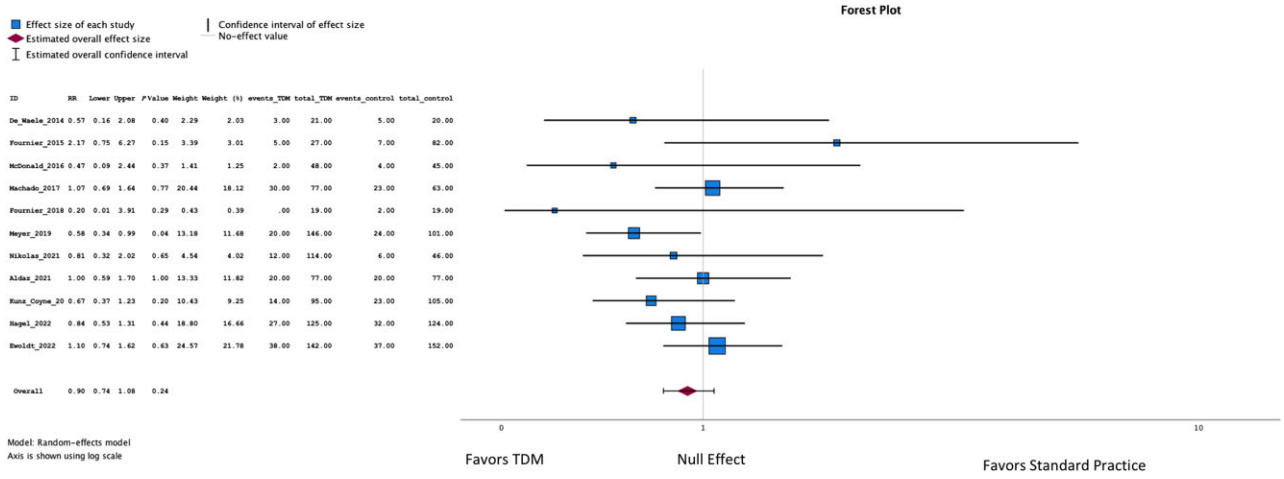

Figure 1. Combined forest plot of Ewoldt et al and Mangalore et al data on 28-day all-cause mortality. Abbreviation: RR, relative risk; TDM, therapeutic drug monitoring.

breakpoints or epidemiologic cutoffs. Despite the current interest and ongoing research, we now have results from two large randomized controlled trials in critically ill patients, powered for clinical outcomes that do not demonstrate benefit of TDM for patients [3, 5]. Therefore, at present we do not believe there is sufficient evidence to recommend widespread adoption of TDM in critically ill patients prescribed β-lactams.

Notes

Author Contributions. T. Z. wrote the manuscript. B. D. did the meta-analysis and helped with revisions.

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Applying Desirability of Outcome Ranking End Point to Randomized Trial of Sulopenem for the Treatment of Complicated Urinary Tract Infections

To the Editor—We read Howard-Anderson et al's article [1] describing the application of a desirability of outcome ranking (DOOR) end point to 3 complicated urinary tract infection (cUTI) trials and Rodriguez-Baño and Gutiérrez-Gutiérrez's companion editorial [2] with great interest. We conducted a phase 3 cUTI trial to compare intravenous (IV) ertapenem (stepped down to either oral ciprofloxacin or amoxicillin-clavulanate) to IV sulopenem (stepped down to oral sulopenem etzadroxil + probenecid) [3]. Using the US Food and Drug Administration's (FDA's) current definition of a successful response, that is, one that requires both clinical cure and microbiologic eradication, sulopenem's overall success rate was 67.8% while ertapenem's was 73.9% (treatment difference −6.1%, 95% confidence interval [CI], −12.0 to −.1). The conclusion, based on overall success, is that sulopenem is not noninferior to ertapenem in the treatment of cUTI. Notably, however, clinical success rates at test of cure that were determined using a patient-reported symptom assessment questionnaire were high in both treatment groups (89.4% for sulopenem, 88.4% for ertapenem). The difference in overall success rates was due to the lower incidence of asymptomatic bacteriuria (ASB) among patients who received ertapenem and stepped down to ciprofloxacin. Thus, the clinical relevance of a conclusion of noninferiority depends on whether or not ASB nearly 2 weeks after completion of therapy increases the risk of near-term treatment failure. In our study, the presence of ASB post-treatment was not a marker of subsequent clinical failure. Because ASB does not affect the way a patient feels, functions, or survives, Howard-Anderson et al did not include it as part of the primary end point in their analyses [1]. We performed a desirability-of-outcome ranking using their ranks (1 through 5) and definitions (Table 1).

