

# Piperacillin-Tazobactam

Piperacillin Sodium and Tazobactam Sodium - Antipseudomonal Penicillin & Beta-Lactamase Inhibitor

Antimicrobials / Penicillins

Evidence status: current

## ICU High-Yield Summary

Workhorse ICU antipseudomonal penicillin providing broad Gram-negative, Gram-positive, and anaerobic coverage - best administered as an extended 4-hour infusion, but carries synergy for AKI when combined with Vancomycin.

## Mechanism of Action

### PBP Inhibition + Beta-Lactamase Suicide Inactivation

1. Piperacillin binds essential PBPs (PBPs 1b, 2, and 3), blocking peptidoglycan transpeptidation. 2. Tazobactam irreversibly binds and inactivates plasmid-mediated beta-lactamases (TEM, SHV, penicillinases). 3. Protects piperacillin from enzymatic degradation, restoring activity against beta-lactamase-producing pathogens. 4. Results in cell wall disruption and bactericidal cell lysis.

## ICU Clinical Reasoning

### Why I Choose It

First-line empiric monotherapy for HAP/VAP, intra-abdominal sepsis, and febrile neutropenia when *Pseudomonas* is suspected. | Comprehensive single-agent coverage including *Pseudomonas aeruginosa* AND obligate anaerobes (*B. fragilis*). | Prolonged/extended infusion can improve pharmacodynamic target attainment (%fT > MIC), especially in severe illness or higher MIC pathogens; BLING III did not prove a statistically significant 90-day mortality benefit for continuous over intermittent beta-lactam infusion.

### Why I Avoid / Key Limitations

Observational studies have reported more creatinine-defined AKI with vancomycin plus piperacillin-tazobactam, but causality is uncertain; the randomized ACORN trial found no significant difference in AKI/death between piperacillin-tazobactam and cefepime (most participants also received vancomycin). | Inferior to Meropenem for ESBL bacteremia (MERINO trial). | Unreliable against AmpC hyperproducing Enterobacterales.

### Bedside Pearl

Use an institutionally validated prolonged/extended-infusion regimen when PK/PD optimization is desired, with renal/CRRT adjustment. Do not switch piperacillin-tazobactam to cefepime solely because of an assumed universal AKI advantage; ACORN found no significant AKI/death difference and cefepime carries important neurotoxicity risk in renal dysfunction.

## Dosing & Administration

### Routine ICU Dosing

Standard ICU Regimen: 4.5 g IV every 6 hours as an extended 4-hour infusion (or 3.375 g IV q6h over 4h).

### Hemodialysis

U.S. labeling for intermittent hemodialysis: 2.25 g IV every 12 hours for labeled indications other than nosocomial pneumonia, or 2.25 g every 8 hours for nosocomial pneumonia, plus 0.75 g after each hemodialysis session on dialysis days. Extended-infusion institutional protocols may differ and should be labeled as such.

### CRRT

CRRT dosing is effluent- and MIC-dependent. Extended infusion is reasonable for PK/PD target attainment, but the dose/interval should follow the local CRRT antimicrobial protocol (and beta-lactam TDM where available) rather than a universal 3.375 g q6h regimen.

### Renal Dose Table

CrCl > 50 mL/min: 4.5 g IV every 6 hours (extended infusion over 4h). | CrCl 20-50 mL/min: 3.375 g IV every 6 hours (extended infusion over 4h). | CrCl < 20 mL/min: 2.25 g IV every 6 hours (extended infusion over 4h).

### Syndrome-Specific Regimens

Hospital-Acquired / Ventilator-Associated Pneumonia (HAP/VAP): 4.5 g IV every 6 hours (extended 4-hour infusion). | Complicated Intra-Abdominal Infection (cIAI): 4.5 g IV every 6 hours (extended 4-hour infusion).

## Organ Failure Considerations

### Renal Failure & AKI

Primary renal elimination; dose/interval must be adjusted to kidney function and renal-replacement modality. Observational studies associate vancomycin plus piperacillin-tazobactam with more creatinine-defined AKI, but ACORN did not show greater AKI/death versus cefepime; monitor kidney function rather than assuming a fixed causal 2- to 3-fold risk.

### Hepatic Impairment

No primary hepatic dose adjustment required.

