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Citation

Kaye, Keith S., John J. Engemann, Essy Mozaffari, and Yehuda Carmeli. 2004. Reference group choice and antibiotic resistance outcomes. *Emerging Infectious Diseases* 10(6): 1125-1128.

Published Version

doi:10.3201/eid1006.020665

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Reference Group Choice and Antibiotic Resistance Outcomes

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Two types of cohort studies examining patients infected with methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant enterococci (VRE) were contrasted, using different reference groups. Cases were compared to uninfected patients and patients infected with the corresponding, susceptible organism. VRE and MRSA were associated with adverse outcomes. The effect was greater when uninfected control patients were used.

Although several investigators have performed outcomes studies of patients infected or colonized with antimicrobial resistant bacteria, the design and interpretation of results with various methods has not been discussed (1). Typically, these outcomes studies use a cohort design and study patients infected with resistant bacteria (the exposure of interest for cases), who are compared either to patients without infection selected from a similar population (2–6) or to patients infected with corresponding, susceptible bacteria (e.g., comparing patients with methicillin-resistant *Staphylococcus aureus* [MRSA] to patients with methicillin-susceptible *S. aureus* [MSSA]) (7–13) (Online Appendix, available at http://www.cdc.gov/ncidod/eid/vol11no6/02-0665_app.htm). When cases are compared to an uninfected reference group or “control group,” the effect of a new, antimicrobial-resistant bacterial infection is assessed. When case-patients are compared to reference patients or “controls” infected with the corresponding susceptible bacteria, the impact of acquiring a resistance determinant is measured. Both types of comparison are valid and important, but they address different clinical scenarios.

We examined how the choice of the reference group might influence results of outcomes studies pertaining to antimicrobial resistant bacteria. We compared and contrasted the results of outcomes cohort studies for resistant bacteria by using the two different reference groups

discussed previously. We used results from original studies of MRSA and vancomycin-resistant enterococci (VRE) (9,10) that initially used one reference group. In our study, we performed additional analyses comparing case-patients to different reference patients and contrasted the results.

The Study

Both MRSA and VRE studies were designed as cohort studies and are discussed in detail elsewhere (9,10) (Online Appendix). Cases were defined as patients with MRSA surgical site infection (SSI) (i.e., the exposure of interest for study 1) and VRE wound infection (i.e., the exposure of interest for study 2). In each study, two different reference groups were used in separate analyses. Control group A included patients who did not have an infection caused by the target pathogen (*S. aureus* or enterococci). Control group B included patients with infection caused by the susceptible phenotype of the target pathogen (i.e., MSSA and vancomycin-susceptible enterococci [VSE]).

In both studies, three outcomes were examined: death, length of hospital stay, and total hospital charges. Hospital charges were variable direct charges obtained from hospital financial databases and are a surrogate for cost. Hospital costs were estimated using a cost-to-charge ratio of 0.7 (14).

Outcomes studies of antimicrobial drug resistance are notoriously hard to perform because of confounding variables related to underlying coexisting conditions (1). To control for confounding, we analyzed several variables, including individual coexisting conditions, the Charlson score, the American Society of Anesthesiologists-Physical Status (ASA) score, and duration of hospitalization before infection (Online Appendix). These variables were analyzed in multivariable analysis. Each of the outcomes was analyzed independently. The inverse log value was calculated for β coefficients of variables included in the predictor models, and these effect measures were described as the odds ratio (OR) for death rate and the multiplicative effects (ME) on length of stay and charges.

In the analysis comparing patients with SSI caused by MRSA to uninfected controls, the study cohort included 314 patients: 121 MRSA SSI cases and 193 uninfected surgical controls (Online Appendix). In multivariable analysis, MRSA SSI was significantly associated with death (OR = 11.4, $p < 0.001$). In the analysis comparing patients with MRSA SSI to patients with SSI caused by MSSA, the same 121 MRSA case-patients were compared to 165 control-patients with MSSA SSI. In multivariable analysis, MRSA SSI was significantly associated with death (OR = 3.4, $p = 0.003$). Additional covariates included in the adjusted models for death are listed in the footnotes of Table 1 and are discussed in the Online Appendix. The

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Table 1. Outcomes and adjusted analyses for MRSA for study 1^a

Outcome	Cases	Controls	Adjusted analyses		
			OR (95% CI) ^b	Attributable to MRSA	p value
Three analyses comparing patients MRSA cases (n = 121) and uninfected controls (n = 193)					
Deaths	20.7%	2.1%	11.4 (2.8 to 34.9) ^c	–	< 0.001
Hospital days after surgery, mean per case	29.1	6.1	3.2 (2.7 to 3.7) ^d	13.4	< 0.001
Charges (\$), mean/case	118,414	34,395	2.2 (2.0 to 2.6) ^e	41,274	< 0.001
Three analyses comparing MRSA cases (n = 121) and MSSA controls (n = 165)					
Deaths	20.7%	6.7%	3.4 ^f	–	0.003
Hospital days after infection, mean per case	22.0	13.2	1.2 ^g	2.6	0.11
Charges (\$), mean per case	118,414	73,165	1.2 ^h	13,901	0.03

^aOR, odds ratio; CI, confidence interval; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-susceptible *S. aureus*.

