"first-line" antibiotics, generally beta-lactams or fluoroquinolones. We concur with the need to improve on the existing multidrug-resistant (MDR), extremely drug-resistant (XDR), and pandrug-resistant definitions [2] as they do not help with actual therapeutic choices. However, DTR does not help significantly because with introduction of new antibiotics, the definition of DTR will shift/mutate/evolve, including the assessment on what constitutes first-line treatment. We also agree that the use of older, often toxic agents is not ideal, even when they are demonstrated to be active in vitro, if there are newer alternatives. We think the term "carbapenem-resistant" when appropriately applied encompasses most DTR gram-negative infections and it provides useful phenotypic characteristics that enable pathogen-directed treatment. Carbapenem-susceptible infections that may be extended-spectrum beta-lactamase (ESBL) producers and also resistant to fluoroquinolones should not be considered DTR.

We were also puzzled why this examination of the Premier Database did not identify *Stenotrophomonas maltophilia* as an important DTR pathogen that causes bloodstream infections (BSIs) in the United States. We examined a similar Premier dataset specifically for BSIs [3] and found that *S. maltophilia* is the most common etiology of carbapenem-resistant gram-negative BSIs. There may be 2 reasons for this. First, the Centers for Disease Control and Prevention/European Centre for Disease Control and Prevention definitions for MDR, XDR, and Physicians Desk Reference only focused on acquired resistance, while *S. maltophilia* is intrinsically resistant to most beta-lactams due to the presence of chromosomal ESBL (L2) and metallo-carbapenemase (L1) [4]. Second, the algorithm that the authors used required susceptibility testing to a given antibiotic, and most clinical microbiology laboratories do not test carbapenems for *S. maltophilia*. In our analysis of the Premier dataset, we considered all BSI isolates of *S. maltophilia* as carbapenem resistant. From 43 095 gram-negative bacteremias, 3.5% were caused by carbapenem-resistant gram-negative pathogens. *Stenotrophomonas maltophilia* was the most common species at 32%, while *Pseudomonas aeruginosa* caused 25% of infections, *Klebsiella pneumoniae* caused 17%, *Acinetobacter baumannii* caused 15%, *Proteus mirabilis* caused 8%, and *Escherichia coli* caused 3%. Importantly, of all carbapenem-resistant gram-negative BSIs, carbapenem-resistant *Enterobacteriaceae* only accounted for 28%.

Trimethoprim/sulfamethoxazole (TMP/SMX) is considered the "gold standard" [5] for the treatment of *S. maltophilia*, and indeed >95% are susceptible to this drug. However, TMP/SMX is not a first-line agent in bacteremia; thus, *S. maltophilia*, by definition, should be considered DTR. Whether or not resistance is acquired or intrinsic does not change how difficult it is to treat an infection.

Recently approved new antibiotics and others likely to be approved will render the DTR definition obsolete. What we really need now are rapid diagnostics for identification and susceptibility data that provide actionable information, especially for gram-negative BSIs.

Note

Potential conflicts of interest. Both authors: No reported conflicts of interest. Both authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

Roger M. Echols[1] and Glenn S. Tillotson[2]

[1]ID3C3c, Easton, Connecticut, and [2]GST Micro LLC, Henrico, Virginia

References

1. Kadri SS, Adjemian J, Lai YL, et al; National Institutes of Health Antimicrobial Resistance Outcomes Research Initiative. 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. Magiorakos AP, Srinivasan A, Carey RB, et al. Multidrug-resistant, extensively drug-resistant and pandrug-resistant bacteria: an international expert proposal for interim standard definitions for acquired resistance. Clin Microbiol Infect **2012**; 18:268–81.
3. Cai B, Echols R, Rudin D, Morgan G, Nagata S. Risk factors for carbapenem-resistant gram-negative bloodstream infections (BSI) in U.S. hospitals (2010–2015). Open Forum Infect Dis **2018**; 5(Suppl 1):S638.
4. El Chakhtoura NG, Saade E, Iovleva A, et al. Therapies for multidrug resistant and extensively drug-resistant non-fermenting gram-negative bacteria causing nosocomial infections: a perilous journey toward "molecularly targeted" therapy. Expert Rev Anti Infect Ther **2018**; 16:89–110.
5. Wang YL, Scipione MR, Dubrovskaya Y, Papadopoulos J. Monotherapy with fluoroquinolone or trimethoprim-sulfamethoxazole for treatment of *Stenotrophomonas maltophilia* infections. Antimicrob Agents Chemother **2014**; 58:176–82.

