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# Beyond Carbapenems: Navigating Novel B-Lactam Combinations and the Resurgence of Older Antimicrobials in ESBL-Mediated UTIs: A Comprehensive Review

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**Abstract** **Review Article**

Extended-spectrum β-lactamase (ESBL)-producing Enterobacterales represent a growing therapeutic challenge in urinary tract infections (UTIs). While carbapenems have traditionally been the mainstay of treatment, several novel antibiotics have emerged as carbapenem-sparing alternatives. This review examines the role of newer β-lactam/β-lactamase inhibitor combinations and siderophore cephalosporins in managing ESBL-mediated UTIs, with emphasis on clinical efficacy, antimicrobial stewardship considerations, pharmacokinetic/pharmacodynamic properties, safety profiles, and appropriate patient selection. Additionally, the reemergence of older antibiotics including fosfomycin, aminoglycosides, and polymyxins is discussed in the context of contemporary antimicrobial resistance. Current evidence from both North American and European guidelines supports preferential reservation of newer agents for carbapenem-resistant infections, with traditional oral agents and carbapenems remaining first-line for most ESBL-mediated UTIs when susceptible.

**Keywords:** ESBL-producing Enterobacterales, Complicated urinary tract infections (cUTI), Carbapenem-sparing strategies, β-lactam/β-lactamase inhibitor combinations, Antimicrobial stewardship, Novel antibiotics.



## INTRODUCTION

ESBL-producing Enterobacterales have become increasingly prevalent causes of both community-acquired and healthcare-associated UTIs. These organisms produce enzymes that hydrolyze most β-lactam antibiotics, including third-generation cephalosporins, limiting therapeutic options and often necessitating carbapenem use. The emergence of carbapenem resistance has intensified the need for effective carbapenem-sparing strategies. Several novel antibiotics with activity against ESBL producers have been developed and approved for UTI treatment, offering new therapeutic paradigms while raising important questions about optimal utilization.

The Infectious Diseases Society of America (IDSA) 2024 guidance emphasizes that for uncomplicated cystitis caused by ESBL-producing Enterobacterales, nitrofurantoin and trimethoprim-sulfamethoxazole remain preferred treatment options when susceptible, with fluoroquinolones and carbapenems reserved as alternatives. For pyelonephritis and complicated UTIs, trimethoprim-sulfamethoxazole, ciprofloxacin, or levofloxacin are preferred when susceptible, with carbapenems recommended when resistance or toxicities preclude their use, or in critically ill patients [1].

Notably, the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) guideline published in December 2021 recommended a more restrictive approach, limiting carbapenem use exclusively for severe presentations of extended-spectrum cephalosporin-resistant Enterobacterales infections, specifically septic shock or bloodstream infection [2]. This contrasts with the IDSA's initially more liberal carbapenem recommendations, highlighting ongoing international debate regarding optimal carbapenem-sparing strategies [2-3].

This review examines how newer antibiotics fit within these treatment paradigms, their specific role in managing ESBL-mediated UTIs, and the reemergence of older antibiotics as valuable therapeutic options.

**Novel β-Lactam/β-Lactamase Inhibitor Combinations**

**Ceftazidime-Avibactam**

Ceftazidime-avibactam combines a third-generation cephalosporin with a novel non-β-lactam β-lactamase inhibitor. Avibactam successfully protects ceftazidime against hydrolysis by ESBL enzymes through direct binding and inhibition. In vitro surveillance data demonstrate that ceftazidime-avibactam exhibits 100% susceptibility against ESBL-producing Enterobacterales, superior to ceftolozane-tazobactam (90.2% susceptibility) [4-5].

Clinical trial data support its effectiveness in complicated UTIs (cUTIs). In a randomized trial comparing ceftazidime-avibactam to best available therapy for cUTI, microbiological response rates at day 21-25 were 76.3% for Escherichia coli and 76.4% for Klebsiella pneumoniae [6]. A meta-analysis of five randomized controlled trials demonstrated clinical response rates of 91% for ceftazidime-avibactam versus 89% for carbapenems in ESBL-producing infections (RR 1.02, 95% CI 0.97-1.08), establishing non-inferiority for mild to moderate cUTIs and intra-abdominal infections [7].

