work found more specific than lower thresholds [7]. Ceftriaxone non-susceptibility remains an imperfect surrogate, though. It can result from mechanisms other than ESBLs, and some uncommon ESBLs escape a purely phenotypic screen. Rapid molecular tests or validated phenotypic β-lactamase assays are still worth using when available.

The list of preferred agents for ESBL-E uUTI is now longer: a single aminoglycoside dose, gepotidacin, nitrofurantoin, pivmecillinam, oral sulopenem and trimethoprim–sulfamethoxazole (TMP-SMX). Gepotidacin, a first-in-class oral topoisomerase inhibitor, is backed by two phase 3 trials [8]. Pivmecillinam is a narrow-spectrum oral β-lactam that Europe has used for decades, and it usually exhibits good activity against ESBL-producing urinary isolates [9,10]. Sulopenem etzadroxil–probenecid offers an oral thiopenem, but we should use it with care, since the use of carbapenem-class drugs in the community is a real stewardship concern [11].

Gepotidacin, nitrofurantoin, pivmecillinam and TMP-SMX could cut the use of fluoroquinolones and intravenous carbapenems, provided they stay where they belong, in cystitis. Pyelonephritis, bacteremia and other invasive infections are a different matter: neither the evidence nor the drug exposure at the site of infection supports them there.

In cUTI, piperacillin–tazobactam may be considered for patients who are not critically ill and not bacteremic, while carbapenems remain preferred for severe infection due to ESBL-E. This is consistent with the direction of the mortality signal in the MERINO trial and with long-standing concerns about the inoculum effect, β-lactamase burden and unreliable MIC testing in the presence of enzymes such as OXA-1 [12]. Cefepime–enmetazobactam looks promising, and the guidance rightly points out that it has never been compared with carbapenems in clinical studies [5].

Intravenous fosfomycin is listed as an alternative, especially for *E. coli* [5], but the trials disagree. ZEUS reported high cure rates, whereas FOREST did not demonstrate non-inferiority to its comparator regimen [13,14]. The high sodium load, a problem for older patients and those with heart disease, and the uncertainty created by chromosomal fosA genes further limit its use.

3. AmpC-Producing *Enterobacterales*

Hafnia alvei now joins *Enterobacter cloacae complex*, *Klebsiella aerogenes* and *Citrobacter freundii* in the group at moderate risk of clinically significant inducible AmpC production. This is one more reason to discard the SPICE/SPACE mnemonics, which lump together species that behave quite differently. *Serratia marcescens*, *Morganella morganii* and *Providencia* spp. carry a much lower risk of AmpC derepression. They can usually be treated according to susceptibility results, unless a high-inoculum infection without adequate source control calls for more caution.

For moderate-risk species, cefepime is still the main carbapenem-sparing agent when the MIC falls in the susceptible or susceptible dose-dependent range (up to 8 µg/mL) [15]. Piperacillin–tazobactam is still discouraged for invasive infection, a position supported by observational data showing worse outcomes than with cefepime or carbapenems [16].

One change is refreshingly pragmatic. Ceftriaxone is still not suggested for invasive infection due to moderate-risk species. However, if it was started empirically for a non-severe infection, source control has been achieved and the patient is clearly improving,

completing the course with ceftriaxone may be reasonable [5]. Many clinicians already do this, and it is helpful to see it acknowledged.

4. Carbapenem-Resistant *Enterobacterales*

No section shows the shift towards mechanism-based therapy better than the one on CRE. In the United States, as in Europe, NDM-producing and OXA-48-like-producing *Enterobacterales* are on the rise [17,18]. The label "CRE" alone no longer tells us which of the newer β-lactams to choose. Laboratories should establish whether a carbapenemase is present and, whenever possible, which family it belongs to.

For KPC producers, meropenem–vaborbactam is now slightly favored, followed by ceftazidime–avibactam and then imipenem–relebactam [5]. The ranking comes from observational comparisons, but it also reflects a difference that matters at the bedside. Resistance emerges in roughly 10% of patients during ceftazidime–avibactam therapy, compared with less than 3% with the carbapenem/β-lactamase inhibitor combinations [19,20].

For NDM producers, aztreonam–avibactam and cefiderocol are the preferred agents, and ceftazidime–avibactam plus aztreonam is the alternative when the fixed combination cannot be obtained. The two preferred drugs are not interchangeable for every isolate. PBP3 insertions, CMY variants, permeability defects, iron-transport mutations, the site of infection and the reliability of MIC testing can all tip the balance. Phase 3 data on aztreonam–avibactam are encouraging, yet few patients with confirmed NDM-producing *Enterobacterales* were enrolled [21,22].

