Meropenem and piperacillin/tazobactam optimised dosing regimens for critically ill patients receiving renal replacement therapy

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Abstract

Purpose: Optimal dosing of meropenem and piperacillin/tazobactam in critically ill patients receiving renal replacement therapy (RRT) is uncertain due to variable pharmacokinetics. We aimed to develop generalisable optimised dosing recommendations for these antibiotics. Methods: Prospective, multinational pharmacokinetic study including patients requiring various forms of RRT. Independent population PK models were developed, externally validated and applied to perform Monte Carlo dosing simulations using Monolix and Simulx. We calculated the probability

that these dosing regimens achieved standard and high therapeutic unbound antibiotic concentrations over 100% of the dosing interval for the treatment of Enterobacterales and Pseudomonas aeruginosa. Results: We enrolled 300 patients from 22 intensive care units across 12 countries receiving continuous veno-venous haemodialysis (13.0%), haemofiltration (23.3%), haemodiafiltration (48.4%) or sustained low-efficiency dialysis (15.3%). Models were developed using data from 234 patients (8322 samples) and validated with 66 additional patients (560 samples). Predictive performance was high, with mean prediction errors of – 5.2% for meropenem and – 16.9% for piperacillin. Dosing simulations showed that meropenem and piperacillin/tazobactam dosing requirements were dependent on urine output and RRT intensity and duration ($p < 0.05$). In all scenarios, extended/continuous infusions led to a better achievement of effective concentrations with lower daily doses compared to short infusion. Dosing nomograms were developed to inform dosing for different RRT settings, urine outputs, and target concentrations. Conclusion: RRT intensity and duration and urine output determine meropenem and piperacillin/tazobactam dosing requirements in critically ill patients receiving RRT. Extended/continuous infusions facilitate the attainment of effective concentrations. © The Author(s) 2025.

Author keywords

Critically ill patients; Dosing nomograms; Meropenem; Pharmacokinetics; Piperacillin/tazobactam; Renal replacement therapy

Indexed keywords

MeSH

Aged; Anti-Bacterial Agents; Critical Illness; Female; Humans; Intensive Care U
Meropenem; Middle Aged; Monte Carlo Method; Piperacillin, Tazobactam Drug
Prospective Studies; Renal Replacement Therapy

EMTREE drug terms

antibiotic agent; creatinine; hypertensive factor; meropenem; piperacillin plus tazobactam; antiinfective agent; meropenem; piperacillin plus tazobactam

EMTREE medical terms

abdominal infection; adult; algorithm; Article; artificial ventilation; bacterial infection; chronic kidney failure; continuous hemodialysis; continuous infusion; continuous renal replacement therapy; controlled study; creatinine blood level; critically ill patient; decision making; dosing interval; drug dose regimen; effective concentration; Enterobacterales; extended daily dialysis; female; hemodiafiltration; hemofiltration; human; intensive care unit; intubation; major clinical study; male; minimum inhibitory concentration; Monte Carlo method; mortality; nomogram; optimal drug dose; prediction error; probability; prospective study; Pseudomonas aeruginosa; renal replacement therapy; respiratory tract infection; Sequential Organ Failure Assessment

Score; simulation; urine volume; aged; clinical trial; critical illness; middle aged; multicenter study; procedures; therapy

Chemicals and CAS Registry Numbers

Unique identifiers assigned by the Chemical Abstracts Service (CAS) to ensure accurate identification and tracking of chemicals across scientific literature.

creatinine	19230-81-0, 60-27-5
meropenem	96036-03-2
piperacillin plus tazobactam	157044-21-8

Anti-Bacterial Agents

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