

Update on antimicrobial pharmacotherapy against multidrug-resistant Gram-negative bacilli

Melania Íñigo¹
José Luis Del Pozo^{1,2,3,4}

Treatment of infections caused by carbapenemase-producing *Enterobacterales*

¹Department of Clinical Microbiology, Clínica Universidad de Navarra, Madrid, Spain

²Infectious Diseases Division, Clínica Universidad de Navarra, Pamplona, Spain

³Department of Clinical Microbiology, Clínica Universidad de Navarra, Pamplona, Spain

⁴Instituto de Investigación Sanitaria de Navarra (IdiSNA)

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ABSTRACT

Antibiotic resistance is one of the main threats to public and individual health worldwide. In the last two decades, an increase in the detection of carbapenem-resistant *Enterobacterales* has been reported. The treatment of infections caused by these strains is a therapeutic challenge. The use of carbapenems may be beneficial depending on MIC value and source of infection. New drugs, with different activity against the different classes of carbapenemases, are developed showing significant benefits.

Keywords: Carbapenem resistant *Enterobacterales*, carbapenemases

INTRODUCTION

Antibiotic resistance is one of the main threats to public and individual health worldwide. *Enterobacterales* can acquire numerous resistance-encoding plasmids, specially *Klebsiella pneumoniae*. Two decades ago, carbapenemase-producing *Enterobacterales* (CPE) began to spread. The most clinically relevant carbapenemases in *Enterobacterales* belong to classes A (i.e., mainly KPC type), B (i.e., metallo-beta-lactamases, VIM, IMP and NDM types) and D (i.e., mainly OXA-48 type). These enzymes exhibit significant variations in hydrolytic efficiency and are characterized by elevated minimal inhibition concentration (MIC) of carbapenems compared to the epidemiological cutoff values. The combination with other resistant mechanisms, like decreased outer membrane permeability or extended spectrum beta-lactamase (ESBL) production, are also frequently described. In addition, CPE often coharbor resistance mechanisms against other antimicrobial classes such as fluoroquinolones, aminoglycosides, tetracyclines, and trimethoprim-sulfamethoxazole.

CPE cause serious infections, especially in immunocompromised patients, prolong hospital stays and increase mortality rates, ranging from 24% to as high as 70%, depending on the study population. Despite the need to establish effective early treatments, the few therapeutic options available limit the alternatives [1].

EPIDEMIOLOGY OF CARBAPENEMASES

Isolates of carbapenem-resistant *Enterobacterales* (CRE) are increasingly being described. The SENTRY Antimicrobial Surveillance Program analyzed the CRE isolates obtained during the period 1997–2016 in 42 countries from the main geographical regions. A statistically significant increase in CRE rates was reported over time for the overall isolates and breakdowns by all regions and infection sources. CRE rates increased from 0.6% in 1997–2000 to 2.9% in 2013–2016 with gradual increases of 0.8%–0.9% per period since 2005–2008. In this study, a representative number of CRE isolates was analyzed for the presence of carbapenemase encoding genes. KPC producers were the most frequently detected, with rates maintained throughout the study, while a notable increase in MBL (mainly by NDM) and OXA-48 isolates was reported. The detection of double carbapenemases (e.g., KPC+MBL, MBL+OXA-48 or KPC+OXA-48) was only reported during the second period [2].

In the same line, in the epidemiological survey carried out in 2018, all 37 participating European countries reported CPE isolates, whereas in the previous study performed in 2015, three countries had still not identified a single case. Overall, 11 countries reported a worsened epidemiological situation of CPE than in 2015, 25 countries described no change, and one country reported an improvement of the CPE epidemiological situation. Twenty out of 37 countries reported inter-institutional spread of CPE within the country, and compared with 2015, 4 additional countries reported regional or inter-regional spread in 2018, thus increasing the number of countries with regional or inter-regional spread to 16 [3].