**Meropenem-Vaborbactam**

Meropenem-vaborbactam pairs a carbapenem with a cyclic boronic acid β-lactamase inhibitor. While the carbapenem component alone provides sufficient activity against ESBL producers, the combination is FDA-approved for cUTI including pyelonephritis. The TANGO I trial demonstrated superiority over piperacillin-tazobactam, with overall success rates of (98.2% vs 94.8%) at end of intravenous treatment, and (74.5% vs 71.4%) at test-of-cure [8]. Efficacy remained consistent across varying minimum inhibitory concentrations, supporting its reliability in ESBL infections.

**Cefepime-Enmetazobactam**

Cefepime-enmetazobactam represents a newer addition, combining a fourth-generation cephalosporin with a novel β-lactamase inhibitor. In a randomized trial of 678 patients with cUTI or acute pyelonephritis, cefepime-enmetazobactam demonstrated superior overall success compared to piperacillin-tazobactam (79.1% vs 58.9%, treatment difference 21.2%, 95% CI 14.3-27.9%) [9]. Notably, among patients with ESBL-producing pathogens (20.9% of the study population), the treatment difference favored cefepime-enmetazobactam by approximately 30%, highlighting its particular utility in this population [10]. Additionally, recurrence rates were significantly lower with cefepime-enmetazobactam (11.3% vs 29.4%), suggesting superior microbiological eradication [9]. This combination was approved for use by the European Medicines Agency (EMA) and FDA in 2024 [10].

**Imipenem-Cilastatin-Relebactam**

This combination adds relebactam, a β-lactamase inhibitor, to the established carbapenem imipenem-cilastatin. Like meropenem-vaborbactam, the carbapenem component provides inherent activity against ESBL producers. It is FDA-approved for cUTI including pyelonephritis and represents another carbapenem-based option when non-carbapenem alternatives are unsuitable.

**Siderophore Cephalosporins**

**Cefiderocol**

Cefiderocol represents a novel mechanism of action, utilizing a siderophore moiety to hijack bacterial iron transport systems, achieving high periplasmic concentrations. It demonstrates stability against ESBLs, AmpC β-lactamases, and carbapenemases [11-12]. FDA-approved for cUTI including pyelonephritis, cefiderocol showed non-inferiority to imipenem-cilastatin in a phase II trial, with composite clinical and microbiological response rates of (72.6% vs 54.6%) in the microbiological intent-to-treat population [12].

In the CREDIBLE-CR trial evaluating carbapenem-resistant infections, cefiderocol demonstrated particular efficacy in cUTI subgroups, with numerically higher clinical cure rates compared to best available therapy, and lower relapse rates (3% vs 11%) [13]. Its broad activity against multidrug-resistant organisms, including ESBL producers, positions it as a valuable option, though current guidelines recommend reserving it for carbapenem-resistant infections.

**Reemergence of Older Antibiotics**

The escalating prevalence of ESBL-producing Enterobacterales has prompted renewed interest in older antibiotics that were previously relegated to second-line status. These agents, including fosfomycin, aminoglycosides, polymyxins, temocillin, and pivmecillinam, offer valuable alternatives in specific clinical scenarios, though their use requires careful consideration of efficacy, toxicity, and antimicrobial stewardship principles.

**Fosfomycin**

Fosfomycin, a phosphonic acid derivative first discovered in 1969, has experienced a resurgence as a treatment option for ESBL-mediated UTIs. The IDSA guidelines recommend oral fosfomycin as an alternative treatment option exclusively for uncomplicated ESBL-producing E. coli cystitis [1,14]. Susceptibility of E. coli to fosfomycin is not routinely tested by most clinical microbiology laboratories, but E. coli resistance to fosfomycin remains rare in the United States [1].

Fosfomycin is not suggested for infections caused by K. pneumoniae and several other gram-

negative organisms that frequently carry fosA hydrolase genes, which may lead to clinical failure [1,14]. A randomized, open-label trial indicated that a single dose of oral fosfomycin is associated with higher clinical failure than a 5-day course of nitrofurantoin for uncomplicated cystitis [14].

For pyelonephritis and cUTI, fosfomycin is not suggested given its limited renal parenchymal concentrations [1,14]. However, more data are needed to evaluate the role of oral fosfomycin as an oral step-down agent for patients with pyelonephritis or cUTI, particularly when administered as a multidose regimen after several days of preferred therapy [1,14]. A clinical trial of 97 women with E. coli pyelonephritis who received up to 5 days of intravenous therapy and were subsequently transitioned to either once-daily 3-g doses of oral fosfomycin or twice-daily 500-mg doses of oral ciprofloxacin for 10 days of total therapy identified similar clinical cure percentages in both groups (75% vs 65%, respectively) [14]. However, only approximately 6% of isolates were ESBL-producing, limiting generalizability to more drug-resistant phenotypes [14].

