Anatomic, Geographic, and Taxon-Specific Relative Risks of Carbapenem Resistance in the Health Care System of the U.S. Department of Defense

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Carbapenem-resistant *Pseudomonas aeruginosa*, *Acinetobacter* spp., and *Enterobacteriaceae* pose urgent public health threats. The differential burden, relative risks, associations with antimicrobial consumption, and temporal trends of those taxa in large, geographically diverse U.S. health systems remain under reported. Electronic records of all patients in a geographically dispersed 280-hospital managed-care system from 2005 to 2014 were reviewed. Carbapenem-resistant strains were identified based on Clinical and Laboratory Standards Institute guidelines and breakpoints. A total of 360,000 potentially carbapenem-resistant strains were identified from 14.7 million cultures (80% infecting and 20% surveillance). Isolation of bacteria overseas or isolation from the bloodstream was associated with a higher relative risks of carbapenem resistance (CR; \(P < 0.0001\)). *Enterobacteriaceae* were isolated 11 times more frequently than *P. aeruginosa* and *Acinetobacter* spp. However, compared to *Enterobacteriaceae*, the CR levels were 73-fold and 210-fold higher in *P. aeruginosa* and *Acinetobacter* spp., respectively. Significant differences in the relative risk of CR between taxa, anatomic, and geographic locations persisted after adjustment for other variables, the biggest differences occurring between taxa. Overall, CR rates increased for *Enterobacteriaceae* (\(P = 0.03\)) and decreased for *Acinetobacter* spp. and *P. aeruginosa* (\(P < 0.0001\)). These data provide a useful baseline for resistance trending and have implications for surveillance. Infections acquired overseas and bloodstream infections are particularly important areas for continued monitoring.

Carbapenems are one of the most important classes of antimicrobials because they remain effective against most infections increasingly caused by multidrug-resistant (MDR) and extended-spectrum β-lactamase-producing Gram-negative bacteria. Although the Centers for Disease Control and Prevention lists carbapenem-resistant *Enterobacteriaceae* (CRE) as an urgent public health threat (1) and recent focus has been on CRE (2, 3), *Pseudomonas aeruginosa* and *Acinetobacter* spp. are also of great concern because they frequently complicate the care of immunocompromised patients and patients injured by war or natural disasters (4–6). Furthermore, data on the burden of CR in these species, especially at the population level, remain sparse. Similarly, data are scant on whether overseas locations are associated with increased relative risk of CR, which is relevant because the number of individuals and populations (including military populations) that are mobile or displaced by conflict has increased (7, 8). Finally, selection pressure from antibiotic use is a major driver of antimicrobial resistance, with even brief exposure in the form of prophylaxis for traveler’s diarrhea elevating the risk of certain types of antimicrobial resistance (9–11). However, relative risk and antimicrobial use-resistance associations at the population level or the level of an entire health system in the United States remain incompletely understood and infrequently reported.

We sought to determine here (i) the combined burden of carbapenem-resistant bacteria (CRB) (including *Acinetobacter* spp. and *Pseudomonas aeruginosa* and how that differed from resistance levels in *Enterobacteriaceae*) in the health care system of the U.S. Department of Defense (DOD), a large and geographically diverse managed health system; (ii) whether military treatment facilities (MTFs) located overseas or outside the contiguous U.S. (OCONUS) had an increased relative risk of isolation of a CRB compared to facilities in the contiguous United States (CONUS); (iii) whether certain anatomic sites, such as the bloodstream, had a higher risk of isolation of CRB; and (iv) whether DOD health care databases and electronic health records can be leveraged to explore antibiotic use-resistance relationships.

