Infectious Diseases Society of America 2024 Guidance on the Treatment of Antimicrobial-Resistant Gram-Negative Infections: Supplemental Material

The following are notes related to **Table 1** "Suggested dosing of antibiotics for the treatment of antimicrobial-resistant infections in adults, assuming normal renal and hepatic function"

Agent	Notes
Amikacin	The panel suggests using adjusted body weight for patients >120% of ideal body weight. The panel suggests that amikacin be used for pyelonephritis or complicated urinary tract infections if timely, routine therapeutic drug monitoring (TDM) and subsequent dose adjustments, as needed, are possible. The panel suggests targeting an area under the curve over 24 hours (AUC_{0-24}) to minimum inhibitory concentration (MIC; AUC_{0-24}/MIC) ratio of 80 – 100. An acceptable, but less preferred, alternative approach is to target a peak/MIC ratio of 8 – 10 or use a nomogram-based approach. As these targets require a specific MIC value, organism-specific MIC values are preferred, if available. An alternative approach is to forgo evaluations of AUC/MIC for pyelonephritis or complicated urinary tract infections (cUTIs), and instead, focus efforts on monitoring the amikacin trough to evaluate for nephrotoxicity. Data supporting the safety of amikacin AUC_{0-24}, irrespective of MIC, in excess of 300 mg*hr/L are limited, and such exposures are not routinely recommended. The panel suggests maintaining amikacin trough concentrations <5 mg/L as they are associated with a reduced risk of toxicity. If pharmacokinetic calculations for an individual regimen suggest the use of a dose which confers an unacceptably high risk of nephrotoxicity, alternate agents may be necessary, even in the setting of reported organism susceptibility. The above suggested amikacin dosing strategies are informed by the following references: Rougier F, et al. Clin Pharmacokinet. 2003;42:493. Drusano GL and Louie A. Antimicrob Agents Chemother. 2011;55:2528-31. Drusano GL, et al. Clin Infect Dis. 2007; 45:753-60. Pai MP, et al. Diagn Microbiol Infect Dis. 2014;78:178-187.
Ampicillin-sulbactam	The panel suggests 9 grams total daily dose of the sulbactam component of ampicillin-sulbactam for the treatment of CRAB infections. Safety concerns with high dose ampicillin-sulbactam were not identified in the literature. The rationale behind this dosage is described in the AMR Guidance document. Suggested dose adjustment strategies for high-dose ampicillin-sulbactam are available in Jaruatanasirikul S, et al. European Journal of Pharmaceutical Sciences. 2019;136:104940. Commercially available susceptibility testing methods in the United States evaluate ampicillin-sulbactam at a fixed ratio of 2:1 (i.e., 2 parts ampicillin to 1 part sulbactam). The numbers to the right of the hyphen or dash of ampicillin-sulbactam MICs is the sulbactam MIC. The sulbactam MIC can be used to evaluate sulbactam

	susceptibility. The panel suggests reconstituting and preparing high-dose ampicillin- sulbactam to the maximum concentration reported in the FDA-approved product labeling.
Ceftazidime-avibactam PLUS aztreonam	The panel suggests administration of ceftazidime-avibactam 2.5 grams intravenously (IV) every 8 hours and aztreonam 2 grams IV every 8 hours administered simultaneously. The panel suggests 3-hour infusions of both agents to increase the time of the free drug concentrations above the MIC. Ceftazidime-avibactam and aztreonam are Y-site compatible (O'Donnell JN, et al. Clin Ther. 2020;42:1580- 1586.e2). Aztreonam given as 2 grams IV every 6 hours, infused over 3 hours, can be considered in patients with augmented renal clearance with at least weekly monitoring of liver function. The panel suggests caution with the use of aztreonam continuous infusion, particularly at doses of 8 grams daily, due to potential increased risk of liver enzyme elevation. The panel suggests developing paneled orders in the electronic medical record to facilitate simultaneous administration via Y-site administration. A hollow-fiber infection model demonstrated killing of an NDM-producing *E. coli* with simultaneous administration of a two-hour infusion of ceftazidime-avibactam, 2.5 grams every 8 hours, and aztreonam 2 grams every 8 hours in some experiments; increased bacterial killing and reduced bacterial regrowth was observed when dosed as ceftazidime-avibactam 2.5 every 8 hours plus aztreonam 2 grams every 6 hours. (Lodise TP, et al. J Antimicrob Chemother. 2020;75:2622-2632). Monte Carlo simulations using a population pharmacokinetic model derived from patients receiving the combination suggested that aztreonam given every 6 hours may only be necessary in patients with augmented renal clearance (Falcone M, et al. J Antimicrob Chemother 2021;76:1025-1031). Comparative effectiveness studies have not compared the two dosing approaches. The safety of aztreonam with or without ceftazidime-avibactam was assessed in a healthy volunteer study (Lodise TP, et al. Antimicrob Agents Chemother. 2022;66:e0093622. Lodise TP, et al. Antimicrob Agents Chemother. 2022;66:e0093522). These data suggest a dose-dependent effect of aztreonam on elevated liver enzymes with resolution upon withdrawal of the drug. The clinical significance of these data remain unclear; caution is warranted with aztreonam at doses of 8 grams daily, especially as a continuous infusion. The above suggested dosing strategies are informed by the following references: Lodise TP, et al. J Antimicrob Chemother. 2020;75:2622-2632. Falcone M, et al. Clin Infect Dis. 2021;72:1871-1878. Falcone M, et al. J Antimicrob Chemother. 2021;76:1025-1031. Lodise TP, et al. Antimicrob Agents Chemother. 2022;66:e0093622. Lodise TP, et al. Antimicrob Agents Chemother. 2022;66:e0093522.
Ertapenem	The panel suggests administration of 1 gram of ertapenem IV every 24 hours, infused over 30 minutes. Higher doses of ertapenem (e.g., 1.5 grams) or more frequent dosing (e.g., every 12 hours) may circumvent some of the probability of target