The picture for cefiderocol is mixed. In the GAME CHANGER trial, survival was lower with cefiderocol than with standard therapy in the small subgroup with NDM-producing *Enterobacterales* bloodstream infection [23]. Other cefiderocol trials pointed the opposite way [24]. In our view these inconsistent subgroup estimates do not discredit cefiderocol, but they do show how limited the clinical evidence behind some recommendations still is.

For OXA-48-like producers, ceftazidime–avibactam remains the preferred agent. Apparent susceptibility to meropenem–vaborbactam or imipenem–relebactam should not drive the choice, because vaborbactam and relebactam inhibit OXA-48-like enzymes poorly.

5. *Pseudomonas aeruginosa* with Difficult-to-Treat Resistance

Four newer β-lactams are available for DTR *P. aeruginosa*: cefiderocol, ceftazidime–avibactam, ceftolozane–tazobactam and imipenem–relebactam. The guidance asks laboratories to test all of them [5]. In cUTI any of the four may be preferred if the isolate is susceptible. Outside the urinary tract, ceftazidime–avibactam, ceftolozane–tazobactam and imipenem–relebactam are preferred, and cefiderocol is an alternative.

Real-world support for imipenem–relebactam is growing [25]. The update nonetheless cites observational studies in which non-susceptibility to imipenem–relebactam emerged during therapy about as often as with ceftazidime–avibactam or ceftolozane–tazobactam. Overall, the guidance estimates that resistance to the newer β-lactams emerges in about 20% of DTR *P. aeruginosa* isolates [5].

The most visible change is the preference for ceftolozane–tazobactam in pneumonia. It rests on CACTUS, an observational study in which ceftolozane–tazobactam achieved more clinical success and fewer recurrences than ceftazidime–avibactam, with similar mortality [26]. The pulmonary PK/PD profile of ceftolozane–tazobactam makes the finding biologically plausible. Still, there is no randomized head-to-head trial, and readers should keep that in mind.

Because the two drugs share a cephalosporin core, resistance selected by one often compromises the other. Previous exposure therefore matters even before a new antibiogram is available.

A new question deals with carbapenemase-producing *P. aeruginosa*. For KPC-producing strains, cefiderocol, ceftazidime–avibactam or imipenem–relebactam may be used if the isolate is susceptible; ceftolozane–tazobactam cannot be expected to overcome KPC. For metallo-β-lactamase (MBL) producers (NDM, VIM or IMP), cefiderocol is preferred.

Here the guidance parts ways with its *Enterobacterales* recommendations. Aztreonam–avibactam is not reliably active against MBL-producing *P. aeruginosa*, in which efflux and other chromosomal mechanisms undermine it [27]. Ceftazidime–avibactam plus aztreonam is kept for salvage when cefiderocol cannot be used. The contrast is a useful reminder that detecting a resistance gene is where interpretation starts, not where it ends.

6. Carbapenem-Resistant *Acinetobacter baumannii*

CRAB is still the area with the weakest evidence. The 2026 guidance now consistently refers to "invasive" CRAB infection. The wording has real stewardship weight: CRAB is often recovered from respiratory or wound samples of critically ill patients, in whom colonization and infection are hard to tell apart.

In the ATTACK trial, sulbactam–durlobactam plus imipenem was associated with lower 28-day mortality, a higher rate of clinical cure and much less nephrotoxicity than colistin plus imipenem [28]. Once invasive infection is established, sulbactam–durlobactam plus imipenem or meropenem is now the first choice. High-dose ampicillin–sulbactam with a second agent is reframed as a bridge until sulbactam–durlobactam can be obtained. Cefiderocol, minocycline and polymyxin B are alternatives when it cannot.

Durlobactam does not inhibit MBLs. For NDM-producing CRAB, cefiderocol, minocycline, polymyxin B or tigecycline may be considered, and the supporting evidence is scant. Observational meta-analyses suggest better survival with cefiderocol than with mostly polymyxin-based comparators, whereas randomized trials have produced neutral or conflicting results [29].

7. *Stenotrophomonas maltophilia*

The recommendations for *S. maltophilia* have changed the most [5]. Cefiderocol monotherapy is now preferred, while aztreonam–avibactam, levofloxacin, minocycline and TMP-SMX are alternatives, usually as part of combination therapy. For TMP-SMX in particular, this reverses decades of practice.