Fosfomycin represents an alternative option for the treatment of prostatitis caused by ESBL-producing E. coli when preferred options (carbapenems, trimethoprim-sulfamethoxazole, or fluoroquinolones) cannot be tolerated or do not test susceptible [1,14]. In an observational study, fosfomycin dosed at 3 g orally daily for 1 week, followed by 3 g orally every 48 hours for 6-12 weeks, was associated with clinical cure in 82% of males with chronic bacterial prostatitis [14].

**Aminoglycosides**

Aminoglycosides, including gentamicin, tobramycin, amikacin, and plazomicin, remain treatment options for many ESBL-producing Enterobacterales and have a particular role in UTIs due to their predominantly renal elimination and concentration in the urinary tract [1,10].

For uncomplicated cystitis, a single intravenous dose of an aminoglycoside is an alternative treatment option for ESBL-producing infections [1,14]. Aminoglycosides are nearly exclusively eliminated by the renal route, and a single intravenous dose is generally effective for uncomplicated cystitis with minimal toxicity, though robust clinical trial data are lacking [1].

For pyelonephritis and cUTI, aminoglycosides are alternative options, though they are considered alternative rather than preferred agents because of their associated nephrotoxicity risk [1,10,14]. Animal models suggest aminoglycosides concentrate in the renal parenchyma. In a clinical trial of 609 adults receiving plazomicin for cUTI infections, clinical relapse occurred in (2% vs 7%) and increases in serum creatinine levels of ≥0.5 mg above baseline occurred in (7% vs 4%) of patients in the plazomicin and meropenem groups, respectively [1]. In general, higher percentages of Enterobacterales clinical isolates are susceptible to plazomicin compared to other aminoglycosides, though other aminoglycosides are likely equally effective for the treatment of ESBL-producing pyelonephritis or cUTI if susceptibility is demonstrated [1,14].

Aminoglycosides may be reasonable to consider for completing treatment courses (e.g., transitioning from another agent for terminal doses) given their prolonged duration of activity in the renal cortex and the convenience of once-daily dosing [1]. Duration-dependent risks of nephrotoxicity should be considered with all aminoglycosides. Of note, in 2023 the Clinical and Laboratory Standards Institute (CLSI) revised gentamicin, tobramycin, and amikacin breakpoints for the Enterobacterales, which may affect susceptibility reporting [1].

**Polymyxins**

Polymyxins, including colistin and polymyxin B, are cationic compounds that interact with lipopolysaccharides of the outer membrane of gram-negative bacteria to cause increased permeability and cell death [10]. These agents were previously considered for carbapenem-resistant Enterobacterales (CRE) therapy but have considerable toxic effects, particularly nephrotoxicity, and have largely been replaced by novel β-lactam and β-lactamase inhibitor combinations [10].

The IDSA guidelines suggest that polymyxins be avoided for the treatment of CRE infections, with the exception of colistin as an alternative agent against CRE cystitis [14]. Polymyxin B should not be used as treatment for CRE cystitis because of its predominantly nonrenal clearance. Observational and clinical data indicate increased mortality and excess nephrotoxicity associated with polymyxin-based regimens relative to comparator agents. Concerns about the clinical effectiveness of polymyxins and accuracy of polymyxin susceptibility testing led the CLSI to eliminate a susceptible category for colistin and polymyxin B [14].

For ESBL-producing Enterobacterales specifically, a retrospective cohort study of 396 patients with ESBL-producing E. coli and K. pneumoniae infections compared loading dose colistin (95 patients) with carbapenems (301 patients) [15]. Loading dose colistin provided higher 30-day mortality when compared with the carbapenem group (HR 7.97; 95% CI 3.68-17.25), and was independently associated with clinical failure (HR 4.30; 95% CI 1.93-9.57) and bacteriological failure (HR 9.49; 95% CI 3.76-23.96) [15]. These findings suggest that colistin should be recommended as an alternative for treatment of ESBL-producing Enterobacterales only in circumstances where carbapenems cannot be utilized.