	attainment issues with ertapenem in obese or critically ill patients with hypoalbuminemia, respectively. Data supporting these alternative dosing strategies are limited. (Chen M, et al. Antimicrob Agents Chemother. 2006;50:1222-1227. Lass J, et al. Case Reports in Critical Care. 2017;5310768. Goutelle S, et al. J Antimicrob Chemother. 2018;73:987-994. Ferry T, et al. Open Forum Infectious Diseases. 2016; 3(suppl_1).
Gentamicin	The panel suggests using adjusted body weight for patients >120% of ideal body weight. The panel suggests that gentamicin be used for pyelonephritis or complicated urinary tract infections if timely, routine TDM and subsequent dose adjustments, as needed, are possible. The panel suggests targeting an AUC_{0-24}/MIC ratio of 80 – 100. An acceptable, but less preferred, alternative approach is to target a peak/MIC ratio of 8 – 10 or use a nomogram-based approach. As these targets require a specific MIC value, organism-specific MIC values are preferred, if available. An alternative approach is to forgo evaluations of AUC/MIC for pyelonephritis or cUTIs, and instead, focus efforts on monitoring the gentamicin trough to evaluate for nephrotoxicity. Data supporting the safety of gentamicin AUC_{0-24}, irrespective of MIC, in excess of 100 mg*hr/L are limited and such exposures are not routinely recommended. The panel suggests maintaining gentamicin trough concentrations <1 mg/L as they are associated with a reduced risk of toxicity. If pharmacokinetic calculations for an individual dosage regimen suggest the use of a dose which confers an unacceptably high risk of nephrotoxicity, alternate agents may be necessary, even in the setting of reported organism susceptibility. The above suggested gentamicin dosing strategies are in part informed by the following references: Rougier F, et al. Clin Pharmacokinet. 2003;42:493. Drusano GL and Louie A. Antimicrob Agents Chemother. 2011;55:2528-31. Drusano GL, et al. Clin Infect Dis. 2007; 45:753-60. Pai MP, et al. Diagn Microbiol Infect Dis. 2014;78:178-187.
Imipenem-cilastatin	The imipenem-cilastatin dose includes only imipenem. As an example, 500 mg imipenem-cilastatin is equivalent to 500 mg imipenem. A prolonged infusion (i.e., 3 hours) is suggested for infections other than uncomplicated cystitis. This may be challenging given the short stability of imipenem-cilastatin once reconstituted. If 3- hour infusions are logistically challenging, 30-minute infusions can be considered.
Imipenem-cilastatin-relebactam	The imipenem-cilastatin-relebactam dose includes imipenem, cilastatin, and relebactam. As an example, imipenem-cilastatin-relebactam 1.25 grams of imipenem is equivalent to 500 mg imipenem, 500 mg cilastatin, and 250 mg relebactam.
Meropenem	Meropenem has limited availability as 2-gram vials for IV infusion. If 2-gram vials are unavailable, when the agent is stored in automated drug cabinets and prepared using reconstitution drug delivery systems, the panel suggests administering two 1-gram vials successively over 90 minutes each, if administering meropenem over 3 hours.