Correspondence:
José Luis Del Pozo
Department of Clinical Microbiology & Infectious Diseases Division, Clínica Universidad de Navarra, Pamplona, Spain
E-mail: jdelpozo@unav.es

In Spain, in a national study involving 42 hospitals conducted over a 5-year period (2010–2014) with isolates of *K. pneumoniae* obtained from blood cultures, resistance to imipenem increased from 0,27% in 2010 to 3,46% in 2014, and 86% of these isolated produced carbapenemases (i.e., mainly OXA-48, followed by VIM, KPC, IMP and GES) [4]. In another prospective multicenter Spanish study (with 83 hospitals participating) from February to May 2013, the impact of CPE from clinical infections and carriers was analyzed. The percentages of CPE isolates significantly diverse between species, being significantly higher in *K. pneumoniae* (75.4%) than in *Enterobacter cloacae* (35.1%) and *Escherichia coli* (33%). Again, the most detected carbapenemase was OXA-48 (71.5%), followed by VIM (25.3%), KPC (2.1%) and IMP (1.6%) [5].

Infections caused by CPE are associated with increased mortality. In the systematic review and metaanalysis published by Falagas et al collecting all data available until 2012, attributable deaths to CRE infections were analyzed. The number of deaths was 2-fold higher among patients with bacteremia caused by CRE than among patients with bacteremia caused by carbapenem-susceptible isolates. Those studies showed that many patients with infections caused by CRE had not received adequate empirical treatment, which could explain this increase in mortality [6].

CAN WE STILL USE CARBAPENEMS TO THREAT CARBAPENEM-RESISTANT INFECTIONS?

The use of imipenem or meropenem in monotherapy for the treatment of CPE infections is associated with therapeutic failure when isolates show high MIC values. A large review analyzed 15 studies with 50 patients with carbapenem-resistant (CR) *K. pneumoniae* infections treated in monotherapy with carbapenems. Twenty-nine of these isolates exhibited carbapenem MICs ≤ 2 mg/L, 13 equal to 4 and 8 mg/L, and 8 isolates ≥ 8 mg/L. Therapeutic failure increased from 29.4% for MICs ≤ 1 mg/L to 75.0% for MICs > 8 mg/L, showing some therapeutic benefit in infections caused by strains with intermediate susceptibility to carbapenems (28.6% and 33.3% of failure for MICs 4 and 8 $\mu\text{g/ml}$, respectively) [1]. Carbapenem display time-dependent bactericidal killing when free drug concentrations remain above the MIC for 40 to 50% of the time between dosing intervals. Monte Carlo simulation models of different dosing regimens of carbapenems indicate that prolonging the infusion time from 30 min to 3 h increases the probability of bactericidal target attainment at each MIC value. In addition, for isolates with high MICs, only the high-dose/prolonged-infusion regimen displays a relatively high probability of bactericidal target attainment [7].

COMBINED TREATMENT

A combination therapy with ≥ 2 active drugs, including a carbapenem, has been reported as the lowest failure rate (8.3%) in the treatment of infections by carbapenemase-producing *K. pneumoniae* in comparison to other regimens, such as combination therapy with ≥ 2 active drugs not including a

carbapenem, monotherapy with an aminoglycoside, monotherapy with a carbapenem, monotherapy with tigecycline, monotherapy with colistin and inappropriate therapy. The highest rate of therapeutic failure was presented by patients with inappropriate therapy, followed by patients receiving monotherapy with colistin, combination therapy with ≥ 2 active drugs not including a carbapenem and monotherapy with tigecycline [1].

Tumbarello et al reported the survival benefits of non-empirical regimens that include 2 or 3 active drugs (as compared with monotherapy) in the treatment of infections caused by KPC-producing *K. pneumoniae*. In this large multicenter cohort study, combination regimens that include meropenem provided appreciable therapeutic benefits when the meropenem MIC was ≤ 8 mg/L, but no benefits were obtained when the meropenem MIC exceeds 32 mg/L [8].

In the same line, a prospective cohort study including episodes of bacteremia caused by colistin-resistant and high-level meropenem-resistant (≥ 64 mg/L) KPC-producing *K. pneumoniae* showed that the combination therapy (e.g., tigecycline + gentamicin, tygeciline + fosfomycin, gentamicin + fosfomycin, or tigecycline + fosfomycin + gentamicin) was associated with reduced mortality (25%) compared to the use of these antibiotics in monotherapy (43.8%) [9].

Gutiérrez-Gutiérrez et al reported data obtained in a retrospective cohort study of bloodstream infections (BSI) caused by CPE. In this study, 26 tertiary hospitals of 10 countries participated and compared 30-day all-cause mortality between patients receiving appropriate or inappropriate therapy, and among those patients receiving appropriate therapy, combination therapy or monotherapy. Lower mortality was significantly lower in patients receiving appropriate (38.5%) than inappropriate (60.6%) therapy, but overall mortality was not different between those receiving combination therapy (39%) and monotherapy (41%). Combination therapy was associated with improved survival only in patients with high mortality score [10].