Correspondence: G. S. Tillotson, GST Micro LLC, Henrico, VA (gtillotsonconsult@yahoo.com).

Clinical Infectious Diseases® 2019;69(9):1641–1642

DOI: 10.1093/cid/ciz184

Reply to Raoult and Rolain, and to Echols and Tillotson

To the Editor—We appreciate the letters submitted by Raoult et al [1] and Tillotson et al [2] in response to our article on difficult-to-treat resistance (DTR) in select taxa of Gram-negative bloodstream infection (GNBSI) at US hospitals [3]. DTR was defined as resistance to all first-line (high-efficacy, low-toxicity) agents, which for the study period and chosen GNBSIs meant β-lactams (including carbapenems) and fluoroquinolones. The developers of DTR would like to address a few comments in the letters and reinforce key aspects about this metric.

We agree with Raoult et al [1] that the march of antibiotic resistance has appeared recently to somewhat stabilize [4]. However, complacency induced by this apparent lull would be a major mistake and contrary to the history of antibiotic resistance and our understanding of evolution biology. Furthermore, characterizing DTR as "rare" and "with nonsignificant consequences" is misleading. Although the prevalence of DTR in GNBSI of 1% may seem low, over half of the hospitals distributed across all 9 US census regions displayed at least 1 case. Estimating mortality attributable to resistance is challenging [5, 6] and as we

have conceptually shown, varies considerably by site, onset and severity of the infection as well as the calipers used for comparison [7]. Notwithstanding, nearly one in every two patients with DTR GNBSIs died (crude mortality = 43%), which upon risk adjustment still represents a 40% higher adjusted mortality risk compared to those with nonresistant GNBSI (adjusted risk ratio, 1.4; 95% confidence interval [CI], 1.2–1.6; $P < .001$).

The DTR concept was specifically developed to capture excess mortality attributable to both discordant empirical regimens and subsequent reliance on less effective and/or more toxic "reserve" compounds (eg, colistin, tigecycline and aminoglycosides). Hence, Raoult et al's suggestion that any increase in mortality due to DTR "should have been corrected with the use of appropriate [reserve] compounds" appears to entirely miss the point of our article. Importantly, injudiciously expanding the empiric use of reserve agents as suggested by Raoult et al would be of questionable benefit and potentially harmful [8].

Tillotson et al raise several important issues that warrant emphasis, including the importance of carbapenem resistance as an epidemiologic designation and the need for the DTR definition to evolve over time. We emphasize in our manuscript [3] that "DTR is not a fixed phenotype but rather a flexible framework." Much like revision of clinical guidelines and susceptibility breakpoints, the rubric of antibiotics involved in defining DTR will also require periodic revision in order to remain up-to-date. We believe this dynamic quality of DTR, is in fact a strength that enables us to continue to capture how resistance is perceived and confronted at the bedside. The 77-year-long human experiment with antibiotics has taught us that pathogens evolve under antibiotic selective pressure and mobile genetic elements enable strategic co-existence and global dissemination of resistance traits. Consequently, it is unrealistic for any traditional antibiotic to remain perennially and universally active [9]. Furthermore, the influx of new antibiotics, their changing supply, access and cost logistics and evolving evidence regarding their use collectively infuses a dynamic aspect into our armamentarium. These moving parts preclude any static definition of co-resistance from remaining consistently indicative of the same treatment constraints over time. The "carbapenem resistant" label is no exception. Even though it has enabled us to gauge the extent of resistance to this important antibiotic category, carbapenem resistance has a different connotation (relative to "difficult-to-treat") today than it did a few years ago [10]. Notably, our study [3] demonstrated that carbapenem-resistant isolates of *Pseudomonas aeruginosa,* a frequent and important healthcare-associated pathogen, are more likely than not to be susceptible to other βlactams and/or fluoroquinolones–a profile that is clearly not DTR.

Importantly, the concept of DTR is scalable to non-bloodstream sites, as well as other bacterial problem-pathogens such as enterococci and even *Stenotrophomonas maltophilia* as suggested by Tillotson et al. However, there is not one universal definition of DTR that can be applied to all pathogens. Although *Stenotrophomonas maltophilia* is intrinsically carbapenem resistant, its clinical and epidemiologic implications are substantially different from the bacterial taxa we selected to illustrate the utility of the DTR concept. Intrinsic resistance to carbapenems does pose "difficulty" by virtue of a higher likelihood of inappropriate empiric therapy, yet targeted therapy is generally less challenging given that relatively high levels of susceptibility to trimethoprim-sulfamethoxazole and levofloxacin [11].

