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MAJOR ARTICLE

Acquisition of Antibiotic-Resistant Gram-negative Bacteria in the Benefits of Universal Glove and Gown (BUGG) Cluster Randomized Trial

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Background. The Benefits of Universal Glove and Gown (BUGG) cluster randomized trial found varying effects on methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant *Enterococcus* and no increase in adverse events. The aim of this study was to assess whether the intervention decreases the acquisition of antibiotic-resistant gram-negative bacteria.

Methods. This was a secondary analysis of a randomized trial in 20 hospital intensive care units. The intervention consisted of healthcare workers wearing gloves and gowns when entering any patient room compared to standard care. The primary composite outcome was acquisition of any antibiotic-resistant gram-negative bacteria based on surveillance cultures.

Results. A total of 40 492 admission and discharge perianal swabs from 20 246 individual patient admissions were included in the primary outcome. For the primary outcome of acquisition of any antibiotic-resistant gram-negative bacteria, the intervention had a rate ratio (RR) of 0.90 (95% confidence interval [CI], .71–1.12; $P = .34$). Effects on the secondary outcomes of individual bacteria acquisition were as follows: carbapenem-resistant Enterobacteriaceae (RR, 0.86 [95% CI, .60–1.24; $P = .43$), carbapenem-resistant *Acinetobacter* (RR, 0.81 [95% CI, .52–1.27; $P = .36$), carbapenem-resistant *Pseudomonas* (RR, 0.88 [95% CI, .55–1.42]; $P = .62$), and extended-spectrum β-lactamase–producing bacteria (RR, 0.94 [95% CI, .71–1.24]; $P = .67$).

Conclusions. Universal glove and gown use in the intensive care unit was associated with a non–statistically significant decrease in acquisition of antibiotic-resistant gram-negative bacteria. Individual hospitals should consider the intervention based on the importance of these organisms at their hospital, effect sizes, CIs, and cost of instituting the intervention.

Clinical Trials Registration. NCT01318213.

Keywords. antibiotic resistance; barrier precautions; contact precautions.

Antibiotic resistance is associated with considerable morbidity, mortality, and costs [1, 2]. The estimated cost of antibiotic resistance in the United States is more than $4 billion per year [2]. Healthcare-associated infections are the most common complication of hospital care, affecting an estimated 1 in every 20 inpatients [3]. Antibiotic-resistant gram-negative bacteria continue to emerge and rank highly on the list of pathogens causing national healthcare-associated infections [4, 5].

Tremendous controversy exists about the relative advantages and disadvantages of contact precautions [6, 7]. Previously, we published a cluster randomized trial titled the Benefits of Universal Glove and Gown (BUGG) that showed no statistically significant effect on the composite primary outcome of methicillin-resistant *Staphylococcus aureus* (MRSA) or vancomycin-resistant *Enterococcus* (VRE) acquisition [8]. However, this composite outcome result was driven by differing effects on MRSA and VRE; there was a large and statistically significant decrease of individual patient MRSA acquisition and no effect on VRE acquisition. Importantly, the study also showed no increase in adverse events and improved hand hygiene compliance on room exit with the intervention.

Antibiotic resistant gram-negative bacteria are among the most important threats to human health, being categorized by the Centers for Disease Control and Prevention (CDC) as "urgent" and "serious" threats [9]. Interventions recommended by national organizations include the use of contact precautions to prevent the spread of these bacteria to other patients [10, 11]. However, no randomized trials have assessed the impact of contact precautions on antibiotic-resistant gram-negative bacteria.

In the current study, we used previously collected and stored perianal samples from the BUGG cluster randomized trial to assess if wearing gloves and gowns for all patient contact in the intensive care unit (ICU) reduces acquisition rates of antibiotic-resistant gram-negative bacteria, including carbapenem-resistant *Pseudomonas aeruginosa*, carbapenem-resistant

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Acinetobacter baumannii, extended-spectrum β-lactamase (ESBL)–producing Enterobacteriaceae, and carbapenemase-producing Enterobacteriaceae (CPE).