The rationale is mainly microbiological and pharmacological. Susceptibility of *S. maltophilia* to cefiderocol approaches 100%, human-simulated exposures are favorable, and in neutropenic animal models cefiderocol was bactericidal and improved survival compared with TMP-SMX [30]. Clinical evidence, however, is sparse and does not show superiority, a point also made by EUCAST [31]. Comparative studies of the older agents are heterogeneous and have not identified a clear winner either [32].

The guidance is open about these limitations [5]. We read the recommendation as a reasoned expert preference under uncertainty, not as the product of robust trials. A stable patient who is clearly improving on a well-tolerated drug to which the isolate is susceptible does not need an automatic switch. In hemorrhagic pneumonia, bacteremia, neutropenia or clinical instability, on the other hand, the limits of bacteriostatic agents and the risk of emerging resistance make a bactericidal, highly active drug such as cefiderocol an attractive choice. As always with *S. maltophilia*, the first question is whether the isolate is causing invasive disease at all.

In Table 1 the most rilevant changes in the 2026 IDSA guidance as previously discussed are reported, with their practical implications.

Table 1. Main changes in the 2026 IDSA guidance on antimicrobial-resistant Gram-negative infections and their practical implications.

Domain	Main 2026 Change	Bedside Implication
General	Updated cUTI definition, pediatric dosing source, dosing table and 2026 CLSI breakpoints	Define the syndrome before interpreting the antibiogram; check current dosing and breakpoints
ESBL-E	New oral options for uUTI; cefepime–enmetazobactam and IV fosfomycin	More carbapenem-sparing options for uUTI
AmpC-E	*Hafnia alvei* added to the moderate-risk inducible AmpC group; selected non-severe, improving infections may be completed with ceftriaxone	Base decisions on species, syndrome, source control and clinical response rather than on mnemonics
CRE	Aztreonam–avibactam added to the options for NDM producers	Rapid carbapenemase identification becomes key to choosing therapy, alongside AST
DTR P. aeruginosa	Ceftolozane–tazobactam preferred for pneumonia; new question on carbapenemase producers; emphasis on emergent resistance	Test all newer antipseudomonal β-lactams; repeat AST if the patient relapses during treatment
CRAB	Sulbactam–durlobactam plus a carbapenem is now the first choice	Distinguish invasive infection from colonization
S. maltophilia	Cefiderocol monotherapy preferred; aztreonam–avibactam, levofloxacin, minocycline and TMP-SMX are alternatives, usually in combination	Weak clinical evidence calls for caution; individualize therapy and do not read the drug list as a universal ranking

AmpC-E: AmpC β-lactamase-producing *Enterobacterales*; AST: antimicrobial susceptibility testing; CLSI: Clinical and Laboratory Standards Institute; CRAB: carbapenem-resistant *Acinetobacter baumannii*; CRE: carbapenem-resistant *Enterobacterales*; cUTI: complicated urinary tract infection; DTR *P. aeruginosa: Pseudomonas aeruginosa* with difficult-to-treat resistance; ESBL-E: extended-spectrum β-lactamase-producing *Enterobacterales*; TMP-SMX: trimethoprim–sulfamethoxazole; uUTI: uncomplicated urinary tract infection.

8. Conclusions

Taken together, the 2026 guidance describes a joint diagnostic and stewardship pathway, which some call a theragnostic approach. Identifying KPC, an MBL or an OXA-48-like enzyme now changes treatment directly. The document is written for the United States, however, and its regulatory and epidemiological context does not transfer automatically to regions where other resistance profiles prevail and drug availability differs.

The focus on NDM among the MBLs is a case in point. Other MBLs, such as VIM, matter a great deal in several regions, and cefiderocol activity against MBL producers varies widely with the specific enzyme [33]. Clinicians in Europe and elsewhere should adapt the algorithms to local enzymes, breakpoints, drug access and ecology rather than copy them as they stand.

Some principles have not changed. A microbiology report should be read together with the site of infection, its severity, previous antibiotic exposure and previous isolates. Source control is essential. In sepsis and septic shock, empirical therapy must be active and broad, and it should be narrowed as soon as a susceptible pathogen is identified. Resistant organisms do not automatically need longer courses than susceptible ones. Colonization is not infection. Finally, the newer agents will remain effective only if we use them wisely.

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