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CEFEPIME/ZIDEBACTAM: A NOVEL STRATEGY AGAINST MULTIDRUG-RESISTANT GRAM-NEGATIVE INFECTIONS AND ITS POTENTIAL RELEVANCE TO SEPSIS

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Background: Sepsis is life-threatening organ dysfunction caused by a dysregulated host response to infection. Antimicrobial resistance, particularly among Gram-negative pathogens, complicates timely effective treatment and increases the risk of treatment failure. Although established antibiotics remain essential, resistance mechanisms can limit the activity of existing agents, creating a need for new therapeutic strategies.

Objective: To summarize the rationale, mechanisms of action, and available clinical evidence for cefepime/zidebactam, and to assess the limits of current evidence regarding its potential relevance to sepsis and septic shock.

Methods: A focused narrative review was conducted of regulatory information, clinical-trial findings, and published descriptions of the combination's microbiological and pharmacological properties.

Results: Cefepime is a fourth-generation cephalosporin that primarily targets penicillin-binding protein 3 (PBP3). Zidebactam is a non-β-lactam antibacterial agent that targets PBP2 and inhibits selected β-lactamases. Their complementary activity can enhance bacterial killing and retain in-vitro activity against certain difficult-to-treat Gram-negative organisms, including some isolates carrying carbapenemases; activity is not universal and susceptibility testing remains essential. In the phase III ENHANCE-1 trial of adults with complicated urinary tract infection, including pyelonephritis, the composite clinical and microbiological response was 89.0% (250/281) with cefepime/zidebactam versus 68.4% (93/136) with meropenem at the test-of-cure visit. On 29 May 2026, the US Food and Drug Administration approved the combination for adults with complicated urinary tract infections, including pyelonephritis, caused by designated susceptible organisms. This approval does not establish an indication for sepsis or septic shock.

Conclusion: Cefepime/zidebactam is an important addition to the evolving antimicrobial-resistance landscape, combining established β-lactam therapy with a complementary PBP-targeting mechanism. The phase III findings support its approved use in specified complicated urinary tract infections. Further dedicated clinical evidence is needed before its efficacy in sepsis and septic shock can be concluded. In critically ill patients, treatment decisions should integrate prompt appropriate therapy, source control, microbiological results, local resistance patterns, and applicable prescribing guidance.

Keywords: Cefepime/zidebactam; antimicrobial resistance; Gram-negative bacteria; sepsis; septic shock.