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Measuring Impact of Antimicrobial Resistance

To the Editor: *Staphylococcus aureus* and *Enterococcus faecium* commonly cause healthcare-associated bloodstream infections (BSI) in the intensive care unit (ICU). Antimicrobial resistance is increasing in both organisms. The impact of antimicrobial resistance on dying of BSI has been studied extensively (1,2). Many studies have concluded that BSI caused by an antimicrobial-resistant organism results in higher death rates (1,3–8). However, as discussed in a recent report by Kaye et al., "outcome studies of antimicrobial drug resistance are notoriously hard to perform because of confounding variables related to coexisting conditions" (9). Indeed, almost all studies have shown that infections with antimicrobial-resistant organisms occur later in hospitalization than infections with antimicrobial-susceptible organisms, which suggests that differences in death rates may be, at least in part, caused by a difference in the patients' underlying illnesses and protracted hospital course. We report 2 additional methodologic issues that can affect estimates of the impact of antimicrobial resistance: combining different organisms and combining populations from different types of ICUs.

The original objective of our multicenter observational study was to quantify the clinical impact of antimicrobial resistance in *S. aureus* and *E. faecium* infections when these bacteria cause a specific type of infection: a monomicrobial, ICU-attributable, central vascular catheter–associated bloodstream infection (CVC-BSI). We studied 187 adult ICU patients with BSI caused by *S. aureus* and *E. faecium* at 3 tertiary care institutions from 1994 to 1999. The institutional review boards of each institution and the Centers for Disease Control and Prevention approved this study. Severity of illness was measured with an APACHE II score at ICU admission and on day 7 in the ICU (if applicable). The score would indicate the patient's risk of dying in the hospital before a BSI developed by using a measure validated for predicting in-hospital deaths in ICU patients (10).

The study population stratified by organism is shown in the Table. Fifty-eight percent of patients had CVC-BSI with *S. aureus*, and 42% had CVC-BSI with *E. faecium.* Overall, 58% of the organisms causing CVC-BSI were resistant to oxacillin if *S. aureus* or to vancomycin if *E. faecium*. However, patients with *E. faecium* CVC-BSI were more likely to be infected with antimicrobial-resistant bacteria (69% versus 50%, p<0.01), and had a higher mortality rate (54% versus 34%, p<0.01) than patients with *S. aureus* CVC-BSI. This finding indicates that the type of organism (*E. faecium* versus *S. aureus*) confounds the association between resistance and death. In addition, the distribution of ICU type by organism varies, which suggests that patient populations infected with these 2 different organisms were different in other

Table. Description of 187 adult patients with central vascular catheter-associated bloodstream infections with *Staphylococcus aureus* or *Enterococcus faecium* attributable to the intensive care unit*

Characteristics	*S. aureus* (n = 109)	*E. faecium* (n = 78)	p value
Patient demographics			
Male (%)	74	56	0.02
Mean age, y (SD)	58 (17)	56 (16)	0.32
Type of ICU			<0.01
Cardiac (%)	20	10	
Cardiothoracic surgery (%)	6	6	
Medical (%)	20	40	
Neurologic/neurosurgical (%)	6	0	
Surgical (%)	20	37	
Trauma (%)	28	6	
Severity of illness			
Mean APACHE II score at ICU admission (SD)	19 (8)	21 (9)	0.12
Mean APACHE II score within 7 days of BSI (SD)	17 (8)	20 (8)	0.05
Resistant infections (%)	50	69	0.01
In-hospital death rate (%)	34	54	<0.01

*SD, standard deviation; ICU, intensive care unit.

ways. Thus, confounding factors for the association between resistance and death may differ for *E. faecium* and *S. aureus*, and analysis of the 2 organisms should be conducted separately. This is consistent with the results of Kaye et al. who showed that the effect of resistance was higher for *S. aureus* (odds ratio [OR] 3.4) than for *E. faecium* (OR 2.5) by using separate analyses to show death rates (9). Furthermore, these researchers found different confounding factors in the adjusted analysis of *S. aureus* than in the adjusted analysis of *E. faecium*. Because of the need to conduct separate analyses, which reduced our statistical power, our study was ultimately unable to show a difference in death rates if it existed.

In summary, future studies measuring the impact of antimicrobial resistance on death rates should be restricted to a specific type of infection cause by a single organism in a uniform setting using a validated system to predict mortality in that setting. As such, future studies should involve multiple study sites.

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Antimicrobial Resistance in *Campylobacter*

To the Editor: Iovine and Blaser (1) write, "This therapeutic use [of enrofloxacin] was withdrawn (2) but is now under appeal" and "Despite the restrictions on enrofloxacin use, emergence of fluoroquinolone-resistant *Campylobacter* species, with poultry as an important source, has been documented in the United States… Therefore, our conclusion remains: use of enrofloxacin in poultry materially contributed to increase in human infection by fluoroquinolone-resistant *Campylobacter* species."

These claims propagate the following important errors. First, the therapeutic use of enrofloxacin was not withdrawn. Judge Davidson's order to withdraw the approval was an initial decision, to which exceptions were filed in 2004. A final decision rests with the US Food and Drug Administration Commissioner.

Second, poultry has not been identified as an important source of fluoroquinolone resistance in human *Campylobacter* isolates. The raw data of the cited Smith et al. article (3) indicate a nonsignificant negative association between chicken consumption and fluoroquinolone resistance in human isolates. Substantial resistance levels in Northern Hemisphere countries with and without enrofloxacin use, which occurred well before fluoroquinolones were ever used in animals (3–5), also suggest that attribution of such resistance to enrofloxacin is simplistic.

Finally, rational decision-making is based on probable future consequences of a decision, not past history or causes of the current situation. Iovine and Blaser's claim, "Thus the decision to withdraw therapeutic use of enrofloxacin (3) was warranted," is not implied, even if enrofloxacin use