**MATERIALS AND METHODS**

The health care system of the DOD, its beneficiaries, and detailed methods for mining electronic health care records (EHR) have been described previously (3, 12). Briefly, patients of all ages, including neonates and geriatrics, are treated in approximately 288 fixed-location facilities throughout

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the contiguous United States, Alaska, and Hawaii. Fixed MTFs are also located in Guam, Italy, Germany, Kuwait, Japan, South Korea, and Spain. Transient medical surgical hospitals were and/or are located in Iraq and Afghanistan. Beneficiaries include active duty, family members of active duty service members, and retirees. The average annual number of beneficiaries eligible to receive care is 9.2 million. In terms of processes and quality, overseas facilities (except those in combat zones) are comparable to CONUS facilities in that they are held to the same requirements for Joint Commission accreditation. Similarly, clinical laboratories at fixed MTFs of the DOD are accredited by the College of American Pathologists and perform identification and susceptibility testing according to Clinical and Laboratory Standards Institute (CLSI) guidelines. Automated identification and susceptibility platform use across the DOD is fairly constant, with the Phoenix and Vitek II platforms in use by ca. 80% of hospitals and the MicroScan by ca. 20% (primarily by mobile hospitals in austere environments). This proportion of use was also stable over the entire study period. Since the health system of the DOD is geographically dispersed throughout the world, it is subject to the same influences from regional and global emergences of carbapenemase-encoding genes such as blaKPC, blaNDM, blaOXA-23, etc., that occurred and have been documented in the literature during this study period. Soon after the start of conflicts in Iraq and Afghanistan in 2001, the DOD health system began to see significant increases in multidrug and carbapenem-resistant Gram-negative bacteria. There were no major breakthroughs used were those in informational supplements M100-S16 to M100-S24 (15). To further mitigate this constraint, we also leveraged a large repository of centrally tested and characterized isolates from the DOD health system. A total of 9,000 unique (one isolate per patient per year) MDR Enterobacteriaceae, Acinetobacter spp., and P. aeruginosa underwent same-day plate testing by the referral laboratory (16, 17). The distribution of the MICs for each of the carbapenems are presented in Table 1.

Unadjusted relative risk (RR) estimates and their 95% confidence intervals (95% CI) were calculated in Excel using formulae identical to those available elsewhere (https://www.medcalc.org/calc/relative_risk.php), which included smoothing techniques for zero counts. Adjusted RR estimates (adjusted for the categorical covariates of calendar year, specimen source, and patient location) were computed with PROC GENMOD in SAS 9.4, using Poisson regression-based methods as described previously (18). The smoothing procedure suggested by Gauvreau and Pagano (19) was utilized for calculations involving zero counts in one or more cells of the contingency table.

**RESULTS**

Of 14,725,478 clinical cultures in the study time frame, 366,075 grew a target organism. We determined that 21, 8, 2, and 2% of the cultures were Acinetobacter spp., Klebsiella spp., P. aeruginosa, and E. coli, respectively, and the remainder were infecting isolates. Regardless of susceptibility, Enterobacteriaceae were isolated at 11 times the rate of P. aeruginosa and Acinetobacter spp. The rate of target organisms that were carbapenem resistant ranged from 1.25/1,000 organisms for E. coli to 277/1,000 organisms for Acinetobacter spp. (Table 2). The unadjusted relative risk for carbapenem resistance was 73-fold higher (95% CI = 66.6 to 80.1) in nonfermenters compared to fermenters (Table 3).

For all taxa combined, OCONUS locations were associated with a significantly increased risk of having a resistant organism: an adjusted RR of 1.39 (95% CI = 1.26 to 1.52; P < 0.0001). Similarly, for all taxa combined, isolation from blood was associated with a significantly higher relative risk of being CR compared

### TABLE 1 Distribution of carbapenem MICs in a representative sample of multidrug-resistant isolates from the DoD health system (one isolate per patient per year)

