testing, as well as individualized dosing of drugs in effective multidrug regimens. Although such approaches may be more expensive than "flat dosing" it may be crucial to reduce the risk of drug resistance and its subsequent spread [15].

The added value of repurposed drugs and innovative methods of individually tailored drug delivery should be considered in tandem with genomic tools to guide optimal treatment and the urgent search for new treatment approaches.

Note

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Effects of Including Variables Such as Length of Stay in a Propensity Score Analysis With Costs as Outcome

To the Editor—We read with great interest the recent article by Klein and colleagues [1] regarding the impact of methicillin-resistant *Staphylococcus aureus* (MRSA) infections compared with methicillin-susceptible *Staphylococcus aureus* (MSSA) infections on hospitalization costs and mortality. As the authors correctly noted, the epidemiology of MRSA and MSSA, as well as prescribing patterns of physicians, have changed greatly in the last decade, necessitating studies on this important subject using more recent data.

However, the interpretation of a propensity score analysis requires careful attention to the details of the covariates used to derive the propensity score, a point made in a recent letter to *Clinical Infectious Diseases* [2]. Although the inclusion of baseline subject characteristics such as age, race, hospital region, and Charlson comorbidity index was appropriate in the study by Klein et al, the inclusion of characteristics that occur downstream from the acquisition of MRSA or MSSA infection may lead to difficulty in interpreting the results. Specifically, because length of stay and number of procedures performed were used as covariates to derive the propensity score with the outcome of cost of hospitalization, the results should be assessed with caution. Length of stay, in addition to possibly being associated with medical comorbidities [3], may serve as a primary mechanism by which a MRSA infection would lead to healthcare costs that are higher than costs of a MSSA infection [4], although the impact on costs of prolonging length of stay remains controversial [5]. Adjusting for these intermediate variables, known as mediators [6], in studies that use propensity scores complicates the interpretation of results.

Causal diagrams are frequently used in epidemiology to clarify complex relationships between covariates and to identify variables to include in or exclude from adjusted analyses [7]. We depict proposed relationships between MRSA infections, length of stay, increased number of procedures, other mechanisms of increased costs, and the costs themselves in Figure 1.

Adjustment for increased length of stay and increased number of procedures leads to an analysis in which the estimate of the effect of MRSA infection on costs only includes *c*, the effect of mechanisms that lead to increased costs that do not relate to increased length of stay or increased number of procedures.

To illustrate the concept with a different hypothetical example, suppose that the use of vancomycin for MRSA infections leads to increased vancomycin-induced nephrotoxicity and subsequent increased length of stay due to the need to manage acute

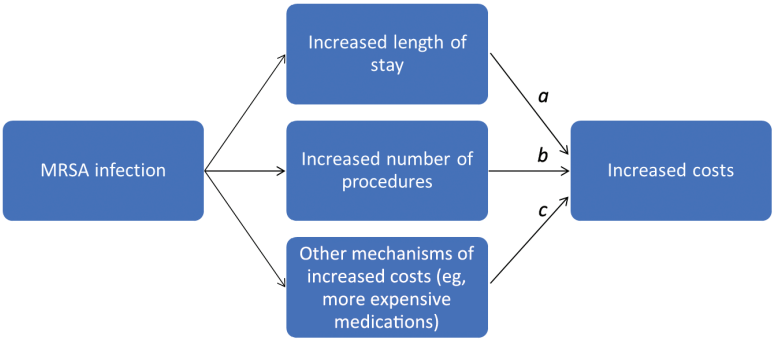

Figure 1. Causal diagram showing proposed relationships between MRSA infections, length of stay, increased number of procedures, other mechanisms of increased costs, and the costs of hospitalization. Abbreviation: MRSA, methicillin-resistant *Staphylococcus aureus*.

kidney injury. In a study of vancomycin compared with another antimicrobial for the treatment of MRSA infections in inpatients, suppose that a researcher used a propensity score analysis. The inclusion of length of hospital stay in the propensity score would adjust away the effect on the cost of vancomycin, resulting in increased length of hospital stay.

In the study by Klein et al, adjustment for potential mediators in the propensity score analysis leads to an analysis the outcome of which is the extent to which MRSA infection, compared with MSSA infection, leads to increased or decreased healthcare costs *not* associated with length of stay, need for procedures, or severity of illness. However, we do not believe that this was the authors' intent.

The presence of confounders of these intermediate variables (such as baseline comorbidities and their effect on both MRSA risk as well as length of stay) further complicates the analysis; a recent review discusses analytic methods for the problem of confounded intermediates [8].

We would be curious to see the results of an analysis that excludes from the propensity score derivation potential mediators of cost such as increased length of stay and increased number of procedures.

Notes

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Reply to Hemmige and David

To the Editor—Methicillin-resistant *Staphylococcus aureus* (MRSA) remains among the leading causes of mortality in the United States due to antibiotic-resistant infections [1]. However, as we recently reported, rates of methicillin-susceptible *S. aureus* (MSSA) increased between 2010 and 2014 [2], as did the costs for treating these infections [3]. In fact, our estimates for 2014 found that the average costs of MSSA pneumonia and other infections (which are primarily skin and soft tissue infections) were higher than comparable MRSA infections [3]. These results utilized propensity score matching (PSM) to reduce biases and dependence on model formulation in the results.

Hemmige and David [4] expressed concern that the inclusion of patient length of stay (LOS) and the number of procedures performed in the analysis may have biased the outcomes by being one of the causal factors driving the differences in costs between MRSA and MSSA infections. In developing the paper, we included LOS as a matching parameter because there is also a causal relationship between LOS and the acquisition of hospital-acquired infections (HAIs) [5–7], and *S. aureus* is a common HAI-causing pathogen [1]. Additionally, a multitude of factors, not just infections, can affect a patient's LOS, and we did not have information on infection timing. We were thus more concerned about the potential of matching patients with short and long LOSs that were due to other factors. We accounted for this in two ways. First, we matched on stratified LOS: ≤7, 8–14, 15–20, and 21+ days. Second, we conducted a subanalysis of patients with relatively short LOSs (≤10 days) and no mortality to reduce the bias from other factors driving LOS [3]. With regards to procedures, we included