Interestingly, recent research has challenged conventional antimicrobial susceptibility testing (AST)

for colistin against mcr-positive strains. A 2025 study demonstrated that colistin retained bactericidal activity against mcr-1+ E. coli, K. pneumoniae, and Salmonella enterica when tested in tissue culture medium containing physiological bicarbonate, and synergized with human serum to kill pathogens [16]. At clinically achievable concentrations, colistin killed mcr-1+ strains in freshly isolated human blood and was effective as monotherapy in a murine E. coli bacteremia model. These findings suggest that colistin, currently dismissed based on conventional AST, may offer clinical benefit against mcr-1+ infections when evaluated under more physiological conditions, warranting reconsideration in clinical microbiology practices and future trials for high-risk patients [16].

**Temocillin and Pivmecillinam**

Temocillin and pivmecillinam (mecillinam) represent older β-lactam antibiotics that have maintained activity against ESBL-producing Enterobacterales and are experiencing renewed interest, particularly in Europe. A recent Irish study of 60 ESBL-producing Enterobacterales bloodstream infections demonstrated that temocillin, mecillinam, cefiderocol, amikacin, and fosfomycin displayed excellent activity against all ESBL isolates tested, with susceptibility rates of ≥85%. These agents offer promising carbapenem-sparing alternatives, particularly in regions where carbapenem resistance is increasing [17].

Pivmecillinam has extensive activity against ESBL-producing Enterobacterales with more than 80% of isolates being susceptible to treatment [10]. After longstanding use in Europe, pivmecillinam was approved by the FDA in 2024 for use in uncomplicated UTIs in female patients 18 years and older [10]. In France, following publication of new UTI management guidelines in December 2015, the use of pivmecillinam increased dramatically by 7,430% between 2014 and 2019, while fluoroquinolone use decreased substantially, suggesting successful implementation of carbapenem-sparing strategies [18].

**Pharmacokinetic and Pharmacodynamic Considerations**

The newer β-lactam/β-lactamase inhibitor combinations demonstrate favorable pharmacokinetic properties for UTI treatment, with predominantly renal excretion achieving high urinary concentrations. Ceftazidime-avibactam dosing (2,000/500 mg every 8 hours as 2-hour infusions) was optimized through population pharmacokinetic modeling to achieve joint pharmacodynamic targets: 50% free time above the MIC for ceftazidime and 50% free time above a critical avibactam threshold concentration of 1 mg/L [19]. This dosing regimen achieves 95% probability of target attainment against MICs ≤8 mg/L regardless of age, obesity, augmented renal clearance, or infection severity.

Cefepime-enmetazobactam exhibits similar pharmacokinetic profiles for both components, with comparable urinary excretion and half-lives, facilitating fixed-ratio dosing [9]. The combination demonstrates enhanced potency against ESBL producers compared to piperacillin-tazobactam, with lower recurrence rates following treatment, suggesting superior microbiological eradication [9].

Meropenem-vaborbactam maintains efficacy across varying MICs, with consistent clinical success rates independent of pathogen susceptibility patterns [8]. The carbapenem component provides inherent activity against ESBL producers, while vaborbactam extends coverage to carbapenemase-producing organisms.

Cefiderocol's unique siderophore-mediated iron transport mechanism achieves high periplasmic concentrations, demonstrating stability against ESBLs, AmpC β-lactamases, and carbapenemases [11-12]. This trojan horse strategy results in superior tissue penetration and microbiological eradication rates, with lower relapse rates (3% vs 11%) compared to best available therapy in carbapenem-resistant infections [13].

**Dosing Adjustments in Renal Impairment**

All novel agents require dose modifications in patients with reduced creatinine clearance due to predominantly renal elimination. For ceftazidime-avibactam, dose adjustments are required for creatinine clearance ≤50 mL/min, with modified dosing intervals and quantities to maintain therapeutic exposures while avoiding accumulation [19-20]. Alternative regimens using prolonged infusions of full doses at extended intervals (every 12 or 24 hours) have been proposed as cost-effective strategies that maintain adequate probability of target attainment while reducing dosing errors and nursing workload [21].

Ceftolozane-tazobactam demonstrates graded increases in exposure with declining renal function, with 1.4-fold increases in mild impairment, 2.5-fold in moderate impairment, and 4.4-fold dose-normalized increases in severe impairment [22]. Hemodialysis effectively removes both components, with approximately 66% and 56% reductions in ceftolozane and tazobactam exposure, respectively, necessitating post-dialysis supplementation.

Population pharmacokinetic modeling has established that pediatric patients with renal impairment require equivalent dose adjustments (in quantity and/or interval) as adults to achieve comparable exposures [20]. Time-varying creatinine clearance serves as a key covariate on clearance for both aztreonam and avibactam, with infection type (particularly complicated intra-abdominal infections) affecting clearance and volume of distribution [23].