| Organism (no. of strains) | ≤0.5 | 1 | 2 | >4 | 8 | >8 | Total | % Intermediate or resistant |
|---------------------------|------|---|---|----|---|----|-------|-----------------------------|
| Acinetobacter spp. (2,205) |      |   |   |    |   |    |       |                             |
| Ertapenem                 | 1    |   |   |    |   |    | 10    | 56.55                        |
| Imipenem                  | 646  | 312| 62 | 50 | 1,135| 2,205|       |                             |
| Enterobacter spp. (674)    |      |   |   |    |   |    |       |                             |
| Ertapenem                 | 543  | 39 | 36 | 23 | 33 |    | 674   |                             |
| Imipenem                  | 470  | 135| 52 | 7  | 64 |    | 674   | 30.27                        |
| Escherichia coli (4,831)   |      |   |   |    |   |    |       |                             |
| Ertapenem                 | 4,754| 11| 14 | 10 | 42 |    | 4,831 | 15.1                         |
| Imipenem                  | 4,757| 27 | 14 | 11 | 21 |    | 4,830 | 1.51                         |
| Klebsiella spp. (1,222)    |      |   |   |    |   |    |       |                             |
| Ertapenem                 | 982  | 13 | 32 | 22 | 173|    | 1,222|                             |
| Imipenem                  | 1,034| 21 | 27 | 27 | 113|    | 1,222| 15.38                        |
| Pseudomonas spp. (1,433)   |      |   |   |    |   |    |       |                             |
| Ertapenem                 | 1    |   |   |    |   |    | 9     |                             |
| Imipenem                  | 158  | 246| 102| 110| 817|    | 1,433| 64.69                        |
to all other anatomic sites; an adjusted RR of 1.94 (95% CI = 1.68 to 2.23; P < 0.0001) (Table 4).

For nonfermenters alone (P. aeruginosa and Acinetobacter spp.), a higher relative risks of CR was observed for isolates recovered from the bloodstream and for isolates recovered from overseas locations. For fermenters (Enterobacteriaceae), a higher relative risk of CR was associated with blood isolation (Table 5). Even after adjusting for the other variables in the models, (adjusting for year and patient geographic location in the anatomic source model, and year and anatomic source in the geographic location model) there is an increased risk of carbapenem resistance for blood infection in both fermenters (adjusted RR = 2.21; 95% CI = 1.27 to 3.83) and nonfermenters (adjusted RR = 1.91; CI = 1.65 to 2.21). There is also an increased risk of carbapenem resistance for OCONUS locations for nonfermenters (adjusted RR = 1.43; 95% CI = 1.30 to 1.58) (Table 5).

When species were considered individually, the relative risk of CR was higher for A. baumannii (RR = 1.27; 95% CI = 1.12 to 1.45) and K. pneumoniae (RR = 1.83; 95% CI = 1.10 to 3.03) isolated OCONUS compared to CONUS (Table S1 in the supplemental material). Upon examining anatomic sites, E. coli (RR = 2.15; 95% CI = 1.02 to 4.55), we found that A. baumannii (RR = 1.45; 95% CI = 1.19 to 1.77) and P. aeruginosa (1.61; 95% CI = 1.30 to 1.99) had a higher risk of being carbapenem resistant if they were cultured from the blood versus other body sites (unpublished data [available upon request from the corresponding author]).

**DISCUSSION**

This report is notable for its size and duration, encompassing 14.7 million cultures spanning 10 years, totaling 92 million patient-years of surveillance. Significant differences in the relative risk of CR between taxa, anatomic, and geographic locations persisted after adjustment for other variables (including lactose fermentation). The most striking differences occurred between taxa. These data strongly support anecdotal observations among medical and laboratory DOD personnel, i.e., that an OCONUS location increases the relative risk of acquiring a carbapenem-resistant isolate, especially for Klebsiella and Acinetobacter spp. Also, the more serious infections (i.e., bacteremia) were more likely to be CR, particularly for E. coli, Acinetobacter spp., and P. aeruginosa. Finally, the rate of CR in this population is increasing for Enterobacteriaceae (P for trend = 0.03) but decreasing for Acinetobacter spp. and P. aeruginosa (P for trend < 0.0001). This study has several important limitations. One limitation is that outcomes (even in the in the same study) can vary depending on what is measured for resistance and use, e.g., dichotomous, categorical, or continuous data, as well as individual drugs, drug categories, or spectrum (20). A second is that cohorts and denominators are based on relatively conservative deduplication meth-