^bOdds ratio for deaths, and multiplicative effect (ME) for continuous outcomes (length of stay and charges).

^cAdjusted for American Society of Anesthesiologists-Physical Status (ASA) score >3 and age.

^dAdjusted for ASA score, duration of surgery, hospital, renal disease, diabetes, and length of hospital stay before surgery.

^eAdjusted for ASA score, hospital, duration of surgery, renal disease, length of hospital stay, and intensive care unit (ICU) stay before surgery.

^fAdjusted for ASA score >3, duration of surgery, and age.

^gAdjusted for ASA score, renal disease, diabetes mellitus, hospital, duration of surgery, and length of stay before infection.

^hAdjusted for ASA score, duration of surgery, length of hospital and ICU stay before infection, hospital, renal disease, and diabetes.

effect of MRSA on deaths was approximately threefold greater for the analysis using uninfected controls than for the analysis using MSSA controls.

In the analysis comparing patients with SSI caused by MRSA to uninfected controls, multivariable modeling demonstrated that MRSA SSI was significantly associated with an increased length of stay (ME = 3.2, $p < 0.001$). Having an MRSA SSI was associated with an average adjusted attributable increase of 13.4 hospital days per case. In the analysis comparing patients with MRSA SSI to controls with SSI due to MSSA, a trend was seen toward an association between MRSA SSI and total hospital days (ME = 1.20, $p = 0.11$). Methicillin resistance was associated with an average adjusted attributable increase of 2.6 days per case, although this did not reach statistical significance. Additional covariates included in the adjusted models for length of stay are listed in the footnotes of Table 1 and are discussed in the Online Appendix. The effect of MRSA on length of stay was approximately threefold greater (11 days) for the analysis using uninfected controls than for analysis B using MSSA controls.

In the analysis comparing patients with SSI due to MRSA to uninfected controls, multivariable modeling showed that MRSA SSI was significantly associated with increased hospital charges (ME = 2.2, $p < 0.001$). MRSA was associated with mean adjusted additional attributable charges of \$41,274 per case and an attributable cost of \$28,891 per case. In the analysis comparing patients with SSI due to MRSA to controls with SSI due to MSSA, MRSA was significantly associated with increased hospital charges (ME = 1.2, $p = 0.03$). Methicillin resistance was associated with mean adjusted additional attributable charges of \$13,901 per MRSA SSI case and an attributable cost of \$9,731 per case. Additional covariates included in the adjusted models for cost are listed in the

footnotes of Table 1 and are discussed in the Online Appendix. The effect of MRSA on cost was approximately twofold greater (\$15,000) for the analysis using uninfected controls than for the analysis using controls with SSI due to MSSA.

In the analysis comparing patients with wound infection due to VRE to uninfected controls, 99 patients with VRE wound infection were compared to 280 matched controls who were not infected with enterococci (Online Appendix). In adjusted analysis, VRE wound infection was not an independent predictor of deaths (OR 2.0, $p = 0.13$). In the analysis comparing patients with wound infection due to VRE to control patients with wound infection due to VSE, the same 99 VRE wound infection cases were compared to 213 control patients with VSE wound infections. In multivariable analysis, VRE was significantly associated with mortality (OR 2.5, $p = 0.04$). Additional covariates included in the adjusted models for death rates are listed in the footnotes of Table 2 and are discussed in the Online Appendix. The magnitude of effect of VRE on deaths was similar for both analyses.

In the analysis comparing patients with wound infection due to VRE to uninfected controls, multivariable modeling showed a significantly longer duration of hospitalization after inclusion in the cohort for VRE cases than for controls not infected with enterococci (ME 1.8, $p < 0.001$, average adjusted attributable increase of 6.2 days in length of stay). In the analysis comparing patients with wound infection due to VRE to control patients with VSE wound infection, length of stay after isolation of enterococci was similar among VRE cases and VSE controls (mean of 15.2 vs. 13.6 days, $p = 0.5$) and the differences in length of stay remained non-significant in multivariate analysis (ME = 1.0, $p = 0.5$). Additional covariates included in the adjusted models for length of stay are listed in the

Table 2. Outcomes and adjusted analyses for vancomycin-resistant enterococci (VRE) in study 2

