Appendix

Several studies have analyzed attributable outcomes of patients infected with resistant bacteria who are compared to reference patients infected with corresponding, susceptible bacteria (1–32). We have conducted two studies, both at teaching hospitals. Study 1 (methicillin-resistant *Staphylococcus aureus* [MRSA]) was conducted at Duke University Medical Center, a 900-bed tertiary care academic medical center, and Durham Regional Hospital, a 350-bed community hospital, both located in Durham, North Carolina. Study 2 (vancomycin-resistant enterococci [VRE]) was conducted at Beth Israel Deaconess Medical Center, West Campus, a 320-bed urban tertiary care teaching hospital in Boston, Massachusetts. In both studies, data were abstracted from various sources, including computerized hospital databases (e.g., accounting, administrative, infection control, and microbiology databases) and patient medical records and were compiled into a single dataset (Access, Microsoft Corp., Redmond, WA). In both studies, organisms were identified from clinical specimens by using standard microbiologic methods that are in accordance with the National Committee for Clinical Laboratory Standards guidelines. Exact methods of data collection, assembly, and microbiology are described elsewhere (33,34).

To control for confounding, we used multivariable analysis, examining each of the outcomes independently. The following variables were analyzed as potential confounders: patient demographics, admitting diagnosis, coexisting conditions, and number of days in hospital and intensive care before cohort inclusion. For study 2, propensity score for likelihood of being a VRE case (35), having a major surgical procedure, and being infected with *Clostridium difficile* or MRSA were also analyzed.

Statistical analysis was performed on Stata (Stata Corp., College Station, TX) software and/or on SAS 8.1 (Cary, NC). Age was analyzed with the Student *t* test. and other continuous and ordinal variables were compared with the two-sided Wilcoxon rank sum test. The Fisher exact test was used to analyze dichotomous variables. Spearman correlation coefficients were calculated to detect trends among continuous variables (e.g., between length of hospital stay and continuous independent variables and between cost and continuous independent variables). Matched analyses were used in study 2, for the analysis comparing VRE wound infection to control patients with VSE wound infection (33,36).

Each outcome was examined independently, with multivariate analysis. In both studies, death rates were analyzed with logistic regression (conditional maximum-likelihood in the VRE study, to account for matching) and hospital charges with linear regression. For the MRSA study, total hospital days after infection were analyzed by using linear regression. For length of hospital stay, semiparametric survival models with accelerated failure time (Weibull) were used for the VRE analysis.

For multivariate linear regression, the following data transformation was performed. In the MRSA study, cost and length of hospital stay were log transformed and for the VRE study, cost was log transformed. No log transformation was performed for logistic regression and survival analyses, and no log transformation was performed for univariate or bivariate analyses.

The inverse log value was calculated for ß coefficients of variables included in the predictor models, and these effect measures were described as multiplicative effects (ME) on length of stay and cost. All statistical tests were two-tailed. A $p \leq 0.05$ was considered significant.

Adjusted mean attributable outcomes per resistant infection (VRE and MRSA) were calculated as follows for hospital days and charges. Charges per VRE infection are used as an example:

Mean attributable charges per VRE infection = [(mean charges for control patients) x (inverse log of ß coefficient for adjusted VRE infection variable)] – (mean charges for control patients)

Three groups were studied: 121 MRSA surgical site infection (SSI) cases, 193 uninfected surgical controls, and 165 control patients with MSSA

SSI. Descriptive characteristics of these groups and results of bivariate analyses are in Appendix Table 1.

In the analysis comparing patients with MRSA SSI to uninfected controls, in addition to MRSA, significant predictors of mortality included the American Society of Anesthesiologists-Physical Status (ASA)score >3 and age >73 (Appendix Table 2). When patients with MRSA SSI were compared to control patients with MSSA SSI, in addition to MRSA, significant predictors of death included ASA score >3 and age >61 years. This model was controlled for the confounding effects of operative duration (Appendix Table 3).