**Safety and Tolerability**

Pooled safety data from seven phase II and III trials encompassing 4,050 patients demonstrate that ceftazidime-avibactam exhibits a safety profile consistent with ceftazidime monotherapy. Adverse events occurred in 49.2% of ceftazidime-avibactam-treated patients versus 47.6% of comparator-treated patients, with the most common being diarrhea, nausea, headache, vomiting, and pyrexia. Discontinuations due to adverse events were infrequent (2.5% vs 1.7%), and serious adverse events occurred in (8.7% vs 7.2%) for ceftazidime-avibactam and comparators, respectively [24].

Drug-related adverse events occurred in 10.7% of ceftazidime-avibactam patients, with no impact from intrinsic factors (age, renal function) or extrinsic factors (geographical origin). Potentially clinically significant laboratory abnormalities were infrequent with no identified safety concerns [24]. This favorable safety profile extends across all approved indications including complicated UTI, complicated intra-abdominal infections, and nosocomial pneumonia.

Meropenem-vaborbactam demonstrated superior overall success rates (98.2% vs 94.8% at end of intravenous treatment) compared to piperacillin-tazobactam in the TANGO I trial, with comparable safety profiles [8]. Cefepime-enmetazobactam showed similar tolerability to piperacillin-tazobactam, with the added benefit of significantly lower recurrence rates [9].

**Antimicrobial Stewardship Considerations**

Current IDSA guidelines emphasize carbapenem-sparing strategies for ESBL-mediated UTIs [1,14]. For uncomplicated cystitis, nitrofurantoin and trimethoprim-sulfamethoxazole remain preferred when susceptible, with fluoroquinolones and carbapenems reserved as alternatives. For pyelonephritis and cUTI, trimethoprim-sulfamethoxazole and fluoroquinolones (when susceptible) are preferred, with carbapenems recommended when resistance or toxicities preclude their use, or in critically ill patients [1].

The ESCMID guideline published in December 2021 recommended a more restrictive approach than the initial IDSA guidance, limiting carbapenem use exclusively for severe presentations of extended-spectrum cephalosporin-resistant Enterobacterales infections, specifically septic shock or bloodstream infection [2]. This European perspective emphasizes carbapenem-sparing strategies even more strongly, reflecting concerns about rising carbapenem resistance rates globally [2-3].

A comprehensive European review stratified treatment recommendations by patient severity: for Group 1 patients (severe infections, high-risk sources, or severely immunocompromised), carbapenems remain the treatment of choice; for Group 2 (non-severe infections from intermediate-risk sources), carbapenem alternatives may be considered; and for Group 3 (non-severe UTI), non-carbapenem antibiotics including β-lactam/β-lactamase inhibitor combinations, cephamycins, temocillin, and aminoglycosides can be utilized in selected cases [3].

The newer β-lactam/β-lactamase inhibitor combinations and cefiderocol, while effective against ESBL producers, are preferentially reserved for carbapenem-resistant organisms to preserve their activity [1,14]. However, specific clinical scenarios may warrant their use for ESBL infections, including polymicrobial infections with difficult-to-treat resistant Pseudomonas aeruginosa, drug interactions (e.g., concomitant valproic acid use contraindicating carbapenems), or documented carbapenem resistance.

Notably, piperacillin-tazobactam and cefepime should not be used for ESBL-mediated cUTI despite occasional in vitro susceptibility, due to concerns about β-lactamase inhibitor efficacy, inoculum effects, and clinical trial data showing inferior outcomes [1,25]. While ESCMID guidelines recommend against cefepime use for third-generation cephalosporin-resistant Enterobacterales due to paucity of data, IDSA guidelines state that cefepime use could be appropriate for AmpC-producing Enterobacterales at moderate risk of considerable AmpC production [10].

**Oral Step-Down Therapy**

Data from observational studies support the use of oral step-down therapy for Enterobacterales bloodstream infections, including those caused by antimicrobial-resistant isolates, after appropriate clinical milestones are achieved [1]. Based on the high bioavailability and sustained serum concentrations of oral trimethoprim-sulfamethoxazole and fluoroquinolones, these agents should be treatment considerations for patients with ESBL-producing infections if susceptibility to one of these agents is demonstrated, the patient is hemodynamically stable, reasonable source control has occurred and concerns about insufficient intestinal absorption are not present [1].

