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The rapid escalation of antimicrobial resistance (AMR) poses a major threat to global public health, with carbapenem-resistant Enterobacterales (CRE) designated as an urgent threat. The most challenging subset of these pathogens includes those that produce Ambler Class B metallo-β-lactamases (MBLs), such as New Delhi metallo-β-lactamase (NDM) and Verona integron-encoded metallo-β-lactamase (VIM). Because MBLs can hydrolyze virtually all β-lactam antibiotics except monobactams—and are frequently co-produced alongside serine β-lactamases that degrade monobactams—treatment options have been dangerously limited.

Aztreonam-avibactam (commercially branded as Emblaveo), the first fixed-dose combination of a monobactam and a β-lactamase inhibitor, addresses this medical vulnerability.

Mechanism of Action: The Power of Targeted Synergy

The efficacy of the aztreonam-avibactam combination relies on a complementary molecular strategy designed to overcome multi-layered bacterial resistance mechanisms:

- **Aztreonam (ATM):** As a monobactam antibiotic, aztreonam binds with high affinity to penicillin-binding protein 3 (PBP-3) in Gram-negative bacteria, disrupting cell wall synthesis. Structurally, it is inherently stable against degradation by Class B MBLs. However, its standalone clinical utility against CRE is compromised because these pathogens almost universally co-produce Class A (e.g., KPC), Class C (e.g., AmpC), or Class D (e.g., OXA-48) serine β-lactamases, which readily hydrolyze aztreonam.
- **Avibactam (AVI):** A potent, non-β-lactam β-lactamase inhibitor, avibactam covalently and reversibly inhibits Class A, Class C, and select Class D serine β-lactamases.

By pairing the two, **avibactam shields aztreonam from serine β-lactamases**, allowing aztreonam to bypass MBL enzymes entirely and successfully exert its bactericidal activity. In vitro evaluations demonstrate that adding avibactam restores aztreonam susceptibility in **over 98% of carbapenem-resistant Enterobacterales isolates**. Note that because this combination specifically

targets aerobic Gram-negative paths, it lacks activity against anaerobic organisms.

Clinical Trial Evidence: REVISIT and ASSEMBLE

The clinical profile of aztreonam-avibactam is supported by two pivotal Phase 3 trials:

Phase 3 evaluations include the **REVISIT** trial, which compared aztreonam-avibactam (with or without metronidazole) against meropenem (with or without colistin) in complicated intra-abdominal infections (cIAI) and hospital-acquired/ventilator-associated pneumonia (HAP/VAP). It achieved a **76.4% adjudicated clinical cure rate** in cIAI versus 74.0% for meropenem. Additionally, the **ASSEMBLE** trial evaluated the combination against Best Available Therapy (BAT) for serious infections specifically caused by MBL-producing Gram-negative pathogens, supporting its therapeutic role in confirmed MBL cases.

Regulatory Status and Indications

Aztreonam-avibactam has achieved critical global regulatory milestones:

- **European Union:** Approved by the European Medicines Agency (EMA) in **April 2024** for cIAI, complicated urinary tract infections (cUTI), HAP/VAP, and limited-option aerobic Gram-negative infections.
- **United States:** Approved by the U.S. Food and Drug Administration (FDA) as Emblaveo on **February 7, 2025**, combined with metronidazole for adult cIAI patients with limited alternatives.

Safety and Tolerability Profile

The safety profile mirrors historical aztreonam monotherapy data. Frequently observed adverse reactions include hepatic transaminase elevations, diarrhea, anemia, hypokalemia, and pyrexia. Standard precautions remain vital regarding hypersensitivity and hepatic monitoring.

Resistance Mechanisms and Future Outlook

Decreased susceptibility typically arises via **PBP-3 insertion mutations** (e.g., in E. coli) or specific **β-lactamase variants** that compromise avibactam efficacy.

Overall, aztreonam-avibactam remains a vital weapon against previously untreatable MBL-producing threats.

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