Unlike the need of Shadok brains to forgo one concept in order to learn another [1, 12], we suggest parallel adoption and concomitant use of important static definitions like carbapenem resistance and dynamic indices like DTR given that they serve unique and complimentary roles.

Notes

Disclaimer. The comments of the authors do not necessarily represent the official position of the National Institutes of Health, nor does mention of trade names, commercial products, or organizations imply endorsement by the US government.

Financial support. This work was supported by the Intramural Research Program of the National Institutes of Health Clinical Center.

Potential conflicts of interest. Both authors: No reported conflicts of interest. Both authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

Sameer S. Kadri and Robert L. Danner

Critical Care Medicine Department, National Institutes of Health Clinical Center, Bethesda, Maryland

References

1. Raoult D, Rolain J. The paradigm of the Shadoks and antibiotic resistance. Clin Infect Dis **2019**; 69:1641
2. Tillotson S, Echols R. DTR, do we need a new definition? Clin Infect Dis **2019**; 69:1641–2.
3. Kadri SS, Adjemian J, Lai YL, et al; National Institutes of Health Antimicrobial Resistance Outcomes Research Initiative (NIH–ARORI). 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.
4. CDC. Antibiotic resistance patient safety Atlas. **2018**. Available at: https://www.cdc.gov/hai/data/portal/patient-safety-atlas.html. Accessed 14 March 2019.
5. Abat C, Rolain JM, Dubourg G, Fournier PE, Chaudet H, Raoult D. Evaluating the clinical burden and mortality attributable to antibiotic resistance: the disparity of empirical data and simple model estimations. Clin Infect Dis **2017**; 65:58–63.
6. Cassini A, Högberg LD, Plachouras D, et al; Burden of AMR Collaborative Group. Attributable deaths and disability-adjusted life-years caused by infections with antibiotic-resistant bacteria in the EU and the European Economic Area in 2015: a population-level modelling analysis. Lancet Infect Dis **2019**; 19:56–66.
7. Kadri SS, Strich JR, Swihart BJ, et al. Attributable mortality from extensively drug resistant Gram-negative infections using propensity-matched tracer antibiotic algorithms. Am J Infect Control **2019**. doi:10.1016/j.ajic.2019.01.010
8. Ong DSY, Frencken JF, Klein Klouwenberg PMC, et al; MARS consortium. Short-course adjunctive gentamicin as empirical therapy in patients with severe sepsis and septic shock: a prospective observational cohort study. Clin Infect Dis **2017**; 64:1731–6.
9. Marston HD, Dixon DM, Knisely JM, Palmore TN, Fauci AS. Antimicrobial resistance. JAMA **2016**; 316:1193–204.
10. Talbot GH, et al. The Infectious Diseases Society of America's 10 x '20 initiative (Ten New Systemic Antibacterial Agents FDA-approved by 2020): is 20 x '20 a possibility? Clin Infect Dis **2019**; 69:1–11.
11. Sader HS, Farrell DJ, Flamm RK, Jones RN. Antimicrobial susceptibility of Gram-negative organisms isolated from patients hospitalised with

pneumonia in US and European hospitals: results from the SENTRY Antimicrobial Surveillance Program, 2009-2012. Int J Antimicrob Agents **2014**; 43:328–34.
12. Wikipedia contributors. Les Shadoks. Wikipedia, The Free Encyclopedia. **2018**. 18:07 UTC. Available at: https://en.wikipedia.org/w/index.php?title=Les_Shadoks&oldid=848086299. Accessed 14 March 2019.

Correspondence: S. S. Kadri, National Institutes of Health, Bethesda, MD 20892 (Sameer.kadri@nih.gov).

Clinical Infectious Diseases® 2019;69(9):1642–4

DOI: 10.1093/cid/ciz186

Methodologic Considerations for Small Cohort Studies

To the Editor—Willekens et al [1] recently published a prospective cohort study in which they assessed the noninferiority of an early switch to oral linezolid compared to standard parenteral therapy (SPT) among *Staphylococcus aureus* bacteremia (SAB) patients. These findings are important due to the scarcity of studies that have assessed the alternatives to SPT for uncomplicated SAB. We offer some considerations regarding the study design that may influence the inferences that could be made related to this study.