If a carbapenem or newer β-lactam/β-lactamase inhibitor combination is initiated and susceptibility to trimethoprim-sulfamethoxazole, ciprofloxacin, or levofloxacin is demonstrated, transitioning to oral formulations of these agents is preferred over completing a treatment course with intravenous therapy. Limiting use of carbapenem exposure will preserve their activity for future antimicrobial-resistant infections, which frequently arise in patients with cUTIs [1].

Clinicians should avoid oral step-down to nitrofurantoin, fosfomycin, amoxicillin-clavulanic acid, omadacycline, or doxycycline for ESBL-producing bloodstream infections or pyelonephritis. Nitrofurantoin

and fosfomycin achieve poor serum concentrations and limited renal parenchymal penetration [1,14]. Amoxicillin-clavulanic acid, omadacycline, and doxycycline have limited data to support their efficacy for ESBL-producing infections outside of uncomplicated cystitis [1].

In cases where fluoroquinolone or trimethoprim-sulfamethoxazole resistance is present, the lack of validated oral alternatives remains a significant therapeutic gap.

**Clinical Outcomes and Comparative Effectiveness**

Direct comparative data between newer agents and carbapenems for ESBL-mediated UTIs remain limited. Most trials have compared novel agents to piperacillin-tazobactam or best available therapy rather than head-to-head with carbapenems. The available evidence suggests:

Ceftazidime-avibactam demonstrates non-inferiority to carbapenems for mild-to-moderate ESBL infections, with clinical response rates of 91% [7].

Meropenem-vaborbactam shows superiority over piperacillin-tazobactam and maintains efficacy across varying pathogen MICs [8].

Cefepime-enmetazobactam demonstrates superiority over piperacillin-tazobactam, particularly pronounced in ESBL-producing infections, with a 30% treatment difference in this subgroup [9].Cefiderocol shows non-inferiority to imipenem-cilastatin with favorable microbiological eradication rates [12].

The clinical trial that established carbapenem therapy as the treatment of choice for ESBL-producing bloodstream infections randomized 391 patients with ceftriaxone non-susceptible E. coli or K. pneumoniae (87% later confirmed to have ESBL genes) to piperacillin-tazobactam or meropenem. The primary outcome of 30-day mortality occurred in 12% and 4% of patients receiving piperacillin-tazobactam and meropenem, respectively [1,10,26]. In the subgroup of 231 patients with ESBL-producing bloodstream infections from a urinary source, higher mortality was identified in the piperacillin-tazobactam group (7% vs 3%), although not achieving statistical significance [1,14]. Reanalysis of the original MERINO data using reference antibiotic susceptibility testing methods indicated that this mortality difference is no longer statistically significant, with further validation studies underway [10].

While individual trial data for agents like ceftazidime-avibactam and cefepime-enmetazobactam show high clinical response rates, the lack of direct head-to-head comparisons between all newer agents and carbapenems remains a barrier to establishing a definitive therapeutic hierarchy. A consolidated summary of these novel agents, including their pivotal trial outcomes and specific regulatory indications, provides a necessary framework for bedside decision-making in ESBL-mediated infections.

**Table 1: Summary of Clinical Efficacy and Trial Data for Novel Antibiotics in cUTI**

| Antibiotic | Mechanism | Pivotal Trial | Key Outcome (vs. Comparator) |
|---|---|---|---|
| Ceftazidime-avibactam | BL/BLI | RECAPTURE | Non-inferior to Doripenem (Combined clinical and microbiological response: 71.2% vs 64.5%; 95% CI: 0.3% to 13.1%). |
| Meropenem-vaborbactam | BL/BLI | TANGO I | Superior to Piperacillin-tazobactam (98.2% success) |
| Cefepime-enmetazobactam | BL/BLI | ALLIUM | Superior to Pip-Tazo (+30% in ESBL subgroup) |
| Cefiderocol | Siderophore | APEKS-NP/CREDIBLE-CR | Non-inferior to Imipenem-cilastatin; lower relapse rates |

**Emergence of Resistance**

A critical consideration in the use of newer antibiotics is the potential for resistance development. For ceftazidime-avibactam, resistance emergence occurs in approximately 10-20% of cases, primarily through mutations in the blaKPC gene causing amino acid changes in the KPC carbapenemase, or through alterations in the omega loop region of AmpC enzymes [1,14]. Meropenem-vaborbactam demonstrates lower resistance emergence (5%), with resistance primarily mediated by changes in permeability and efflux mechanisms rather than β-lactamase modifications [1,14].