**TABLE 2** Rates of carbapenem resistance among selected organisms

| Specimen source | Category | E. coli | K. pneumoniae | K. oxytoca | P. aeruginosa | A. baumannii | Fermenters | Nonfermenters | Total | Rate | n | Rate | n | Rate | n | Rate | n | Rate | n |
|-----------------|----------|---------|---------------|------------|--------------|--------------|-------------|--------------|-------|------|---|------|---|------|---|------|---|------|---|
| Yr              |          |         |               |            |              |              |             |              |       |     |   |      |   |      |   |      |   |      |   |
| 2005            |          | 19      | 0.92          | 4          | 1.34         | 1             | 2.61        | 273           | 93.40 | 203 | 257.29 | 24 | 1.00 | 476 | 128.23 | 500 | 17.98 |   |
| 2006            |          | 26      | 1.18          | 7          | 2.18         | 0             | 0.00        | 211           | 78.12 | 224 | 287.55 | 33 | 1.29 | 435 | 125.00 | 468 | 16.08 |   |
| 2007            |          | 26      | 1.16          | 8          | 2.51         | 1             | 2.43        | 235           | 94.61 | 177 | 306.76 | 35 | 1.35 | 412 | 134.60 | 447 | 15.41 |   |
| 2008            |          | 33      | 1.08          | 7          | 1.72         | 4             | 7.77        | 241           | 84.21 | 138 | 316.53 | 44 | 1.25 | 379 | 114.92 | 423 | 10.99 |   |
| 2009            |          | 48      | 1.47          | 12         | 2.84         | 2             | 3.75        | 219           | 79.12 | 98  | 308.18 | 62 | 1.66 | 317 | 102.72 | 379 | 9.37  |   |
| 2010            |          | 57      | 1.69          | 17         | 3.92         | 1             | 1.88        | 212           | 79.70 | 118 | 322.40 | 75 | 1.95 | 330 | 109.05 | 405 | 9.75  |   |
| 2011            |          | 51      | 1.55          | 25         | 5.52         | 0             | 0.00        | 225           | 83.49 | 115 | 363.92 | 76 | 2.01 | 340 | 112.92 | 416 | 10.18 |   |
| 2012            |          | 35      | 1.07          | 16         | 3.65         | 0             | 0.00        | 216           | 85.01 | 44  | 187.23 | 51 | 1.35 | 260 | 93.66  | 311 | 7.69  |   |
| 2013            |          | 35      | 1.28          | 27         | 7.41         | 2             | 4.37        | 225           | 101.86 | 23  | 127.78 | 64 | 2.03 | 248 | 103.81 | 312 | 9.21  |   |
| 2014            |          | 35      | 0.97          | 18         | 4.00         | 1             | 1.71        | 255           | 94.44 | 21  | 107.69 | 54 | 1.31 | 276 | 95.34  | 330 | 7.49  |   |
| Rate            |          | 365     | 1.25          | 141        | 3.61         | 12            | 2.50        | 2,312          | 87.10 | 1,161| 277.02 | 518| 1.55 | 3,473| 113.00 | 3,991| 10.91 |   |

**TABLE 3** Comparison of relative risks of carbapenem resistance in selected taxa

| Category | Unadjusted RR | 95% CI* |
|----------|---------------|---------|
| Organism |               |         |
| E. coli  | 1.0           |         |
| K. pneumoniae | 2.9 | 2.4–3.5 |
| K. oxytoca | 2.0 | 1.1–3.5 |
| P. aeruginosa | 69.5 | 62.2–77.6 |
| A. baumannii | 220.9 | 196.4–248.5 |

| Fermenters vs nonfermenters | | |
| Fermenters | 1.0 | 66.6–80.1 |
| Nonfermenters | 73.1 | |

*95% CI, 95% confidence interval.
ods, and the latest (i.e., those for 2014) lower CLSI breakpoints could not be applied across the study period. Therefore, the true burden of CR might be higher. However, one can apply the latest CLSI breakpoints to the MICs presented in Table 1 to see the effect burden of CR might be higher. However, one can apply the latest CLSI breakpoints to the MICs presented in Table 1 to see the effect.