The authors compared switching to linezolid between day 3 to 9 in 45 patients with a group of 90 propensity-score-matched patients who received SPT (without early switch to oral linezolid) The literature shows that bacteremia recurs in approximately 9% of patients despite appropriate antimicrobial therapy [2]. However, their study does not describe the smallest detectable difference to assess the noninferiority of the intervention, which determines the study's power and the adequacy of their sample size. Using the expected rate of the outcome in the literature, if the study aimed to detect a 5% noninferiority limit of reduction in the 90-day recurrence rate with 80% power and 5% type I error, at least 406 patients would be required in each treatment arm. Reducing the noninferiority limit to 4% would increase the required sample size to 634/arm [3]. Although the authors acknowledged the low sample size of their study, acknowledging an adequate sample size specific to the research question would help readers to appreciate the relative power of the current study.

In addition, 26 patients who were switched to linezolid outside of the 3- to 9-day range from treatment start and 44 who died ≤7 days after index culture were excluded from analysis. The exclusion of patients who died prior to the follow-up period while patients could have been exposed to the treatment may also introduce survival bias. The patients who survived up to day 7 could have been exposed to either SPT or linezolid and developed the outcome. Taking into account the short follow-up period and small sample size, this bias could be reduced by conducting a nonparametric or semiparametric survival analysis and calculating the relative hazard of death.

Further, to reduce confounding by indication, the authors conducted propensity score matching, which resulted in the exclusion of 17 patients in the SPT group who did not have a match with the linezolid group. The proportion of many risk factors of death remained higher in the SPT group. When the number of patients in the control group is not large enough to allow for complete matching, weighted regression using the propensity score may be more appropriate to address confounding without introducing additional bias [4].

Finally, we believe the authors should have used Fisher exact test instead of χ^2 test to assess group differences for 90-day recurrence and 30-day and 90-day mortality due to having <5 patients in ≥1 column.

In summary, Willekens et al's study spearheads future studies to find alternative oral treatments for uncomplicated SAB. This study could benefit from quantifying the limitations of the study power and from adopting alternative or additional statistical approaches to provide more valid inferences.

Note

Potential conflicts of interest. R. O. reports nonfinancial support from Vanderbilt University and other support from Vanderbilt University and the Tennessee Department of Health during the conduct of the study; nonfinancial support from the Society for Healthcare Epidemiology of America and the US Department of State Fulbright Program; grants from federal funding from the Centers for Disease Control and Prevention (CDC); and personal fees from the Tennessee Department of Health outside the submitted work. P. F. R. reports grant funding from the National Institutes of Health/National Institute of Allergy and Infectious Diseases (K01-AI131895). M. A. K. reports grants and nonfinancial support from the CDC during the conduct of the study; grants and nonfinancial support from the CDC; nonfinancial support from the Society for Healthcare Epidemiology of America, the Council of State and Territorial Epidemiologists, and the National Academy of Sciences, Medicine and Engineering; personal fees and other support from the Infectious Diseases Consultation Corporation; and personal fees and nonfinancial support from MedScape outside the submitted work. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

Rany Octaria,[1] Peter F. Rebeiro,[2,3] and Marion A. Kainer[4]

[1]Vanderbilt Epidemiology PhD Program, Vanderbilt University Graduate School; [2]Department of Medicine, Division of Infectious Diseases & Division of Epidemiology, and [3]Department of Biostatistics, Vanderbilt University School of Medicine; and [4]Healthcare Associated Infections and Antimicrobial Resistance Program, Tennessee Department of Health, Nashville

References

1. Willekens R, Puig-Asensio M, Ruiz-Camps I, et al. Early oral switch to linezolid for low-risk patients with *Staphylococcus aureus* bloodstream infections: a propensity-matched cohort study. Clin Infect Dis **2019**; 69:381–7.
2. Chang FY, Peacock JE Jr, Musher DM, et al. *Staphylococcus aureus* bacteremia: recurrence and the impact of antibiotic treatment in a prospective multicenter study. Medicine (Baltimore) **2003**; 82:333–9.
3. Blackwelder WC. "Proving the null hypothesis" in clinical trials. Control Clin Trials **1982**; 3:345–53.
4. Franklin JM, Eddings W, Austin PC, Stuart EA, Schneeweiss S. Comparing the performance of propensity score methods in healthcare database studies with rare outcomes. Stat Med **2017**; 36:1946–63.

Correspondence: R. Octaria, Vanderbilt PhD Epidemiology Program, Vanderbilt University Graduate School, 2525 West End Avenue, Suite 600, Nashville, Tennessee, 37201 (rany.octaria@vanderbilt.edu).

Clinical Infectious Diseases® 2019;69(9):1644

DOI: 10.1093/cid/ciz201