METHODS

Study Design

This study is a secondary analysis of specimens collected in the BUGG study, a 20-hospital cluster randomized trial of universal glove and gown compared to standard practice. The study was conducted in medical, surgical, and medical-surgical ICUs varying in size from 9 to 36 beds and located across the United States in rural, urban, academic, and nonacademic settings. The primary outcome of the original trial was acquisition of MRSA or VRE. Details of the original study design have been previously published [8]. ICUs were randomized to either the intervention or control arm. The study had a baseline period from 1 September 2011 to 30 November 2011. The study period was from 4 January 2012 to 4 October 2012. The trial was conducted in accordance with the Consolidated Standards of Reporting Trials (CONSORT) guidelines [12].

Intervention and Control Arms

The intervention occurred at the cluster level of the ICU. During the baseline period, all ICUs followed their usual standard of care, which consisted of healthcare workers following CDC contact precautions guidelines (gloves and gowns) for patients known to have antibiotic-resistant bacteria such as VRE and MRSA [11]. After the baseline period, ICUs were randomized, and during the study period, all healthcare workers (nurses, physicians, respiratory therapists, etc) in the 10 ICUs assigned to the intervention arm were required to wear gloves and gowns for all patient contact and when entering any patient room [11, 13]. The 10 control ICUs followed their usual standard of care during the study period. Compliance with glove and gown use was measured by 30-minute direct observation periods on a random sample of rooms. No hospitals performed active surveillance for antibiotic-resistant gram-negative bacteria. All hospitals isolated patients with carbapenem-resistant gram-negative bacteria. Twelve hospitals performed chlorhexidine bathing (5 in the control arm and 7 in the intervention arm) [14].

Outcomes

All patients had ICU admission and ICU discharge perianal cultures. The primary outcome was acquisition of either carbapenem-resistant *Pseudomonas aeruginosa*, carbapenem-resistant *A. baumannii*, ESBL-producing Enterobacteriaceae, or CPE as a composite. Secondary outcomes were each of these antibiotic-resistant gram-negative bacteria analyzed individually. For each patient, acquisition was defined as having an initial ICU surveillance specimen that was negative for an antibiotic-resistant pathogen with a subsequent discharge surveillance specimen within the same ICU admission that was positive for the same antibiotic-resistant pathogen. ICUs did not receive results of the surveillance cultures. Specimens were shipped to and processed at the University of Maryland using a method that did not affect bacterial yield or organism identification [15]. The same laboratory procedures were followed in the baseline and intervention. The same laboratory technicians handled all the specimens. The laboratory technicians were blinded to which study arms the specimens were from. For Enterobacteriaceae, we focused on acquired resistance to carbapenem and ESBLs. Since both of these resistance mechanisms occur by β-lactamases, we performed polymerase chain reaction for the detection of CTX-M, *Klebsiella pneumoniae* carbapenemase (KPC), New Dehli metallo-β-lactamase (NDM), IMP, verona integron-encoded metallo-β-lactamase (VIM), and oxacillinase (OXA) [16, 17]. For *A. baumannii* and *P. aeruginosa* carbapenem resistance, we cultured and performed susceptibility testing. Specimens were first enriched into brain-heart infusion broth with 2 μg/mL of meropenem. These were incubated overnight at 37°C and plated to Cetrimide (Becton Dickinson, Sparks, Maryland) for *P. aeruginosa* and *Acinetobacter* RambaCHROM agar (Molecular Toxicology, Boone, North Carolina) for the isolation of *A. baumannii*. Agar was used following manufacturer instructions. Susceptibility testing using the Vitek 2 assay (bioMérieux, Durham, North Carolina) was performed on all isolates identified as *P. aeruginosa* or *A. baumannii* following Clinical and Laboratory Standards Institute guidelines [18].