## Toxicity & Safety

### Major Warnings

Kidney-function signal with Vancomycin + Pip-Tazo: observational studies report more creatinine-defined AKI, but randomized ACORN data did not show a significant AKI/death difference versus cefepime; interpret changes in creatinine clinically and reassess all nephrotoxic exposures. | Hypokalemia & Sodium Load: Each 4.5g dose contains 11.18 mEq (257 mg) of Na<sup>+</sup>. | Bone Marrow Suppression: Neutropenia and thrombocytopenia with prolonged therapy (>14 days).

### Organ Toxicities

Renal: Acute interstitial nephritis, acute tubular injury (especially with Vancomycin). | Gastrointestinal: Diarrhea, C. difficile colitis, nausea. | Hematologic: Eosinophilia, leukopenia, neutropenia, prolonged bleeding time.

## Drug Interactions

### Bedside Interactions

Vancomycin: The mechanism behind the observational creatinine-defined AKI association is uncertain and may include true nephrotoxicity and changes in tubular creatinine handling.; consequence: Observational AKI association; randomized ACORN did not demonstrate higher AKI/death versus cefepime.; ICU action: Monitor renal function and overall nephrotoxin burden. If kidney injury develops, reassess indication, susceptibility, dosing, hemodynamics, and alternatives rather than reflexively assuming piperacillin-tazobactam is the cause. | Methotrexate: Inhibition of renal tubular secretion of methotrexate; consequence: Increased serum methotrexate levels and severe toxicity; ICU action: Monitor methotrexate levels closely.

## Monitoring & TDM

### Monitoring

Serum creatinine/BUN and urine output; reassess renal dosing and nephrotoxic exposures during evolving AKI | Serum Potassium and Sodium (check for hypokalemia and sodium overload) | CBC with differential weekly during prolonged courses | Infusion duration compliance (ensure 4-hour extended infusion protocol)

## Antimicrobial Spectrum

### Gram Positive

Covered: Methicillin-susceptible *Staphylococcus aureus* (MSSA) | *Streptococcus pneumoniae* | *Streptococcus pyogenes* | *Enterococcus faecalis* (susceptible) | Not covered: Methicillin-resistant *Staphylococcus aureus* (MRSA) | *Enterococcus faecium* | *Listeria monocytogenes*

### Gram Negative

Covered: *Pseudomonas aeruginosa* | *Escherichia coli* (wild-type) | *Klebsiella pneumoniae* (wild-type) | *Proteus mirabilis* | *Enterobacter cloacae* | *Haemophilus influenzae* | Not covered: ESBL-producing *Enterobacterales* (high inoculum failure / MERINO trial) | AmpC derepressed hyperproducers | KPC / NDM Carbapenemase producers | *Stenotrophomonas maltophilia*

### Anaerobes

Covered: *Bacteroides fragilis* | *Bacteroides thetaiotaomicron* | *Peptostreptococcus* spp. | *Fusobacterium* spp. | Not covered: *Clostridioides difficile*

### Notable Gaps

MRSA | *Enterococcus faecium* | ESBL bacteremia | *Stenotrophomonas* | *C. difficile*

## Evidence & Source Traceability

### Claim-Level Citations

ATS/IDSA HAP/VAP Guidelines recommend Pip-Tazo 4.5 g IV q6h extended infusion for empiric antipseudomonal therapy. - Management of Adults With Hospital-acquired and Ventilator-associated Pneumonia: 2016 Guidelines. Clin Infect Dis 2016;63(5):e61-e111. (<https://pubmed.ncbi.nlm.nih.gov/27418577/>) | Observational studies report more creatinine-defined AKI with vancomycin plus piperacillin-tazobactam, but ACORN found no significant AKI/death difference between piperacillin-tazobactam and cefepime and found more neurologic dysfunction with cefepime. - Qian ET, et al. ACORN randomized clinical trial. JAMA. 2023;330(16):1557-1567. doi:10.1001/jama.2023.20583. (<https://doi.org/10.1001/jama.2023.20583>)

### Guideline IDs

vap-guideline-idsa-ats-2016

### Trial IDs

merino-trial-jama-2018 | antibiotic-acorn-trial | sepsis-bling-iii-trial