Cefiderocol resistance mechanisms are diverse, including mutations in TonB-dependent iron transport systems, amino acid changes in AmpC β-lactamases, and increased NDM expression [14]. Notably, cefiderocol resistance appears significantly higher in ceftazidime-avibactam-resistant Enterobacterales (83% vs 7% in susceptible isolates), suggesting cross-resistance patterns [1]. Emerging reports of amino acid insertions in PBP3, the active binding site for both cefiderocol and aztreonam, in NDM-producing E. coli isolates represent a concerning development that could eliminate all β-lactam treatment options, though such cases remain rare in the United States [1,14].

The IDSA recommends repeating antimicrobial susceptibility testing for newer β-lactams when patients previously infected with carbapenem-resistant Enterobacterales present with sepsis-like conditions, and considering alternative novel β-lactam agents if recent ceftazidime-avibactam exposure occurred.[1]

**Patient Selection and Clinical Application**

The choice of antibiotic for ESBL-mediated UTI should be individualized based on infection severity, patient factors, local resistance patterns, and antimicrobial stewardship principles. For uncomplicated cystitis, oral agents (nitrofurantoin, trimethoprim-sulfamethoxazole, fluoroquinolones when susceptible) remain first-line. For pyelonephritis and cUTI, oral fluoroquinolones or trimethoprim-sulfamethoxazole are preferred when susceptible, with carbapenems reserved for resistant isolates or critically ill patients [1].

The newer agents offer valuable alternatives in specific scenarios: patients with carbapenem-resistant co-pathogens, those with contraindications to carbapenems (such as concomitant valproic acid use), or in settings where carbapenem stewardship is prioritized. Early carbapenem therapy in critically ill patients can be de-escalated to oral agents once susceptibilities are known and clinical improvement occurs [1].

For patients who are critically ill and/or experiencing hypoalbuminemia, meropenem or imipenem-cilastatin are the preferred carbapenems over ertapenem. Ertapenem is highly protein bound, and in patients with hypoalbuminemia, the free fraction increases, leading to increased clearance and decreased serum half-life, which may not be optimal with daily dosing [1,10]. An observational study found that hypoalbuminemia (defined as serum albumin ≤2.5 g/dL) was associated with approximately 5-times higher odds of 30-day mortality for patients receiving ertapenem compared to those receiving meropenem or imipenem-cilastatin [1].

**Economic and Stewardship Implications**

While formal cost-effectiveness analyses comparing newer agents to carbapenems for ESBL-mediated UTIs are limited, several factors influence economic considerations. The newer β-lactam/β-lactamase inhibitor combinations carry substantially higher acquisition costs than generic carbapenems, though potential benefits include reduced toxicity (particularly nephrotoxicity compared to aminoglycosides or polymyxins), shorter hospital stays through improved clinical outcomes, and preservation of carbapenem activity through carbapenem-sparing strategies.

Alternative dosing regimens using prolonged infusions at extended intervals may reduce overall drug costs while maintaining therapeutic efficacy, though clinical validation is required before implementation [21]. The ability to achieve early clinical improvement and transition to oral step-down therapy, when susceptibilities permit, can further reduce overall treatment costs and facilitate earlier hospital discharge [1].

From an antimicrobial stewardship perspective, the preferential reservation of newer agents for carbapenem-resistant infections represents a critical strategy to preserve their long-term utility. The IDSA guidelines emphasize that while these agents demonstrate excellent activity against ESBL producers, their use should be restricted to specific scenarios: polymicrobial infections with difficult-to-treat resistant Pseudomonas aeruginosa, drug interactions (e.g., concomitant valproic acid contraindicating carbapenems), documented carbapenem resistance, or carbapenem intolerance [1,14].

**Future Directions**

Several knowledge gaps remain regarding the optimal use of newer antibiotics for ESBL-mediated UTIs. Head-to-head comparative trials between novel agents and carbapenems specifically for ESBL infections are lacking, with most existing data derived from subgroup analyses or observational studies. The role of oral step-down therapy following initial treatment with newer intravenous agents requires further investigation to optimize treatment duration and reduce healthcare costs.

Ongoing surveillance of resistance patterns, particularly the emergence of novel resistance mechanisms such as PBP3 insertions, will be essential to guide future treatment algorithms [1].