Statistical Analysis

The statistical analysis plan was written and sealed prior to the analysis. The analysis was based on the outcome (acquisition yes/no) for each person seen in the study ICUs at either the baseline period (when standard contact precautions were used in all ICUs) or the study period (when half of the ICUs employed universal contact precautions). The probability that each person was classified as having acquired an infection during their ICU stay is a function of the acquisition rate in that ICU at that period, and the number of days between admission specimen collection and discharge specimen collection, which was approximately equal to the patient ICU length of stay. The rate of acquisition in an ICU at a given period was modeled as a multiplicative function of parameters related to period (baseline or study), contact precautions (whether that ICU was using universal or selective precautions during that period), and ICU (treated as a random effect). This corresponds to using a generalized linear mixed model for a binary outcome with a complementary log-log link, random effects for ICUs, and the log of the number of days between swabs as an offset term. The model was fit by maximum likelihood estimation using SAS Proc GLIMMIX. The model resulted in estimates of the mean rate of acquisition during the baseline period, the mean rate during the study period in ICUs that performed selective precautions, the mean rate during the study period in ICUs that performed

universal precautions, and the rate ratio (RR) due to the intervention. Rate ratios adjusted for the admission prevalence at each hospital and in each time period were also calculated. For ease of interpretation, we also present a rate difference, which is the difference in acquisition rates due to the intervention based on the model evaluated at the average ICU. Confidence intervals (CIs) for the rate differences were calculated using the delta method based on the parameter estimates and standard errors from the multiplicative model that we fit.

RESULTS

Twenty ICUs participated in the study and none withdrew. Of the 26 180 patients enrolled in the original study, 20 246 patients had both admission and discharge swabs, including 4243 patients during the baseline period and 16 003 patients during the study period. A total of 40 492 perianal swabs were worked up, including 8486 swabs during the baseline period and 32 006 swabs during the study period. During the study period, compliance with obtaining perianal cultures at admission was 94.92%. Compliance with obtaining perianal cultures at discharge was 85.07%. Compliance with wearing gloves in the intervention ICUs was 86.18% (2787 of 3234), and compliance with gowns was 85.14% (2750 of 3230). In the control group, 10.52% of patients were on contact precautions. In the control ICUs, for patients on contact precautions, compliance with wearing gloves was 84.11% (556 of 661) and compliance with gowns was 81.21% (536 of 660).

Table 1 demonstrates the acquisition rates in the baseline and study periods for both the control group and the intervention group. Baseline rates for the primary outcome were similar in the intervention and control group prior to the randomization. Of note, acquisition rates increased in the study period for both intervention and control groups.

The effects of the intervention on the primary outcome and the secondary outcomes are shown in Table 2 as RRs and in Figure 1 as rate differences. For the primary outcome of acquisition of any antibiotic-resistant gram-negative bacteria, the intervention showed a decrease in acquisition: RR, 0.90 [95% CI, .71–1.12]; $P = .34$) and a rate difference of −2.1 (95% CI, −5.9 to 1.7; $P = .34$). For each individual outcome, the RR was < 1, suggesting a decrease in the rate of acquisition of the antibiotic-resistant bacteria in the intervention group. None of these associations were statistically significant.

Figure 2 demonstrates the prevalence of positive ICU admission cultures by month in both the baseline and study periods. The results demonstrate an increase in positive patients on admission in the study period compared to the baseline period in both the intervention group and control group.

DISCUSSION

Healthcare workers' use of gloves and gowns for all ICU patient contact was associated with a non–statistically significant decrease in acquisition rate of antibiotic-resistant gram-negative bacteria compared to ICUs using contact precautions only for patients known to be colonized with antibiotic-resistant bacteria.

The primary outcome rate ratio was 0.90, indicating a 10% decrease in acquisition rate in intervention units compared to control units. The CIs around this rate ratio ranged from 0.71 to 1.12, indicating that our findings are consistent with the possibility that the intervention resulted in a 29% reduction in acquisition rates, but also that our study is consistent with the possibility of no effect of the intervention. The estimated RRs were all < 1 for the individual gram-negative bacteria, but all were > 0.80. The data indicate the largest potential benefit for carbapenem-resistant *A. baumannii* and the smallest potential benefit for ESBL-producing bacteria, which is consistent with the literature [19–21]. *Acinetobacter baumannii* has data supporting its persistence in the hospital environment and a strong association with risk of transmission to subsequent patients in the same room, which may explain our finding [21–23].

