and non-carbapenemase-producing CRE [94]. Molecular testing can identify specific carbapenemase families (eg, differentiating a KPC from an OXA-48-like carbapenemase). Carbapenemase phenotypic and/or genotypic testing are performed by a minority of clinical microbiology laboratories, but the panel strongly encourages all clinical microbiology laboratories to pursue carbapenemase testing to inform optimal treatment decisions. Treatment recommendations for CRE infections listed below assume that in vitro activity of preferred and alternative antibiotics has been demonstrated.

Question 1: What Are Preferred Antibiotics for the Treatment of Uncomplicated Cystitis Caused by CRE?

Recommendation: Ciprofloxacin, levofloxacin, trimethoprim-sulfamethoxazole, nitrofurantoin, or a single-dose of an aminoglycoside are preferred treatment options for uncomplicated cystitis caused by CRE. Standard infusion meropenem is a preferred treatment option for cystitis caused by CRE resistant to ertapenem (ie, ertapenem MICs $\geq$2 mcg/mL) but susceptible to meropenem (ie, meropenem MICs $\leq$1 mcg/mL), when carbapenemase testing results are either not available or negative. If none of the preferred agents are active, ceftazidime-avibactam, meropenem-vaborbactam, imipenem-cilastatin-relebactam, or cefiderocol are alternative options for uncomplicated CRE cystitis.

Rationale

Clinical trial data evaluating the efficacy of most preferred agents for uncomplicated CRE cystitis are not available. However, as ciprofloxacin, levofloxacin, trimethoprim-sulfamethoxazole, nitrofurantoin, or a single dose of an aminoglycoside all achieve high concentrations in urine, they are expected to be effective for uncomplicated CRE cystitis, when active [4, 18–21]. Meropenem is a preferred agent against uncomplicated CRE cystitis for isolates that remain susceptible to meropenem because most of these isolates do not produce carbapenemases [95]. Meropenem should be avoided if carbapenemase testing is positive, even if susceptibility to meropenem is demonstrated. There is uncertainty about the accuracy of meropenem MICs in these scenarios, and use of meropenem may lead to treatment failure [96]. Some agents listed as alternative options for ESBL-E cystitis (eg, fluoroquinolones) are recommended as preferred agents for CRE cystitis. These agents are not preferred agents for the treatment of uncomplicated ESBL-E cystitis in order to preserve their activity for more invasive infections. They are, however, preferred agents against uncomplicated CRE cystitis because there are generally fewer treatment options available for these infections.

Aminoglycosides are almost exclusively eliminated by the renal route in their active form. A single intravenous dose is generally effective for cystitis, with minimal toxicity [28]. Individual aminoglycosides are equally effective if susceptibility is demonstrated. In general, higher percentages of CRE clinical isolates are susceptible to amikacin and plazomicin than to other aminoglycosides [97, 98]. Plazomicin may remain active against isolates resistant to amikacin [99].

If none of the preferred agents is active, ceftazidime-avibactam, meropenem-vaborbactam, imipenem-cilastatin-relebactam, and cefiderocol are alternative options for uncomplicated CRE cystitis. Data are insufficient to favor 1 agent over the others, but all of these agents are reasonable treatment options based on published comparative effectiveness studies [100–105].

Fosfomycin use should be limited to uncomplicated CRE cystitis caused by *E. coli* as the *fosA* gene (intrinsic to certain gram-negative organisms such as *Klebsiella* spp., *Enterobacter* spp., and *Serratia marcescens*) can hydrolyze fosfomycin and may lead to clinical failure [29, 30]. Randomized controlled trial data indicate that oral fosfomycin is associated with higher clinical failure than nitrofurantoin for uncomplicated cystitis [18].

Colistin is an alternative agent for treating uncomplicated CRE cystitis only if none of the above agents is an option. Colistin converts to its active form in the urinary tract; clinicians should remain cognizant of the associated risk of nephrotoxicity [106]. Polymyxin B should not be used as treatment for uncomplicated CRE cystitis, due to its predominantly nonrenal clearance [107].

Question 2: What Are Preferred Antibiotics for the Treatment of Pyelonephritis and Complicated Urinary Tract Infections Caused by CRE?

Recommendation: Ciprofloxacin, levofloxacin, and trimethoprim-sulfamethoxazole are preferred treatment options for pyelonephritis and cUTI caused by CRE if susceptibility is demonstrated. Extended-infusion meropenem is a preferred treatment option for pyelonephritis and cUTIs caused by CRE resistant to ertapenem (ie, ertapenem MICs $\geq$2 mcg/mL) but susceptible to meropenem (ie, meropenem MICs $\leq$1 mcg/mL), when carbapenemase testing results are either not available or negative. Ceftazidime-avibactam, meropenem-vaborbactam, imipenem-cilastatin-relebactam, and cefiderocol are also preferred treatment options for pyelonephritis and cUTIs caused by CRE resistant to both ertapenem and meropenem.

Rationale

Although the minority of CRE are expected to retain susceptibility to ciprofloxacin, levofloxacin, or trimethoprim-sulfamethoxazole, these agents are all preferred agents to treat CRE pyelonephritis or cUTI after susceptibility is demonstrated [35–37].

Extended-infusion meropenem is a preferred agent against pyelonephritis and cUTI by CRE that remain susceptible to meropenem, because most of these isolates do not produce carbapenemases (Table 1) [90]. Meropenem should be avoided if carbapenemase testing is positive, even if susceptibility to