For trend

| Category | Unadjusted | | | | Adjusted\(^a\) | | |
| --- | --- | --- | --- | | --- | --- |
| Yr | RR | 95% CI | P | P for trend | RR | 95% CI | P | P for trend |
| 2005 | 1.00 | | | | 1.00 | | | |
| 2006 | 0.89 | 0.79–1.01 | 0.08 | | 0.99 | 0.87–1.12 | 0.87 | |
| 2007 | 0.86 | 0.75–0.97 | 0.02 | | 1.08 | 0.95–1.22 | 0.25 | |
| 2008 | 0.61 | 0.54–0.70 | <0.0001 | | 0.92 | 0.81–1.05 | 0.21 | |
| 2009 | 0.52 | 0.46–0.60 | <0.0001 | | 0.87 | 0.76–0.99 | 0.03 | |
| 2010 | 0.54 | 0.48–0.62 | <0.0001 | | 0.93 | 0.82–1.06 | 0.29 | |
| 2011 | 0.57 | 0.50–0.64 | <0.0001 | | 0.96 | 0.84–1.09 | 0.54 | |
| 2012 | 0.43 | 0.37–0.49 | <0.0001 | | 0.77 | 0.67–0.89 | 0.0004 | |
| 2013 | 0.51 | 0.44–0.59 | <0.0001 | | 0.91 | 0.79–1.04 | 0.18 | |
| 2014 | 0.42 | 0.36–0.48 | <0.0001 | | 0.79 | 0.69–0.91 | 0.001 | <0.0001 |

Specimen source

| Category | RR | 95% CI | P | |
| --- | --- | --- | --- | |
| Blood | 4.08 | 3.55–4.69 | <0.0001 | |
| Other | 1.00 | | | |

Patient location

| Category | RR | 95% CI | P | |
| --- | --- | --- | --- | |
| CONUS | 1.00 | | | |
| OCONUS | 1.29 | 1.18–1.41 | <0.0001 | |

Table 4 Adjusted and unadjusted relative risks

\(^a\) That is, adjusted for calendar year, specimen source, and patient location.

Determining whether antibiotic use correlates with antimicrobial resistance is critical for designing antibiotic stewardship programs. Our ability to examine this relationship across the DOD health care system was limited. While patient-days of antibiotic use data are optimal for this analysis, it is nearly impossible to get precise patient-days or patient-years of antibiotic usage for the entire DOD health care system because even with electronic medical records, manual chart review is required to determine the exact start and stop times for each antibiotic prescription. For this reason we did not ask whether individual use correlates with patient-level resistance but instead examined how antibiotic use by an entire managed care system is related or associated with incidences of resistance.

We defined consumption by drug class as the number of antimicrobial prescriptions per antimicrobial class per patient encounter (inpatient or outpatient), meaning that, per encounter, each antimicrobial class was only counted once, irrespective of multiple prescriptions of antimicrobials within the class in that encounter. Consumption by specific drugs in a class was defined as the number of different antimicrobials per class per patient encounter. Using both Pearson product-moment and Spearman rank correlation coefficient tests, we did not detect a statistically significant positive correlation between any single drug or any combination of drugs and CR incidence for any taxa. The strongest associations (\(r > 0.7\)) were for *Acinetobacter* spp. for all single antibiotics and combinations of drugs except carbapenems. The usage values in this study reflect population level data; therefore, the total numbers are very large. However, when \(P\) values are calculated based on the number of pairwise comparisons (here, 5 for each \(R\) value), even those with stronger \(R\) values (\(>0.7\)) do not reach significance. Nonetheless, the associations (or lack thereof) between antibiotic use and resistance are consistent with other studies (3, 21, 22). Furthermore, the measures used provide a baseline estimate that can be used as a crude benchmark for comparing and trending historical or future consumption in this system.

Despite these limitations, the study provides a useful baseline for future resistance trending in this population. The findings also have potential implications for surveillance, since overseas locations are important areas to continue monitoring. The findings have implications for stewardship, since fluoroquinolone and

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TABLE 4 Adjusted and unadjusted relative risks

| Category | RR | 95% CI | P | P for trend |
| --- | --- | --- | --- | --- |
| Specimen source/location | | | | |
| Other | 1.00 | | | |
| Blood/OCONUS | 1.28 | 1.16–1.40 | <0.0001 | |
| Other/OCONUS | 3.88 | 3.34–4.52 | <0.0001 | |
| Blood/OCONUS | 8.42 | 5.84–12.14 | <0.0001 | |
| Fermenters vs nonfermenters | | | | |
| Fermenters | 1.00 | | | |
| Nonfermenters | 73.07 | 66.63–80.13 | <0.0001 | |

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