Outcome	Cases	Controls	Adjusted analyses		
			OR ^a	Attributable to VRE	p value
Three analyses comparing VRE patients (n = 99) and uninfected controls (n = 280)					
Deaths	12.1%	6.1%	2.0 ^b	–	0.13
Length of stay (d), mean per case	15.2	8.5	1.8 ^c	6.2	<0.001
Charges (\$), mean per case	46,660	27,224	1.5 ^d	13,884	<0.001
Three analyses comparing VRE patients (n = 99) and vancomycin-susceptible enterococci (VSE) controls (n = 213)					
Deaths	12.1%	6.6%	2.5 ^e	–	0.04
Length of stay (d), mean per case	15.2	13.6	1.0 ^f	–	0.5
Charges (\$), mean per case	46,600	31,915	1.4 ^g	12,766	<0.001

^aOdds ratio for deaths, and multiplicative effect (ME) for continuous outcomes (length of stay and charges).

^bAdjusted for number of comorbid illnesses and admission to the intensive care unit (ICU).

^cAdjusted for propensity score (i.e., likelihood of being a VRE case [Online Appendix]), being transferred from another institution, renal disease, malignancy, and admission to the ICU.

^dAdjusted for propensity score (i.e., likelihood of being a VRE patient), having had surgery before cohort inclusion, and duration of hospitalization before cohort inclusion.

^eAdjusted for surgery, sex, and admission to the ICU.

^fAdjusted for duration of hospitalization before cohort inclusion, admission to the ICU, and malignancy.

^gAdjusted for having had surgery before inclusion in the cohort, and duration of hospitalization before cohort inclusion.

footnotes of Table 2 and are discussed in the Online Appendix. The effect of VRE on length of stay was approximately twofold greater (6 days) for the analysis using uninfected controls than for the analysis that used VSE controls.

In the analysis comparing patients with wound infection due to VRE to uninfected controls, multivariable modeling demonstrated that VRE cases generated significantly greater hospital charges than controls (adjusted ME = 1.5, $p < 0.001$, mean adjusted additional attributable charges of \$13,884 per VRE wound infection and attributable cost of \$9,719 per infection). In the analysis comparing patients with wound infection due to VRE to controls with VSE wound infection, VRE wound infection was associated with increased hospital charges (ME = 1.4, $p < 0.001$, average adjusted additional attributable charges of \$12,766 per infection and attributable cost of \$8,936 per infection). Additional covariates included in the adjusted models for cost are listed in the footnotes of Table 2 and are discussed in the Online Appendix. The effect of VRE on cost was similar in both analyses.

Conclusions

We examined how the criteria used to select a reference group (i.e., a comparison or control group for cases) influenced outcomes study results. Two types of control patients were studied, and in both types of analyses, VRE and MRSA were associated with significant, adverse clinical outcomes. In general, the effects (i.e., OR or ME) were of greater magnitude when controls not infected with the target organism (and thus representative of a random sample of the source population) were used. This is logical since analyses using uninfected controls assess the effect of acquiring a new infection and a resistant pathogen. When patients who are infected with a susceptible organ-

ism are used as controls, the analysis quantifies only the effect of acquiring a resistance trait.

The differences in results between the two analyses were much greater for the MRSA SSI study than for the VRE wound infection study. The impact on clinical outcomes was two- to threefold greater when patients with MRSA SSI were compared to an uninfected control group as opposed to comparison with control patients infected with MSSA SSI. In contrast, when patients with VRE wound infection were compared to uninfected patients, similar results were obtained as when patients with VSE wound infections were used as controls. We believe that the magnitude of differences in results for the two analyses is directly related to the virulence of the infecting organism (Online Appendix).

The studies were performed in two different geographic locales and by using slightly different analytic methods. While this is a limitation in that cost results are not directly comparable, we feel including these two studies improves the generalizability of our results and strengthens our findings.

For studies of antimicrobial resistance, a reference group must be chosen on the basis of the investigators' objective. From a public health perspective, results from outcomes studies pertaining to antimicrobial resistance are frequently used to help allocate resources for interventions. If the objective of a study is to investigate the independent effects of a resistance trait or phenotype (e.g., methicillin resistance), then the most appropriate control group would consist of patients infected with a susceptible corresponding organism. If the goal is to assess the effect of a new infection caused by a particular pathogen, uninfected control patients would be the preferable comparison group. Alternatively, a complete analysis might include both types of control groups; this analysis would allow the

reader to assess the effect of acquiring a resistance phenotype alone and the impact of acquiring a new infection caused by a resistant bacteria.

Dr. Kaye is an assistant professor of medicine at Duke University Medical Center, where he is director of Hospital Epidemiology and Infection Control and chair of the Antibiotic Evaluation Committee. His research interests include antimicrobial resistance, antimicrobial utilization, selective antimicrobial pressure, surgical site infections, infections in the elderly, and hospital-acquired infections.

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