NOVEL ANTIBIOTICS FOR THE TREATMENT OF CRE INFECTIONS

Infections caused by CRE/CPE are associated high mortality rates. Although, as it has been shown, combined therapy can be beneficial in the treatment of these infections, new drugs are needed to achieve better clinical outcomes and lower mortality rates. Several antibiotics are recently approved (e.g., ceftolozane/tazobactam, ceftazidime/avibactam, meropenem/vaborbactam, plazomicin, imipenem/relebactam, or cefiderocol) [11].

Several studies showed the efficacy of ceftazidime-avibactam (CAV) –a cephalosporin-beta-lactamase inhibitor combination– in the treatment of infections caused by CRE. Van Duin et al reported lower mortality rates in patients with CRE infections treated with CAV (9%) than in those treated with colistin (32%), and inverse probability of treatment weight-

ing-adjusted efficacy of a better clinical outcome (64%) for CAV [12]. Shields et al compared outcomes of patients with CR *K. pneumoniae* BSI receiving definitive treatments containing CAV or alternative regimens (e.g., carbapenem + aminoglycoside, carbapenem + colistin, or other including monotherapy with aminoglycoside or colistin). CAV was associated with higher rates of clinical success and survival than other regimens [13]. Tumbarello et al analyzed 138 cases of KPC-producing *K. pneumoniae* infections treated with CAV as a salvage therapy after a first-line treatment with other antimicrobials, and most cases (78.9%) CAV was administered with at least 1 other active antibacterial agent (e.g., gentamicin, tigecycline, colistin, fosfomycin, and other drugs). The overall 30-day mortality rate was 34.1%, and the highest rate was recorded in patients with bacteremia. The 30-day mortality rate among patients with bacteremia was significantly lower in patients who received CAV (36.5%) than patients without CAV (55.8%), and in patients treated with CAV in monotherapy (40.9%) than patients treated with single-drug (77.8%). A similar difference was observed in patients managed in combination therapy but without statistically significant results. In the multivariate analysis of risk factors for 30-day mortality in patients with bacteremia, receipt of CAV was the sole independent predictor of survival [14].

Relebactam is a novel non-beta-lactam inhibitor of class A carbapenemases and class C cephalosporinases (e.g., AmpC) which, in combination with imipenem, can restore the activity against many imipenem-nonsusceptible *Enterobacterales*. The efficacy of treatment with imipenem/relebactam (IMI/REL) has been reported. In a randomized, controlled, double-blind, phase 3 trial, hospitalized patients with hospital-acquired/ventilator-associated pneumonia, complicated intraabdominal infection or complicated urinary tract infection caused by imipenem-nonsusceptible (but colistin- and IMI/REL-susceptible) pathogens the efficacy of IMI/REL was evaluated. Favorable overall response was observed in 71% IMI/REL and 70% colistin + imipenem patients, day 28 favorable clinical response in 71% and 40%, and 28-day mortality in 10% and 30%, respectively. No statistically significant differences were observed in favorable overall response, but serious adverse occurred in 10% of patients treated with IMI/REL vs 31% of patients treated with colistin + imipenem patients, and treatment-emergent nephrotoxicity in 10% and 56%, respectively. So, this trial presented IMI/REL as an efficacious and well-tolerated treatment option for CRE infections [15]. Vázquez-Ucha et al analyzed the *in vitro* activity of IMI/REL, and other 16 widely used antimicrobials, against a Spanish nationwide collection of CPE. All isolates showed high rates of susceptibility to colistin (86.5%), IMI/REL (85.8%) and CAV (83.8%). Susceptibility rates to other beta-lactams, aminoglycosides, quinolones and fosfomycin were under 80% in all cases and only amikacin retained activity against >75% of the isolates. Antibiotic susceptibility varied widely depending on the type of carbapenemase detected. While CAV was the most active agent against OXA-48 producers (97.7%) followed by IMI/REL (87.9%), IMI/REL was the most active drug (100.0%) against KPC producers (followed by CAV (93.4%)) [16].