How to interpret these results and place these results in the context of our previous results for MRSA and VRE is challenging. The previous study showed a large statistically significant effect on MRSA acquisition and no effect on VRE. It is noteworthy that of the 6 outcomes/individual antibiotic-resistant bacteria analyzed in this study and the original study, for 5 we observed a reduction in the acquisition of antibiotic-resistant bacteria

Table 1. Rate of Acquisition

Organism	No. of Acquisitions/Total Days at Risk (Rate per 1000 Days)			
	Baseline Control Group (n = 2297)	Baseline Intervention Group (n = 1946)	Study Period Control Group (n = 7916)	Study Period Intervention Group (n = 8087)
Pseudomonas	13/10 041 (1.29)	16/8598 (1.86)	124/32 269 (3.84)	130/32 875 (3.95)
Carbapenemase-producing Enterobacteriaceae	31/9951 (3.12)	28/8478 (3.30)	103/32 327 (3.19)	92/33 189 (2.77)
Acinetobacter	16/9948 (1.61)	20/8616 (2.32)	147/32 042 (4.59)	142/32 579 (4.36)
ESBL-producing bacteria	47/9747 (4.82)	37/8294 (4.46)	253/31 323 (8.08)	248/31 901 (7.77)
Any	102/10 062 (10.14)	90/8667 (10.38)	585/32 830 (17.82)	566/33 576 (16.86)

Abbreviations: *Acinetobacter*, carbapenem-resistant *Acinetobacter baumannii*; CPE, carbapenemase-producing Enterobacteriaceae; ESBL, extended-spectrum β-lactamase; *Pseudomonas*, carbapenem-resistant *Pseudomonas aeruginosa*.

Table 2. Effect of the Intervention of Universal Glove and Gown

Organism	RR for Impact of the Intervention (95% CI)	*P* Value	RR for Impact of the Intervention Adjusted for Site-specific Admission Prevalence (95% CI)	*P* Value
Pseudomonas, carbapenem-resistant *Pseudomonas aeruginosa*	0.88 (.55–1.42)	.62	0.78 (.51–1.19)	.25
Carbapenemase-resistant Enterobacteriaceae	0.86 (.60–1.24)	.43	0.88 (.62–1.23)	.45
Acinetobacter	0.81 (.52–1.27)	.36	0.75 (.50–1.13)	.17
ESBL-producing bacteria	0.94 (.71–1.24)	.67	0.95 (.74–1.21)	.67
Any	0.90 (.71–1.12)	.34	0.90 (.73–1.10)	.31

Abbreviations: *Acinetobacter*, carbapenem-resistant *Acinetobacter baumannii*; CI, confidence interval; CRE, carbapenemase-resistant carbapenemase-producing Enterobacteriaceae; ESBL, extended-spectrum β-lactamase; RR, rate ratio.

in the universal glove and gown arm. However, all effect sizes were small, all CIs except that for MRSA overlapped 1, and all *P* values except that for MRSA were > .05. Some would argue that these results are therefore inconclusive and that the original study was underpowered to detect an effect size of 10%–20%, which is what was seen with most of the outcomes. These points and the terminology we have used throughout this manuscript to interpret the results of our study are especially relevant, as many statistical experts and leading journals are moving away from a focus on *P* values and more of a focus on effect size and CIs [24–27].