The DOOR probability that a patient in the sulopenem arm would have a more desirable outcome than a patient

Table 1. Desirability of Outcome Rankings by Treatment Arm

	Ranks					
	1 (most desirable)	2	3	4	5 (Least Desirable)	Total No. of Participants
Sulopenem	608 (87.5%)	77 (11.1%)	4 (0.6%)	4 (0.6%)	2 (0.3%)	695
Ertapenem	599 (85.9%)	95 (13.6%)	3 (0.4%)	0 (0%)	0 (0%)	697

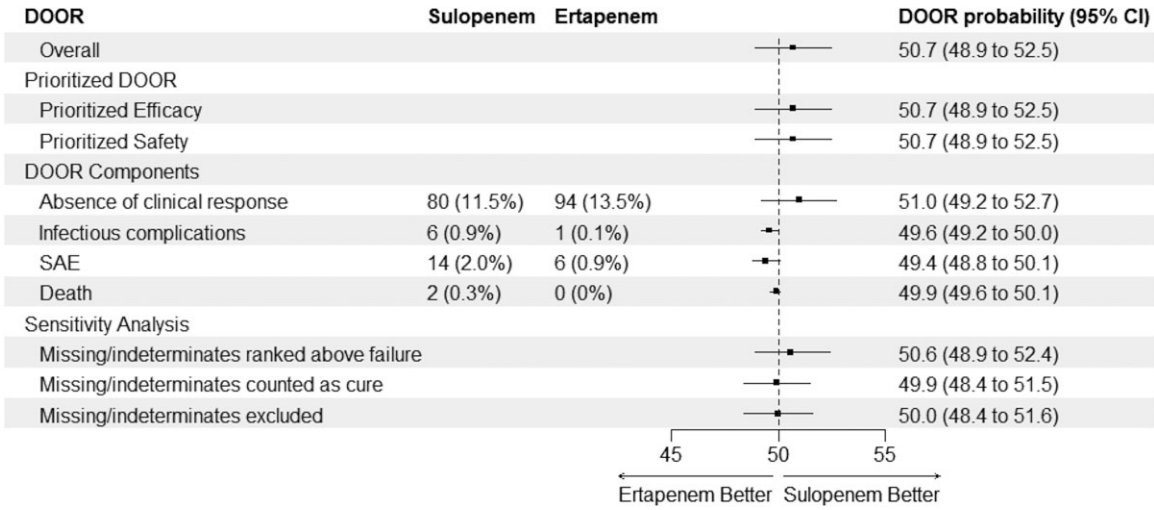

Figure 1. Forest plot demonstrating the desirability of outcome ranking (DOOR) probabilities for the DOOR, DOOR prioritized for efficacy and safety, and the DOOR components. Abbreviation: CI, confidence interval.

in the ertapenem arm is 50.7% (95% CI, 48.9% to 52.5%; Figure 1), indicating that sulopenem provided efficacy that was comparable to that of ertapenem in patients with cUTI [4]. The probabilities for the analyses prioritizing efficacy and safety were identical to the original outcome ranking, and those for the individual components were very similar.

The inclusion of ASB in the primary end point for studies of UTIs (both complicated and uncomplicated) should be reconsidered. Indeed, at the FDA's June 2022 public workshop on UTIs [5], numerous speakers expressed a desire that clinical trial end points focus more on symptomatic improvement rather than microbiological eradication, particularly since a lack of the latter, in the form of ASB, can drive inappropriate antibiotic use, selecting for resistant pathogens among post-treatment flora [6]. This approach would align with what is standard practice for many practicing physicians: not performing follow-up urine cultures on those patients with UTIs whose symptoms resolve while on antibiotics.

Notes

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