Vaborbactam is a boron-based beta-lactamase inhibitor with activity against class A carbapenemases. Combination with meropenem restores activity against KPC-producers. In a phase 3, multinational, open-label, randomized controlled trial, the efficacy and safety of meropenem/vaborbactam (MER/VAR) was evaluated versus the best available therapy (mono/combination therapy with colistin, carbapenems, aminoglycosides, tigecycline or CAV) for the treatment of CRE infections (i.e., bacteremia, hospital-acquired/ventilator-associated bacterial pneumonia, complicated intraabdominal infections, and complicated urinary tract infection/acute pyelonephritis). Day-28 all-cause mortality was 15.6% and 33.3% for MER/VAR and best available therapy, respectively. Treatment-related adverse events and renal-related adverse-events were 24.0% and 4.0% for MER/VAR, and 44.0% and 24.0% for other treatments. So, monotherapy with MER/VAR was reported with increased clinical cure, decreased mortality and reduced nephrotoxicity compared with other drugs [17]. In a multicenter, retrospective cohort study, Ackley et al compared the efficacy and safety of MER/VAR to CAV in the treatment of CRE infections. No significant difference in clinical success, and 30- and 90-day mortality rates were observed between groups, although in patients with recurrent infection, development of resistance occurred in 3 patients receiving CAV in monotherapy (no resistance was detected in patients with MER/VAR treatment) [18].

Cefiderocol is a novel siderophore cephalosporin designed to treat carbapenem-resistant bacteria, with activity against ESBL, AmpC and class A, B and OXA-48 carbapenemases. An open-label multicenter study assessed the efficacy and safety of cefiderocol and best available therapy for the treatment of patients with serious carbapenem-resistant Gram-negative infection. For patients with hospital-acquired pneumonia, clinical cure rate was very similar in both groups (50% and 53% for cefiderocol and best available therapy, respectively). The same clinical cure rate was achieved for both groups in patients with BSI and sepsis (43%). Cefiderocol achieved higher microbiological eradication in patients with complicated urinary tract infection (53%) than in the best available therapy group (20%). At the end of the study, more patients receiving cefiderocol died (34%) than patients receiving best available therapy (18%) [19].

Plazomicin is a new aminoglycoside with activity against ESBL, AmpC and class A and D carbapenemases. In a multicenter, randomized, open-label trial including patients with bloodstream infection or hospital-acquired/ventilator-associated bacterial pneumonia caused by CRE, efficacy and safety of plazomicin versus colistin were evaluated. Among patients with BSI, death from any cause at 28 days or clinically significant disease-related complication occurred more frequently in patients receiving colistin (53%) than in patients receiving plazomicin (14%). In patients with pneumonia, numerically fewer deaths were observed at day 14 among patients who received plazomicin-based treatment [20].

Infectious Diseases Society of America (IDSA) guidelines recommendations are summarized in Table 1. Although it is expected that bacteria will continue developing resistance

Table 1 Summary of treatment of carbapenem-resistance *Enterobacterales* according to IDSA Guidelines.

Source of infection	Preferred treatment	Alternative treatment
Uncomplicated cystitis	Ciprofloxacin, levofloxacin, trimethoprim-sulfamethoxazole, nitrofurantoin or a single dose of an aminoglycoside Meropenem (standard infusion): For cystitis caused by CPE, if ertapenem-resistant, meropenem-susceptible, and no carbapenemases are detected	Ceftazidime-avibactam, meropenem-vaborbactam, imipenem-relebactam, ceftiderocol, colistin (when no alternative options are available)
Pyelonephritis and complicated urinary tract infections	Ceftazidime-avibactam, meropenem-vaborbactam, imipenem-relebactam, ceftiderocol Meropenem (extended infusion), if ertapenem-resistant, meropenem-susceptible, and no carbapenemases are detected	Once-daily aminoglycosides
Infections outside of the urinary tract caused by ertapenem-resistant meropenem-susceptible and carbapenemase testing are neither available or negative	Meropenem (extended infusion)	Ceftazidime-avibactam
Infections outside of the urinary tract caused by ertapenem and meropenem-resistant and carbapenemase testing are neither available or negative	Ceftazidime-avibactam, meropenem-vaborbactam, imipenem-relebactam	Ceftiderocol Tigecycline, eravacycline
Infections outside of the urinary tract caused by carbapenem-resistant and carbapenemase-producer <i>Enterobacterales</i>	Ceftazidime-avibactam, meropenem-vaborbactam, imipenem-relebactam	Ceftiderocol Tigecycline, eravacycline
Infections caused by metallo-beta-lactamase-producers <i>Enterobacterales</i>	Ceftazidime-avibactam + aztreonam, ceftiderocol	Tigecycline, eravacycline
Infections caused by OXA-48 -producers <i>Enterobacterales</i>	Ceftazidime-avibactam	Ceftiderocol Tigecycline, eravacycline

mechanisms against these new antibiotics, their correct use will determine the benefit that we can obtain from them [21].

