Researchers in the mid-19th century were not equipped to design or conduct the clinical trials, nor did they have knowledge of the basic science necessary to establish modern oral rehydration therapy. William Stevens became just an unpleasant footnote, swept aside by overpowering orthodoxy, which itself would pass in time. Were it not for the controversy that he provoked and were he not handicapped by undeveloped research methods, his work might have become an early, imperfect step toward modern oral rehydration therapy, pointing future researchers toward a physiologic approach.

Acknowledgments


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Inconsistencies in a Study of Rifampicin-Miconazole-Impregnated Catheters versus Standard Catheters

To the Editor—We read with interest the article by Lorente et al. [1] regarding the comparison of rifampicin-miconazole–impregnated catheters with standard catheters. We are puzzled by several factual errors and inaccuracies throughout the article.

First, Lorente et al. [1] report using a test that compares continuous outcomes (the Kruskal-Wallis test) to analyze categorical data (namely, sex, diagnosis group, and reason for catheter removal) across catheter types. Second, figures 1 and 2, table 1, and the Results section in their article are internally inconsistent. The Kaplan-Meier curves in the figures suggest that 100% of patients in the standard catheter group experienced catheter-related bacteremia by the end of the follow-up period. In contrast, table 1 and the Results section clearly report that only a minority of patients experienced an event (8 events among 111 femoral standard catheter placements and 6 events among 127 jugular standard catheter placements). Most likely, both figures 1 and 2 are incorrect.

Third, additional information is missing. Because the study was probably retrospective (described as involving a “historical cohort”), the assertion by Lorente et al. [1] that outcome assessment was blinded should be supported by a clear description of the blinding mechanism. The authors should clarify that either the type of catheter was never mentioned in patient notes in their hospital or that an investigator (who was not part of the outcome adjudication panel) was blinded to all patient notes with respect to catheter type before the notes were given to the panel.

Furthermore, although we know the total number of catheters, it is unclear whether a single catheter or multiple catheters were used per patient. Table 1 suggests the latter (at least for some patients), because it reports the frequency of catheters inserted first, second, and third. If this is true, the authors (1) should have used different statistical analyses to account for the nesting of multiple catheters per patient and (2) should have clarified whether there were crossovers between catheter types (and how they were accounted for in the analyses). Use of the catheter as the unit of the analysis may render the comparison of clinical characteristics across groups misleading (e.g., patients who received 3 catheters would be represented 3 times in the counts in table 1). However, even if only 1 catheter per patient was studied, the authors should justify why they studied the first catheter in some patients and the second or third in others.

Most importantly, the study by Lorente et al. [1] was nonrandomized, unadjusted for potential confounders. This is a major flaw, irrespective of the apparent balance between the compared groups in table 1. It is well appreciated that nonrandomized studies are subject to a plethora of biases [2]; even when they are analyzed properly (e.g., with use of propensity score matching [3] or instrumental variable regression [4]), one can never be confident that the findings are unconfounded. Because of the aforementioned caveats, we are skeptical about the findings of the study.

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Reply to Trikalinos and Trikalinos

To the Editor—We read with interest the letter by Trikalinos and Trikalinos [1] about our article [2]. We will attempt to clarify their skeptical opinions.

First, type of catheter is an ordinal variable with 2 levels: nonimpregnated and impregnated. Therefore, this variable allows for classification of the levels with the following order: nonimpregnated as the inferior level and impregnated as the superior level. Moreover, it is known that some variables with only 2 levels are not always nominal variables. In our study, type of catheter is a variable with 2 levels but is also an ordinal variable. A simpler way to understand this is that some studies may include this variable with ≥3 levels, with only modification of the dosage of antibiotic that covers the catheters. The other variables were sex, diagnosis group, and reason for catheter removal; all of these variables were measured by a nominal scale. In addition, there are no statistical reasons that justify which variable must be the row variable and which must be the column variable. Because the variable type of catheter is ordinal and the other variables are measured by a nominal scale, we used the Kruskal-Wallis test for singly ordered tables row by column, as recommended by Mehta and Patel [3].

Second, figures 1 and 2 show cumulative proportions of patients who were free of bacteremia that were calculated on the basis of the patients available for each temporal mark. This is the reason that the numbers of patients at risk in each group are included below the figures.

Third, a strength of our article [2] is that the diagnosis of central venous catheter-related bacteremia was made by an expert panel blinded to the type of catheter: rifampicin-miconazole–impregnated catheters or standard catheters. Another point not mentioned in our article is that an investigator who was not part of the expert panel that adjudicated the outcome blinded to the expert panel the catheter type (with or without antibiotic) inserted in each patient.

Fourth, if a patient developed bacteremia, the catheters inserted after the development of bacteremia were not included in the analyses. Nested analysis needs to be performed with a high proportion of events, but for control of quality, the proportions of patients who needed 1, 2, and ≥3 catheters were 28.4%, 24.2%, and 47.4%, respectively, in the group of patients with impregnated catheters, and 32.9%, 19.0%, 48.1%, respectively, in the group of patients with nonimpregnated catheters (χ² = 1.16; P = .56). The catheter was used as the unit of the analysis (e.g., patients who received 3 catheters were represented 3 times in the counts in table 1). There were no crossovers between catheter types; that is, each patient received catheters with antibiotics or without antibiotics but not both.

Fifth, multivariable statistical analysis requires some conditions to be used. One of these conditions is that the number of variables that can be introduced in a multivariable model depends on the number of available events. In our study [2], there were 8 available events in the group with femoral standard catheters, 0 events in the group with femoral impregnated catheters, 6 events in the group with jugular standard catheters, and 0 events in the group with jugular impregnated catheters. This is reason enough to use permutational inferences, also known as exact nonparametric inference [4].

We hope that the previous notes may help to change the skeptical opinions of our colleagues Trikalinos and Trikalinos [1] in relation to our article.

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The Pharmacokinetics of Polymyxin B Are Dependent on Binding and Release from Deep-Tissue Compartments

To the Editor—In their excellent study of the pharmacokinetics of polymyxin B in critically ill patients, Zavascki et al. [1] did not consider the important role of binding and release of polymyxin B from deep-tissue compartments. When injected into rabbits, polymyxin B binds to membrane phospholipids in liver, kidney, lung, brain, muscle, and heart tissues and accumulates in these tissues with repeated