Study (Date)	Drug(s)	Population (# pts)	Intervention	Outcome
BLING I Continuous Infusion of Beta-Lactam Antibiotics in Severe Sepsis: A Multicenter Double-Blind, Randomized Controlled Trial (2013) *Clin. Infect. Dis*. 2013; 56(2): 236 – 244.	Piperacillin-tazobactam Meropenem Ticarcillin-clavulanate	ICU – Severe Sepsis N = 60	CI vs IB	• 100%ft> MIC 82% in CI vs 29% in IB (*P* = .001). • clinical cure in CI (70% vs 43%; *P* = .037), • No difference in ICU-free days or survival
DALI: Defining Antibiotic Levels in Intensive Care Unit Patients: Are Current β-Lactam Antibiotic Doses Sufficient for Critically Ill Patients? (2014) *Clin. Infect.Dis*. 2014; 58(8): 1072–1083.	Amoxicillin-clavulanate ampicillin, cefazolin, cefepime, ceftriaxone, doripenem, meropenem, and piperacillin-tazobactam	ICU N = 384	PK/PD target achievement	• 16% did not achieve 50% f T>MIC & were 32% less likely to have a positive clinical outcome • Positive clinical outcome was associated with increasing 50% f T>MIC and 100% f T>MIC ratios • significant interaction with sickness severity
BLING II (2015) A Multicenter Randomized Trial of Continuous versus Intermittent β-Lactam Infusion in Severe Sepsis. *Am J Respir Crit Care Med.* 2015;192(11):1298-305.	Piperacillin-tazobactam Ticarcillin-clavulanate Meropenem	ICU N = 432	CI vs IB	No difference in ICU-free days, 90 d survival, clinical cure, organ failure-free days, or duration of bacteremia
Beta-Lactam Infusion in Severe Sepsis (BLISS): a prospective, two-centre, open-labelled randomised controlled trial of continuous versus intermittent beta-lactam infusion in critically ill patients with severe sepsis (2016) *Intensive Care Med.* 2016; 42: 1535–1545.	Cefepime Meropenem Piperacillin-tazobactam	Critically ill with severe sepsis Not on RRT N = 140	CI vs IB	CI - higher clinical cure rates & higher median ventilator-free days) No difference in 14 or 30 d mortality
Is Prolonged Infusion of Piperacillin/Tazobactam and Meropenem in Critically Ill Patients Associated With Improved Pharmacokinetic/Pharmacodynamic and Patient Outcomes? An Observation From the Defining Antibiotic Levels in Intensive Care Unit Patients (DALI) Cohort (2016) *J Antimicrob Chemother.* 2016;71(1): 196–207.	Piperacillin-tazobactam Meropenem	ICU - post hoc analysis N = 211	CI vs IB	• 89% of patients achieved 50% fT>MIC (conservative target) Respiratory infection & CI – better 30 d survival Higher SOFA score (≥9) – CI better clinical cure and survival
BLING III - Protocol A Protocol for a Phase 3 Multicentre Randomised Controlled Trial of Continuous Versus Intermittent β-Lactam Antibiotic Infusion in Critically Ill Patients With Sepsis: BLING III (2019) *Crit Care Resusc*. 2019;21(1):63–68.	Piperacillin-tazobactam Meropenem	ICU with severe sepsis N = 7000	CI vs IB	• primary outcome is all cause mortality within 90 d • secondary outcomes are clinical cure at Day 14; new acquisition, colonization or infection with a multiresistant organism or Clostridium difficile diarrhoea up to 14 days after randomisation, all-cause ICU mortality and all-cause hospital mortality. • tertiary outcomes are ICU length of stay, hospital length of stay and duration of mechanical ventilation and duration of renal replacement therapy up to 90 d.
TARGET – protocol Therapeutic drug monitoring-based dose optimisation of piperacillin/tazobactam to improve outcome in patients with sepsis (TARGET): a prospective, multi-centre, randomised controlled trial (2019) *Trials*. 2019;20(1): 330.	Piperacillin-tazobactam	Adult severe sepsis/septic shock	IB with TDM vs CI no TDM	Protocol – RCT in progress • primary efficacy endpoint is the change in mean total Sequential Organ Failure Assessment (SOFA) score from day 1 after randomization until day 10 or discharge from the intensive care unit or death • secondary outcomes include mortality, clinical cure, microbiological cure, overall antibiotic use, individual components of the primary outcome, adverse events and analysis of PK and (PD) indices
DOLPHIN – Protocol The effect of therapeutic drug monitoring of beta-lactam and fluoroquinolones on clinical outcome in critically ill patients: the DOLPHIN trial protocol of a multi-centre randomised controlled trial (2020) *BMC Infect Dis*. 2020;20(1):57.	cefotaxime, ceftazidime, ceftriaxone, cefuroxime, amoxicillin, amoxicillin - clavulanic acid, flucloxacillin, piperacillin - tazobactam, meropenem, and ciprofloxacin	ICU N = 450		Protocol – RCT in progress • primary outcome will be ICU length of stay • other outcomes amongst all survival, disease severity, safety, quality of life after ICU discharge, and cost effectiveness

Abbreviations:
ICU – intensive care unit
CI – continuous infusion
IB – intermittent bolus