CONFLICT OF INTEREST

Authors declare no conflict of interest

REFERENCES

- 1 Tzouveleki LS, Markogiannakis A, Psychogiou M, Tassios PT, Dailikos GL. Carbapenemases in *Klebsiella pneumoniae* and other *Enterobacteriaceae*: an evolving crisis of global dimensions. *Clin Microbiol Rev.* 2012;25(4):682–707. doi:10.1128/CMR.05035-11
- 2 Castanheira M, Deshpande LM, Mendes RE, Canton R, Sader HS, Jones RN. Variations in the occurrence of resistance phenotypes and carbapenemase genes among *Enterobacteriaceae* isolates in 20 years of the SENTRY antimicrobial surveillance Program. *Open Forum Infect Dis.* 2019;6(Suppl 1):S23–33. doi:10.1093/ofid/ofy347
- 3 Brolund A, Lagerqvist N, Byfors S, Struelens MJ, Monnet DL, Albiger B, et al. Worsening epidemiological situation of carbapenemase-producing *Enterobacteriaceae* in Europe, assessment by national experts from 37 countries, July 2018. *Euro Surveill.* 2019;24(9):1900123. doi:10.2807/1560-7917.ES.2019.24.9.1900123
- 4 Aracil-García B, Oteo-Iglesias J, Cuevas-Lobato Ó, Lara-Fuella N, Pérez-Grajera I, Fernández-Romero S, et al. Rápido aumento de la resistencia a cefalosporinas de 3 a generación, imipenem y de la co-resistencia en 7.140 aislados de *Klebsiella pneumoniae* en hemocultivos (2010–2014) según datos de EARS-Net en España. *Enferm Infecc Microbiol Clin.* 2017;35(8):480–6. doi:10.1016/j.eimc.2016.06.007
- 5 Oteo J, Ortega A, Bartolomé R, Bou G, Conejo C, Fernández-Martínez M, et al. Prospective multicenter study of carbapenemase-producing *Enterobacteriaceae* from 83 hospitals in Spain reveals high in vitro susceptibility to colistin and meropenem. *Antimicrob Agents Chemother.* 2015;59(6):3406–12. doi:10.1128/AAC.00086-15

