

## Estimating the Length of Hospitalization Attributable to Multidrug Antibiotic Resistance

The topic of the economic impact of antibiotic resistance in Gram-negative nosocomial infection assessed in the article by Mauldin et al. (4) carries our particular interest (1, 5). One of the most important determinants of hospital costs is the length of stay (LOS). The median LOSs observed by Mauldin et al. for patients infected with susceptible and multidrug-resistant (MDR) Gram-negative bacteria were 30 days and 47 days, respectively ( $P < 0.0001$ ). Accordingly, hospital costs were significantly higher in the latter group (median cost of \$178,359 versus \$106,293;  $P < 0.0001$ ). As the authors themselves point out, this figure might be an overestimate, as the analysis lacked adjustment for LOS prior to the onset of infection, which is a well-known confounder in studies investigating the clinical and economic impact of MDR bacteria (2). Mauldin et al. did not consider LOS prior to infection because the exact date of infection is difficult to determine and because the infection-associated costs may increase even before the time of diagnosis. We respectfully disagree with the authors, as we believe these are insufficient reasons to exclude LOS prior to infection from the equation. First, difficulty in determining the onset of infection is a problem that is valid for patients infected with either susceptible or multidrug-resistant pathogens. Second, the onset of infection can be determined by initiation of empirical antimicrobial therapy, which is an important determinant of sepsis-related costs (6). Third, the difference in cost due to variability in determination of the onset of infection is outweighed by the magnitude of differences in the LOS prior to onset of infection for patients infected by susceptible and multidrug-resistant pathogens. This is illustrated in a study in which the LOSs of critically ill patients with bacteremia caused by susceptible ( $n = 208$ ) and MDR ( $n = 120$ ) Gram-negative bacilli were compared (3). The median total lengths of hospitalization in patients with bacteremia caused by MDR and susceptible bacteria were 60 days and 47 days ( $P = 0.007$ ), respectively. Yet, this difference was nearly completely due to the difference in the LOS prior to the onset of bacteremia: 23 days and 11 days ( $P < 0.001$ ), respectively. The LOSs after onset of bacteremia (calculated from the day of blood culture sampling) were not different: 35 days and 27 days ( $P = 0.333$ ), respectively. These data illustrate that the confounding potential of LOS prior to infection cannot be disregarded in an analysis aiming to estimate the economic impact of infections caused by MDR pathogens.

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### Authors' Reply

We appreciate the thoughtful comments from Dr. Blot and colleagues. We are in total agreement that, ideally, one should factor out or control for preinfection length of stay (LOS) and hospital costs in attempts to ascertain attributable, infection-related hospital costs. However, our reluctance to attempt this adjustment because of limitations within our database was fully addressed in our paper and identified as a limitation that may have well skewed the dollar differences identified in an upward direction (2). At the same time, we are still concerned with the potential subjectivity of trying to identify the date of infection and again refer to our publication for a full explanation of this reservation. Further, while it is true that at least two studies reported longer preinfection LOSs for infections with multidrug-resistant organisms and those with drug-susceptible organisms (1, 3), whether this is an absolute truism that will be borne out by future research in the area remains to be seen. For example, we did examine LOS preinfection (the onset of infection defined as the day of positive culture) for our patients infected with *Acinetobacter* spp. Mean LOS preinfection for those infected with multidrug-resistant strains was 21 days, while for those infected with susceptible strains, it was 37 days.

Is this apparent exception to the rule due to the organism, patient type, or the vagaries of defining/identifying the date of infection? If this relationship is indeed variable, depending on institutions, type of microorganism, or even patient types, then accounting for preinfection length of stay may be less important. That said, we do agree that attempts to consider only infection-related costs and length of stay should be a methodologic goal of such studies until related uncertainties are resolved.

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