Plazomicin	The panel suggests using adjusted body weight for patients >120% of ideal body weight. The panel suggests that plazomicin be used for pyelonephritis or complicated urinary tract infections if timely, routine therapeutic drug monitoring (TDM) and subsequent dose adjustments, as needed, are possible. The panel suggests targeting an AUC_{0-24}/MIC ratio of 80 – 100. An acceptable, but less preferred, alternative approach is to use a nomogram-based approach. As these targets require a specific MIC value, organism-specific MIC values are preferred, if available. An alternative approach is to forgo evaluations of AUC/MIC for pyelonephritis or cUTIs, and instead, focus efforts on monitoring the plazomicin trough to evaluate for nephrotoxicity. Data supporting the safety of plazomicin AUC_{0-24}, irrespective of MIC, in excess of 315 mg*hr/L are limited, and such exposures are not routinely recommended. The panel suggests maintaining plazomicin trough concentrations <3 mg/L as they are associated with a reduced risk of toxicity. If pharmacokinetic calculations for an individual regimen suggest the use of a dose which confers an unacceptably high risk of nephrotoxicity, alternate agents may be necessary, even in the setting of reported organism susceptibility. The above suggested plazomicin dosing strategies are in part informed by the following reference: Plazomicin Prescribing Information: https://zemdri.com/assets/pdf/Zemdri-plazomicin-pescribing-information-Feb-2023.pdf.
Sulbactam- durlobactam	Sulbactam-durlobactam is available as a co-packaged kit containing 1 single-dose vial of sulbactam 1 gram and 2-single-dose vials of durlobactam 0.5 grams that must be reconstituted and further diluted prior to IV infusion. Unlike many beta-lactam/beta-lactamase inhibitors, dosing is listed for each respective component (i.e., sulbactam 1 gram and durlobactam 1 gram versus the combined dose of 2 grams). Special attention should be given to the ordering, preparation, and administration of this product to avoid medication-related errors.
Tobramycin	The panel suggests using adjusted body weight for patients >120% of ideal body weight. The panel suggests that tobramycin be used for pyelonephritis or complicated urinary tract infections if timely, routine TDM and subsequent dose adjustments, as needed, are possible. The panel suggests targeting an AUC_{0-24}/MIC ratio of 80 – 100. An acceptable, but less preferred, alternative approach is to target a peak/MIC ratio of 8 – 10 or use a nomogram-based approach. As these targets require a specific MIC value, organism-specific MIC values are preferred, if available. An alternative approach is to forgo evaluations of AUC/MIC for pyelonephritis or cUTIs, and instead, focus efforts on monitoring the tobramycin trough to evaluate for nephrotoxicity. Data supporting the safety of tobramycin AUC_{0-24}, irrespective of MIC, in excess of 100 mg*hr/L are limited and such exposures are not routinely recommended. The panel

	suggests maintaining tobramycin trough concentrations <1 mg/L as they are associated with a reduced risk of nephrotoxicity. If pharmacokinetic calculations for an individual dosage regimen suggest the use of a dose which confers an unacceptably high risk of toxicity, alternate agents may be necessary, even in the setting of reported organism susceptibility. The above suggested tobramycin dosing strategies are in part informed by the following references: Rougier F, et al. Clin Pharmacokinet. 2003;42:493. Drusano GL and Louie A. Antimicrob Agents Chemother. 2011;55:2528-31. Drusano GL, et al. Clin Infect Dis. 2007; 45:753-60. Pai MP, et al. Diagn Microbiol Infect Dis. 2014;78:178-187.
Trimethoprim-sulfamethoxazole (TMP-SMX)	Given the toxicities associated with TMP-SMX (e.g., nausea/vomiting, hyperkalemia, fluid overload, possible nephrotoxicity), particularly at higher doses, no established dose-response relationship (Lasko MJ, et al. Antimicrob Agents Chemother. 2022;66(3):e0216721), absence of clinical evidence supporting any particular dose, and evidence that TMP dosing of >15 mg/kg/day may lead to serum sulfamethoxazole levels higher than necessary (Dao BD, et al. Curr Ther Res Clin Exp. 2014;76:104-109), the panel suggests a dose range of 10-15 mg/kg (trimethoprim component) of TMP/SMX for patients with *S. maltophilia* infections.