Clinicians should avoid oral step-down to nitrofurantoin, fosfomycin, amoxicillin-clavulanate, doxycycline, or omadacycline for ESBL-E bloodstream infections. Nitrofurantoin and fosfomycin achieve poor serum concentrations [40, 41]. Amoxicillin-clavulanate and doxycycline achieve unreliable serum concentrations [33, 48]. Omadacycline is a tetracycline derivative with an oral formulation that may exhibit activity against ESBL-producing Enterobacterales isolates but has an unfavorable pharmacokinetic-pharmacodynamic profile [49, 50]. Until more clinical data are available investigating omadacycline's role for the treatment of ESBL-E infections, the panel recommends against its use for this indication.

Question 4: Is There a Role for Piperacillin-Tazobactam in the Treatment of Infections Caused by ESBL-E?

Recommendation: If piperacillin-tazobactam was initiated as empiric therapy for uncomplicated cystitis caused by an organism later identified as an ESBL-E and clinical improvement occurs, no change or extension of antibiotic therapy is necessary. The panel suggests carbapenems, fluoroquinolones, or trimethoprim-sulfamethoxazole rather than piperacillin-tazobactam for the treatment of ESBL-E pyelonephritis and cUTI, with the understanding that the risk of clinical failure with piperacillin-tazobactam may be low. Piperacillin-tazobactam is not recommended for the treatment of infections outside of the urinary tract caused by ESBL-E, even if susceptibility to piperacillin-tazobactam is demonstrated.

Rationale

Piperacillin-tazobactam demonstrates in vitro activity against a number of ESBL-E [51]. Observational studies have had conflicting results regarding the effectiveness of piperacillin-tazobactam for the treatment of ESBL-E infections. An RCT of ESBL-E bloodstream infections indicated inferior results with piperacillin-tazobactam compared to carbapenem therapy (**Question 3**) [34]. A second RCT investigating the role of piperacillin-tazobactam for the treatment of ESBL-E bloodstream infections is ongoing [52]. If piperacillin-tazobactam was initiated as empiric therapy for uncomplicated cystitis caused by an organism later identified as an ESBL-E and clinical improvement occurs, no change or extension of antibiotic therapy is necessary, as uncomplicated cystitis often resolves on its own. At least 3 observational studies have compared the efficacy of piperacillin-tazobactam and carbapenems for the treatment of ESBL-E pyelonephritis or cUTI [53–55]. The most robust observational study included 186 hospitalized patients from 5 hospitals with pyelonephritis or cUTI caused by *E. coli*, *K. pneumoniae*, *K. oxytoca*, or *P. mirabilis*, with confirmation of the presence of ESBL genes in all isolates. This study identified no difference in the resolution of clinical symptoms or 30-day mortality between the groups [53]. A randomized, open-label clinical trial investigating this question was also conducted [56]. The trial included 66 patients with ESBL-producing *E. coli* pyelonephritis or cUTI (with confirmation of the presence of an ESBL gene) randomized to either piperacillin-tazobactam 4.5 g every 6 hours or ertapenem 1 g every 24 hours. Clinical success was similar between both groups at 94% for piperacillin-tazobactam and 97% for ertapenem. These studies suggest noninferiority between piperacillin-tazobactam and carbapenems for pyelonephritis or cUTIs.

In the subgroup of 231 patients with ESBL-E bloodstream infections from a urinary source in the aforementioned RCT comparing the outcomes of patients with *E. coli* or *K. pneumoniae* bloodstream infections treated with piperacillin-tazobactam or meropenem (**Question 3**), higher mortality was identified in the piperacillin-tazobactam group (7% vs 3%) [34], although it did not attain statistical significance. Although the panel is unable to state that piperacillin-tazobactam should be avoided for pyelonephritis or cUTIs, the panel continues to have concerns with the use of piperacillin-tazobactam for the treatment of ESBL-E infections, even if limited to UTIs, and prefers the use of carbapenem therapy (or oral fluoroquinolones or trimethoprim-sulfamethoxazole, if susceptible) [**Question 2**]).

Observational studies have had conflicting results regarding the effectiveness of piperacillin-tazobactam for the treatment of ESBL-E bloodstream infections [26, 53–66]. The effectiveness of piperacillin-tazobactam for the treatment of invasive ESBL-E infections may be diminished by the potential for organisms to have increased expression of the ESBL enzyme or by the presence of multiple β-lactamases [67]. Additionally, piperacillin-tazobactam MIC testing may be inaccurate and/or poorly reproducible when ESBL enzymes are present, or in the presence of other β-lactamase enzymes such as OXA-1, making it unclear if an isolate that tests susceptible to this agent is indeed susceptible [45, 68–71]. For these reasons, the panel recommends avoiding piperacillin-tazobactam for the treatment of invasive ESBL-E infections.

Question 5: Is There a Role for Cefepime in the Treatment of Infections Caused by ESBL-E?

Recommendation: Cefepime is not recommended for the treatment of nonurinary infections caused by ESBL-E, even if susceptibility to the agent is demonstrated. If cefepime was initiated as empiric therapy for uncomplicated cystitis caused by an organism later identified as an ESBL-E and clinical improvement occurs, no change or extension of antibiotic therapy is necessary. The panel recommends avoiding cefepime for the treatment of pyelonephritis and cUTI. Cefepime is also not recommended for the treatment of infections outside of the urinary tract caused by ESBL-E, even if susceptibility to cefepime is demonstrated.

Rationale

No clinical trials comparing the outcomes of patients with ESBL-E bloodstream infections treated with cefepime or