among those with gram-positive infections, this subgroup was underpowered.[136]

Eight RCTs evaluating clinical cure among nonseverely ill patients found no significant benefit with the use of PI β-lactam antibiotics with a RR of 1.00 (95% confidence interval% 0.95–1.06), I^2=32% (Figure S5). These studies included piperacillin–tazobactam[114,116,117,133,137] and cephalosporins (cefuroxime,[138] cefotaxime,[139] cefepime,[118] and ceftazidime[116]). Most trials utilized CI[117,133,137-139] and the three RCTs in cancer patients utilized EI.[113,116,118] A few reported only the combined outcome of both clinical cure and clinical improvement,[116,117,139] and one study evaluated clinical efficacy without a definition.[113] A significant overall response with EI piperacillin–tazobactam or ceftazidime over SI was found among those with documented infection, especially pneumonia.[116] Of note, among patients with complicated intraabdominal infections, >90% received a laparotomy, which may have driven treatment success for these patients.[117] Additionally, many patients were not microbiologically evaluable[116,118,133,138] or pathogens were highly susceptible with low MICs.[113,117,137,139]

Six RCTs[113,116,117,133,137,138] compared microbiological cure between nonseverely ill patients who received PI β-lactam therapy versus SI and none demonstrated a difference, though a trend toward improved bacteriological success with PI β-lactam antibiotics was still observed among nonseverely ill patients (RR 1.06 [95% confidence interval 0.99–1.15], I^2=27%) (Figure S6). The GRADE evidence summary for mortality, clinical cure, and microbiological cure among nonseverely ill adult patients is shown in Table S2.

Patients with CF hospitalized with acute pulmonary exacerbations are often nonseverely ill and there is currently limited evidence on the clinical impact of PI β-lactam antibiotics in this patient population. To date, the largest multicentered, randomized, cross-over trial evaluating CI versus SI β-lactams in patients with CF compared ceftazidime delivered via CI versus three times daily SI and concluded no significant differences between regimens with respect to the primary outcome of change in FEV_1.[54] However, the mean change in FEV_1% predicted was significantly better with CI over SI in patients with resistant bacteria. In addition, the mean difference in time to the next intravenous antibiotics was 0.4 months longer with CI versus SI (p=0.04). Another multicentered, randomized, cross-over study of ceftazidime-delivered CI versus SI found no difference in leukocyte counts, FEV_1, *Pseudomonas* density, and inflammatory biomarkers in patients with CF.[140] Similarly, a prospective cross-over study found no difference in white blood cell counts, *Pseudomonas* density, and pulmonary function in patients with CF treated with CI or SI ceftazidime.[141] Cefepime delivered as CI versus SI was investigated in patients with CF where no difference in bacterial density, inflammatory mediators, or pulmonary function was observed.[57] There are currently no comparative trials evaluating PI versus SI with other antipseudomonal β-lactam antibiotics (i.e., aztreonam, ceftazidime-avibactam, ceftolozane–tazobactam, doripenem, imipenem–cilastatin, meropenem, meropenem-vaborbactam, piperacillin–tazobactam) in patients with CF for the treatment of an acute pulmonary exacerbation.

3.8.3 | Future research needs (Recommendations 7 and 8)

Regarding mortality, all RCTs were underpowered to detect a difference. Further research is needed to determine if the benefit depends upon organism, infection type, method of PI (extended vs continuous), as well as the duration of EI (e.g., 3 vs 4 h), but future studies should be powered for outcomes in patients with a documented infection. In most RCTs of nonseverely ill patients, MICs may have been too low for infusion time to affect clinical outcomes and many studies lacked MIC data. Larger RCTs are needed in hospitalized patients as well as patients in the outpatient setting to determine the role of PI β-lactams. Adequately powered research is also needed to elucidate the clinical effects of PI β-lactams in patients with cancer, febrile neutropenia, augmented renal clearance, and impaired renal function, including those requiring renal replacement therapy.

Most studies were underpowered for microbiological outcomes because few patients have causative organisms isolated and without bacteriologic documentation, patients are not microbiologically evaluable. Additionally, repeat cultures are not often recommended to assess the resolution of infection. Larger studies are needed to better elucidate the effect of PI β-lactam therapy on microbiologic response relative to short β-lactam infusions; however, clinical outcomes should take precedence in clinical decision making.

In nonseverely ill patients, if no differences in clinical outcomes exist, differences in patient/caregiver-oriented endpoints such as line compatibility, nursing time, quality of life measures, and other practical considerations should be taken into account.

3.9 | PICO question IX

Is the use of PI β-lactam antibiotics safer than SI among adult and pediatric patients?

3.9.1 | Recommendation 9

We cannot recommend for or against the use of PI over SI to provide a safety advantage and reduce adverse effects of β-lactam antibiotics. (Conditional recommendation; very low certainty of evidence).

3.9.2 | Evidence summary

Currently, no clinical trials have demonstrated a safety advantage for PI β-lactam antibiotics when compared to administration via SI. Various adverse events within 18 RCTs[49,102,105,108,110-112,115-117,127,128,133,137-139,142,143] and 8 observational studies[122,144-150] include acute kidney injury, diarrhea (including *Clostridioides difficile* infection), phlebitis or infusion-related infections, and transaminitis, with no apparent difference when administration time is prolonged. However, with most studies not