

## **Managing infections by challenging-to-treat antimicrobial-resistant Gram-negative bacteria: supplementary guidance from the Infectious Diseases Society of America (IDSA)**

Professor Mark Wilcox, reviewing Tamma PD, *et al. Clin Infect Dis* ciaa1478, published online 27 Oct 2020.

*Infectious Diseases Society of America (IDSA) provides recommendations for infections caused by three important groups of antibiotic-resistant Gram-negative bacterial pathogens*

In a departure from comprehensive guidelines, this IDSA guidance document provides focused recommendations, as an alternative and complementary resource, to assist clinicians in selecting appropriate treatment options for patients infected with three common and therapeutically challenging Gram-negative bacterial pathogens: extended-spectrum  $\beta$ -lactamase-producing Enterobacterales (ESBL-E); carbapenem-resistant Enterobacterales (CRE); and *Pseudomonas aeruginosa* with difficult-to-treat resistance (DTR-*P. aeruginosa*) (1). These have been designated as urgent or serious threats by the US Centers for Disease Control and Prevention (2). Key recommendations include the following.

### *Infections caused by ESBL-E*

- *Uncomplicated cystitis* should preferably be treated with either nitrofurantoin or trimethoprim-sulfamethoxazole; alternatively, ciprofloxacin, levofloxacin, ertapenem, meropenem or imipenem-cilastatin are recommended when first-line options are unavailable. For *pyelonephritis and complicated urinary tract infections* ([cUTIs], defined as UTIs occurring in association with a structural or functional abnormality), treatment with ertapenem, meropenem, imipenem-cilastatin, ciprofloxacin, levofloxacin or trimethoprim-sulfamethoxazole is recommended. Ciprofloxacin, levofloxacin or trimethoprim-sulfamethoxazole recommendations are based on clinical experience and the ability of these agents to achieve high concentrations in urine. For *infections outside the urinary tract*, carbapenem is preferred. The bioavailability and sustained serum concentrations of oral fluoroquinolones and trimethoprim-sulfamethoxazole make them suitable options for *ESBL-E bloodstream infections*.
- Piperacillin-tazobactam and cefepime should *not* be used to treat ESBL-E infections, even if susceptibility to these drugs is demonstrated.

### *Infections caused by CRE*

- *Uncomplicated cystitis* should be preferably treated with ciprofloxacin, levofloxacin, trimethoprim-sulfamethoxazole, nitrofurantoin or a single dose of an aminoglycoside. *Pyelonephritis and cUTIs* caused by CRE resistant to ertapenem and meropenem can be treated with ceftazidime-avibactam, meropenem-vaborbactam, imipenem-cilastatin-relebactam and cefiderocol. For *infections outside the urinary tract* caused by CRE resistant to ertapenem (but susceptible to meropenem), extended-infusion meropenem is recommended; and for CRE resistant to both ertapenem and meropenem, treatment should be with or ceftazidime-avibactam, meropenem-vaborbactam, or imipenem-cilastatin-relebactam.
- Polymyxin B and colistin should be *avoided* for any CRE infections, and combination antibiotic therapy is not recommended.

#### *DTR-P. aeruginosa infections*

- *Uncomplicated cystitis* should preferably be treated with ceftolozane-tazobactam, ceftazidime-avibactam, imipenem-cilastatin-relebactam, cefiderocol or a single dose of an aminoglycoside. *Pyelonephritis and cUTIs* can be treated with ceftolozane-tazobactam, ceftazidime-avibactam, imipenem-cilastatin-relebactam and cefiderocol. For *infections outside the urinary tract*, ceftolozane-tazobactam, ceftazidime-avibactam and imipenem-cilastatin-relebactam, as monotherapy, are the preferred treatment options.

#### **Comment**

This IDSA document provides easy-to-use and timely recommendations for infections such as uncomplicated cystitis, pyelonephritis and cUTIs, and infections outside the urinary tract caused by ESBL-E, CRE and DTR-*P. aeruginosa*. Reflecting the consensus approach used by a panel of practising infectious disease specialists, this guidance describes ‘real-world’ preferred and alternative treatment options; notably, established antibiotics still have a role. Thus, oral fluoroquinolones, such as ciprofloxacin, for example, are a recommend option for ESBL-E and CRE uncomplicated cystitis and ESBL-E cUTIs. The recommendation is based on clinical experience, as well as recognition of the ability of these agents to achieve high concentrations in urine, their bioavailability and sustained serum concentrations. Despite this, judicious use of oral fluoroquinolones is cautioned when other options are available so as to preserve their activity for future infections and to limit the possibility of adverse events. Similarly, new antibiotic therapies such as  $\beta$ -lactam- $\beta$ -lactamase inhibitors that have a clear role in difficult-to-treat antibiotic-resistant infections should be reserved for where other therapy options are not appropriate. This

guidance is expected to evolve continually, providing effective recommendations to clinicians through iterative review, updates with evidence-based data and inclusion of other problematic Gram-negative pathogens.

## References

1. Kadri SS, Adjemian J, Lai YL, *et al.* Difficult-to-treat resistance in Gram-negative bacteremia at 173 US hospitals: retrospective cohort analysis of prevalence, predictors, and outcome of resistance to all first-line agents. *Clin Infect Dis* 2018; **67**: 1803–14.
2. Centers for Disease Control and Prevention. Antibiotic resistance threats in the United States, 2019. Available at: <https://www.cdc.gov/drugresistance/pdf/threats-report/2019-ar-threats-report-508.pdf>. Accessed 2 November 2020.