- 6 Falagas ME, Tansarli GS, Karageorgopoulos DE, Vardakas KZ. Deaths attributable to carbapenem-resistant *Enterobacteriaceae* infections. *Emerg Infect Dis*. 2014;20(7):1170–5. doi:10.3201
- 7 Daikos GL, Markogiannakis A. Carbapenemase-producing *Klebsiella pneumoniae*: (when) might we still consider treating with carbapenems? *Clin Microbiol Infect*. 2011;17(8):1135–41. doi:10.1111/j.1469-0691.2011.03533.x
- 8 Tumbarello M, Trecarichi EM, De Rosa FG, Giannella M, Giacobbe DR, Bassetti M, et al. Infections caused by KPC-producing *Klebsiella pneumoniae*: differences in therapy and mortality in a multicentre study. *J Antimicrob Chemother*. 2015;70(7):2133–43. doi:10.1093/jac/dkv086
- 9 Daikos GL, Markogiannakis A. Carbapenemase-producing *Klebsiella pneumoniae*: (when) might we still consider treating with carbapenems? *Clin Microbiol Infect*. 2011;17(8):1135–41. doi:10.1128/AAC.00406-17
- 10 Gutiérrez-Gutiérrez B, Salamanca E, de Cueto M, Hsueh P-R, Viale P, Paño-Pardo JR, et al. Effect of appropriate combination therapy on mortality of patients with bloodstream infections due to carbapenemase-producing *Enterobacteriaceae* (INCREMENT): a retrospective cohort study. *Lancet Infect Dis*. 2017;17(7):726–34. doi:10.1016/s1473-3099(17)30228-1
- 11 Koulenti D, Song A, Ellingboe A, Abdul-Aziz MH, Harris P, Gavey E, et al. Infections by multidrug-resistant Gram-negative Bacteria: What's new in our arsenal and what's in the pipeline? *Int J Antimicrob Agents*. 2019;53(3):211–24. doi:10.1093/jac/dkv086
- 12 van Duin D, Lok JJ, Earley M, Cober E, Richter SS, Perez F, et al. Colistin Versus Ceftazidime-Avibactam in the Treatment of Infections Due to Carbapenem-Resistant *Enterobacteriaceae*. *Clin Infect Dis*. 2018;66(2):163–71. doi:10.1093/cid/cix783
- 13 Shields RK, Nguyen MH, Chen L, Press EG, Potoski BA, Marini RV, et al. Ceftazidime-avibactam is superior to other treatment regimens against carbapenem-resistant *Klebsiella pneumoniae* bacteremia. *Antimicrob Agents Chemother*. 2017;61(8). doi:10.1093/cid/cix783
- 14 Tumbarello M, Trecarichi EM, Corona A, De Rosa FG, Bassetti M, Mussini C, et al. Efficacy of ceftazidime-avibactam salvage therapy in patients with infections caused by *Klebsiella pneumoniae* carbapenemase-producing *K. pneumoniae*. *Clin Infect Dis*. 2019;68(3):355–64. doi:10.1093/cid/ciy492
- 15 Motsch J, Murta de Oliveira C, Stus V, Köksal I, Lyulko O, Boucher HW, et al. RESTORE-IMI 1: A multicenter, randomized, double-blind trial comparing efficacy and safety of imipenem/relebactam vs colistin plus imipenem in patients with imipenem-nonsusceptible bacterial infections. *Clin Infect Dis*. 2020;70(9):1799–808. doi:10.1093/cid/ciz530
- 16 Vázquez-Ucha JC, Seoane-Estévez A, Rodiño-Janeiro BK, González-Bardanca M, Conde-Pérez K, Martínez-Gutián M, et al. Activity of imipenem/relebactam against a Spanish nationwide collection of carbapenemase-producing *Enterobacterales*. *J Antimicrob Chemother*. 2021;76(6):1498–510. doi:10.1093/jac/dkab043
- 17 Wunderink RG, Giamarellos-Bourboulis EJ, Rahav G, Mathers AJ, Bassetti M, Vazquez J, et al. Effect and safety of meropenem-vaborbactam versus best-available therapy in patients with carbapenem-resistant *Enterobacteriaceae* infections: The TANGO II randomized clinical trial. *Infect Dis Ther*. 2018;7(4):439–55. doi:10.1007/s40121-018-0214-1
- 18 Ackley R, Roshdy D, Meredith J, Minor S, Anderson WE, Capraro GA, et al. Meropenem-vaborbactam versus ceftazidime-avibactam for treatment of carbapenem-resistant *Enterobacteriaceae* infections. *Antimicrob Agents Chemother* [Internet]. 2020 [citado el 27 de mayo de 2022];64(5). doi:10.1128/AAC.02313-19
- 19 Bassetti M, Echols R, Matsunaga Y, Ariyasu M, Doi Y, Ferrer R, et al. Efficacy and safety of cefiderocol or best available therapy for the treatment of serious infections caused by carbapenem-resistant Gram-negative bacteria (CREDIBLE-CR): a randomised, open-label, multicentre, pathogen-focused, descriptive, phase 3 trial. *Lancet Infect Dis*. 2021;21(2):226–40. doi:10.1016/S1473-3099(20)30796-9
- 20 McKinnell JA, Dwyer JP, Talbot GH, Connolly LE, Friedland I, Smith A, et al. Plazomicin for infections caused by carbapenem-resistant *Enterobacteriaceae*. *N Engl J Med*. 2019;380(8):791–3. doi:10.1056/NEJMc1807634
- 21 Tamma PD, Aitken SL, Bonomo RA, Mathers AJ, van Duin D, Clancy CJ. Infectious Diseases Society of America Guidance on the Treatment of Extended-Spectrum β -lactamase Producing *Enterobacterales* (ESBL-E), Carbapenem-Resistant *Enterobacterales* (CRE), and *Pseudomonas aeruginosa* with Difficult-to-Treat Resistance (DTR-*P. aeruginosa*). *Clin Infect Dis*. 2021;72(7):1109–16. doi:10.1093/cid/ciab295