The question as to what an individual hospital should do with these results is also challenging. One key data point for hospitals to consider is to address the question about how many patients would not acquire antibiotic-resistant gram-negative bacteria in a typical ICU with a universal glove and gown policy. An average ICU has 16 beds and thus has a total of 5840 patient-days. Figure 1 demonstrates that the rate difference of −2.1 per 1000 patient-days means that, on average, the intervention would lead to 2.1 fewer patients acquiring antibiotic-resistant bacteria per 1000 patient-days. Thus, in an average ICU, over a 1-year period, 12 patients would be prevented from acquiring antibiotic-resistant gram-negative bacteria. However, there is uncertainty in this estimate, and our data are consistent with as many as 34 patients prevented, or 10 additional patients caused by universal precautions. The literature suggests that between 10% and 40% of these patients would develop subsequent infections within the same hospitalization with the acquired bacteria [10, 28–34].

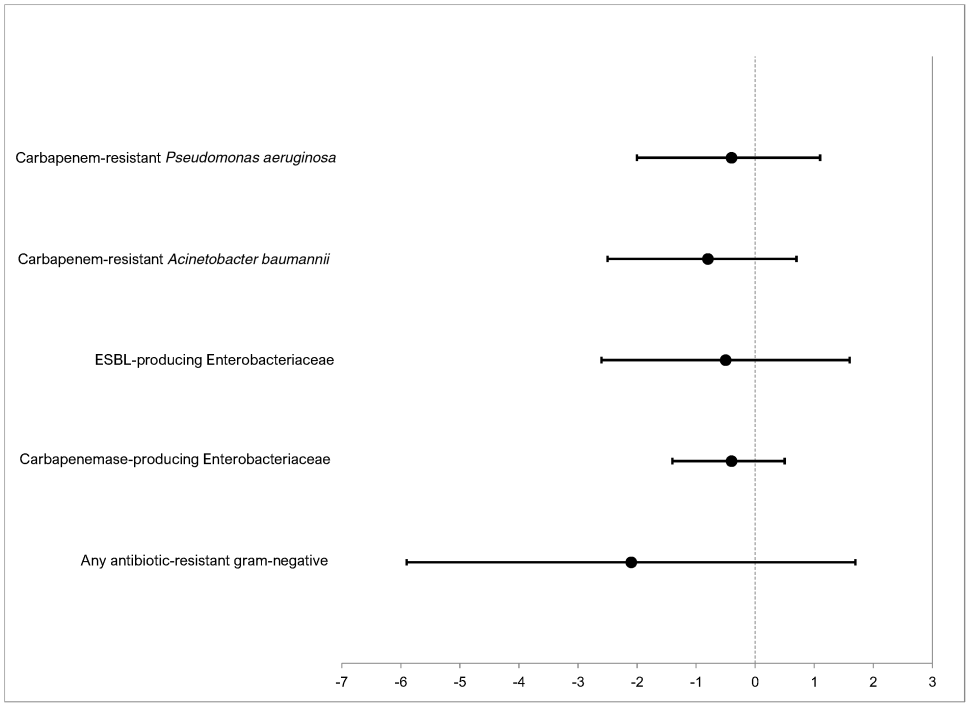

Figure 1. Rate differences (per 1000 person-days) and 95% confidence intervals for the impact of universal glove and gown use, by organism. The rate difference provides a measure of the public health impact of the intervention and describes the number of cases that could be prevented. Abbreviations: ESBL, extended-spectrum β-lactamase.