In the analysis comparing patients with MRSA SSI to uninfected controls, in addition to MRSA, other predictors of increased length of hospital stay included ASA score, duration of surgery, and length of hospital stay before surgery. This model was controlled for the confounding effects of admission to the tertiary care hospital, diabetes, and renal disease (Appendix Table 2). When patients with MRSA SSI were compared to control patients with MSSA SSI, significant predictors of increased length of hospital stay included ASA score, renal disease, duration of surgery, and length of stay before infection. This model was controlled for the confounding effects of diabetes mellitus and admission to a tertiary care hospital (Appendix Table 3).

In the analysis comparing patients with MRSA SSI to uninfected controls, in addition to MRSA, other predictors of increased cost included ASA score, admission to tertiary care hospital, duration of surgery, length of hospital stay, and intensive care unit (ICU) stay prior to surgery. This model was controlled for the confounding effect of renal disease (Appendix Table 2). When patients with MRSA SSI were compared to control patients with MSSA SSI, significant predictors of increased cost, in addition to MRSA, included ASA score, duration of surgery, length of hospital and ICU stay before infection, and admission to a tertiary care hospital. This model was controlled for the confounding effects of renal disease and diabetes (Appendix Table 3).

Three groups of patients were studied: 99 VRE case patients with wound infection, 280 matched controls who were not infected with enterococci, and 213 control patients with VSE wound infections. Descriptive characteristics and results of bivariate analyses are in Appendix Table 4.

In the analysis comparing patients with VRE wound infection to uninfected controls, the impact of VRE wound infection on deaths was controlled for the confounding effects of number of comorbid illnesses and admission to the intensive care unit (ICU) (Appendix Table 5). When patients with VRE wound infection were compared to control patients with VSE wound infection, significant predictors of deaths included admission to the ICU. This model was controlled for the confounding effects of surgery and sex (Appendix Table 6).

In the analysis comparing patients with VRE wound infection to uninfected controls, predictors of increased length of hospital stay, in addition to VRE, included being transferred from another institution, renal disease, malignancy, and admission to the ICU. This model was controlled for the confounding effect of propensity score (i.e., likelihood of having a case of VRE)] (Appendix Table 5). When patients with VRE wound infection were compared to control patients with VSE wound infection, significant predictors of increased length of stay included admission to the ICU. This model was controlled for the confounding effects of duration of hospitalization before cohort inclusion and malignancy (Appendix Table 6).

In the analysis comparing patients with VRE wound infection to uninfected controls, predictors of increased cost, in addition to VRE, included having had surgery before cohort inclusion (Appendix Table 5). This model was controlled for the confounding effects of propensity score (i.e., likelihood of being a VRE case) and duration of hospitalization before cohort inclusion. When patients with VRE wound infection were compared to control patients with VSE wound infection, significant predictors of increased cost, in addition to VRE, included having had surgery before inclusion in the cohort. This model was controlled for the confounding effect of time in hospital before cohort inclusion.

The differences in results between the two analyses are much greater for a virulent primary pathogen than for a nonvirulent, secondary invader. When a virulent pathogen is studied (e.g., *S. aureus*), the infected susceptible group (MSSA) is at much greater risk for adverse clinical outcomes

than the uninfected control group, and analyses comparing resistant cases (MRSA) to these two control groups produce notably different results. Enterococci are often nonvirulent secondary invaders (e.g., colonizers) in wound infections and are frequently part of a mixed flora of infecting pathogens rather than true primary pathogens. The results obtained when patients with VRE wound infection were compared to patients not infected with enterococci were similar to results obtained when patients with VSE wound infections were used as controls. In our opinion, when resistant pathogens of low virulence (e.g., VRE in wounds) are analyzed, the infected susceptible (e.g., VSE) and uninfected control groups approximate one another, and results of analyses comparing resistant cases to these two control groups are similar.

Appendix References

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