The development of rapid diagnostic tests to identify specific resistance mechanisms at the point of care could facilitate more targeted antibiotic selection and reduce unnecessary use of broad-spectrum agents.

Additionally,pharmacokinetic/pharmacodynamic studies in special populations (pregnancy, pediatrics, critically ill patients with augmented renal clearance) will help refine dosing strategies and expand the evidence base for these agents. The potential role of combination therapy to prevent resistance emergence, particularly in high-inoculum or difficult-to-treat infections, warrants further investigation.

The reemergence of older antibiotics, particularly fosfomycin, pivmecillinam, temocillin, and aminoglycosides, requires additional clinical trial data to define their optimal role in contemporary practice. The French experience with pivmecillinam, demonstrating a 7,430% increase in use following updated UTI guidelines while simultaneously reducing fluoroquinolone prescriptions, provides a model for successful implementation of carbapenem-sparing strategies that other countries may emulate. The recent

findings regarding colistin activity against mcr-positive strains under physiological conditions highlight the importance of reassessing conventional antimicrobial susceptibility testing methods and may prompt reconsideration of treatment algorithms for highly resistant infections [10].

International harmonization of guidelines between IDSA and ESCMID recommendations would benefit clinical practice, particularly regarding the threshold for carbapenem use in ESBL infections [10,18]. The ongoing MERINO-2 and MERINO-3 trials may provide additional clarity on the role of piperacillin-tazobactam and other β-lactam/β-lactamase inhibitor combinations in ESBL infections, potentially refining current treatment algorithms [10].

Novel agents currently in development, including aztreonam-avibactam (recently approved by the EMA and FDA), sulbactam-durlobactam, and cefepime-taniborbactam, may further expand therapeutic options for multidrug-resistant gram-negative infections, including those caused by metallo-β-lactamase-producing organisms that are resistant to currently available novel β-lactam/β-lactamase inhibitor combinations. Aztreonam-avibactam, in particular, represents a promising option for NDM-producing Enterobacterales, as aztreonam is inherently stable against metallo-β-lactamases while avibactam protects against co-produced serine β-lactamases.

## CONCLUSION

Novel antibiotics have expanded the therapeutic armamentarium for ESBL-producing Enterobacterales UTIs. Ceftazidime-avibactam, meropenem-vaborbactam, cefepime-enmetazobactam, imipenem-cilastatin-relebactam, and cefiderocol demonstrate efficacy comparable or superior to traditional comparators. However, antimicrobial stewardship principles from both North American (IDSA) and European (ESCMID) guidelines dictate that these agents should be preferentially reserved for carbapenem-resistant infections, with traditional oral agents (nitrofurantoin, trimethoprim-sulfamethoxazole, fluoroquinolones when susceptible) and carbapenems remaining first-line for most ESBL-mediated UTIs.

The reemergence of older antibiotics including fosfomycin, aminoglycosides, pivmecillinam, temocillin, and polymyxins provides additional therapeutic options in carefully selected scenarios, though their use must be balanced against concerns regarding efficacy and toxicity. Fosfomycin represents a valuable alternative for uncomplicated E. coli cystitis and prostatitis, while aminoglycosides offer effective treatment for pyelonephritis and cUTI when nephrotoxicity risk is acceptable. Pivmecillinam and temocillin, with their excellent activity against ESBL producers and favorable safety profiles, represent promising carbapenem-sparing alternatives that are increasingly utilized in European practice. Polymyxins should generally be avoided for ESBL infections except in rare circumstances where no alternatives exist.

The ESCMID guideline's more restrictive approach to carbapenem use, limiting it to severe presentations such as septic shock or bloodstream infection, contrasts with the IDSA's recommendations and reflects the ongoing international debate regarding optimal carbapenem-sparing strategies. A patient-stratified approach, considering infection severity, source, and host factors, may help reconcile these perspectives and optimize individual patient outcomes while preserving antibiotic efficacy for future generations.

Judicious use of newer antibiotics in carefully selected patients can help preserve their activity while providing effective carbapenem-sparing alternatives when clinically appropriate. Early transition to oral step-down therapy with trimethoprim-sulfamethoxazole or fluoroquinolones, when susceptibilities permit, can reduce carbapenem exposure and facilitate earlier hospital discharge while maintaining excellent clinical outcomes. A comprehensive, individualized approach incorporating infection severity, patient factors, local resistance patterns, and antimicrobial stewardship principles remains essential for optimizing outcomes in ESBL-mediated UTIs.

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