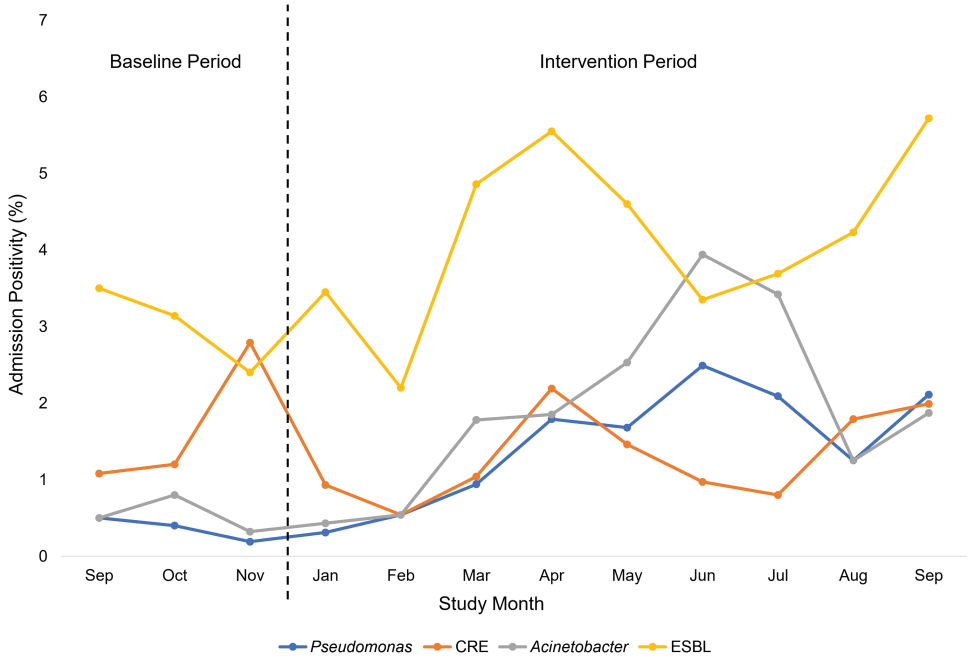

Figure 2. Admission positivity rate per organism, by month. Abbreviations: CRE, carbapenemase-resistant Enterobacteriaceae; ESBL, extended-spectrum β-lactamase.

Antibiotic-resistant gram-negative bacteria have been estimated to increase hospital length of stay by 24% and current admission hospital costs by 29% [35]. Having an antibiotic-resistant bacterial infection has also been shown to increase subsequent readmissions, prescriptions, and inpatient days [36].

One of the few studies to assess the impact of different infection control interventions, including active surveillance and contact precautions on antibiotic-resistant gram-negative bacteria, is the Clinical Trial to Reduce Antibiotic Resistance in European Intensive Cares (MOSAR-ICU) trial [37]. This study was a cluster randomized stepped-wedge design with a sequential set of interventions, with the first being chlorhexidine bathing, the second being hand hygiene initiative, and the last being active surveillance and contact precautions. The outcomes were MRSA, VRE, and highly resistant Enterobacteriaceae. The study's main findings support the use of chlorhexidine bathing and improved hand hygiene for MRSA. Active surveillance and contact precautions for highly resistant bacteria after the chlorhexidine bathing and the hand hygiene intervention were implemented showed no effect on highly resistant Enterobacteriaceae rates. However, it is not clear that the study was powered to detect this difference.

Our study has several limitations: As indicated above, the study was underpowered to detect an effect size that was found. In addition, from the baseline period to the study period, acquisition rates of the gram-negative bacteria increased in both the control and intervention periods. We do not know entirely why this occurred. We think a major reason for this increase was the increase in colonization pressure/admission prevalence of these bacteria during the study period in both the control and intervention sites and may be in part due to seasonal effects [38–40]. Colonization pressure has been well described to be a major driver of acquisition of antibiotic-resistant bacteria [41–43].

Our study has several strengths. The cluster randomized trial design provides stronger evidence than most studies currently used to support or negate infection control interventions, and the primary outcome measurement of acquisition was more objective than clinical culture positivity as used in other studies [44]. In addition, all ICUs enrolled completed the study, which is rare in a study of this size, and compliance with the intervention was high, which demonstrates the feasibility of implementing and sustaining the intervention. Moreover, our results are generalizable to a broad set of hospitals because the study was conducted in medical, surgical, and medical-surgical ICUs varying in size from 9 to 36 beds and located across the United States in rural, urban, academic, and nonacademic settings.

In conclusion, the association of universal glove and gown use in the ICU with acquisition of antibiotic-resistant gram-negative bacteria was inconclusive. The observed rate ratios for all 5 outcomes suggest that the intervention was protective; however, none were statistically significant. Individual hospitals should consider the cost-effectiveness of the intervention based on the effect sizes, CIs, and cost of instituting the intervention when they decide upon whether or not to adopt the intervention.

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