Diagnostic Microbiology and Infectious Disease 81 (2015) 119–125

Contents lists available at ScienceDirect

Diagnostic Microbiology and Infectious Disease

journal homepage: www.elsevier.com/locate/diagmicrobio

Carbapenem-resistant Enterobacteriaceae and the correlation between carbapenem and fluoroquinolone usage and resistance in the US military health system ☆

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ARTICLE INFO

Article history:
Received 1 May 2014
Received in revised form 14 September 2014
Accepted 19 September 2014
Available online 28 September 2014

Keywords:
Antibiotic use
Antibiotic consumption
Healthcare network
Carbapenem resistance

ABSTRACT

Whether carbapenem or fluoroquinolone usage is correlated with carbapenem-resistant Enterobacteriaceae (CRE) has not been investigated at the level of an entire US nationwide managed health care system. We analyzed 75 million person-years of surveillance and 1,969,315 cultures from all 266 hospitals in the geographically dispersed US military health system. Incidences of CRE remained under 1 case per 100,000 person-years. Incidences of CRE increased relative to 2005 baseline levels in 3 of 7 subsequent years, then decreased in 2012 ($P < 0.05$). Incident proportions of carbapenem resistance (CR) differed significantly among years, geographical regions, and bacterial species. Although use and resistance strongly correlated ($R > 0.80$) for several "drug-bug" combinations, none were significant at the national or facility level. One exception was that inpatient consumption of fluoroquinolones was significantly correlated ($P = 0.0007$) with CR in *Escherichia coli* when data from the major referral centers of the Southern and Northern regions were combined.

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1. Introduction

Enterobacteriaceae are leading causes of community- and hospital-acquired infections (Gupta et al., 2011; Nordmann et al., 2011). Antibiotic resistance can rapidly develop and spread in these bacteria through mobile genetic elements readily shared among unrelated species (Gupta et al., 2011; Nordmann et al., 2011).

Carbapenem-resistant Enterobacteriaceae (CRE) have become an especially worrisome global public health crisis (Gupta et al., 2011; Nordmann et al., 2011; Savard and Perl, 2012; Sievert et al., 2013; WHO, 2000). Infections caused by these bacteria can be associated with a mortality rate as high as 80% (Gupta et al., 2011; Snitkin et al., 2012; Tumbarello et al., 2012). Carbapenem resistance (CR) often arises through mechanisms that involve acquisition of multiple drug resistance genes resulting in extremely drug-resistant or pandrug-resistant infections with few or no treatment options (Nordmann et al., 2011; Magiorakos et al., 2013).

CR is increasing worldwide (Nordmann et al., 2011; Gupta et al., 2011; Savard and Perl, 2012), but the burden of such resistance in 1 large and diverse US population, health care beneficiaries of the Department of Defense (DoD), has not been reported. Furthermore, there is conflicting evidence on whether increased antibiotic consumption, in particular of carbapenems and fluoroquinolones, is correlated with this increased resistance (Mutnick et al., 2004; Bruinsma et al., 2002; Ho et al., 2012; Mouloudi et al., 2010; Manikal et al., 2000; SWAB, 2011; Lee et al., 2013). Of note, correlation between antibiotic consumption and resistance in Enterobacteriaceae throughout an entire health care system in the United States has not been reported (Molton et al., 2013).

Previous antibiotic exposure, especially to fluoroquinolones, was correlated with future isolation of CRE in individual patients in case–control studies (Gupta et al., 2011; Hussein et al., 2009; Marchaim et al., 2012). Other studies have not found that association (Mouloudi et al., 2010).

Our objectives were to determine the level of CRE in a geographically dispersed national managed care system, the health system of the DoD, and to determine if total carbapenem or fluoroquinolone consumption throughout the system was correlated with CR. We also provide proportions and rates because the use of only one may not reflect the true burden of resistance or loss of treatment options and also because a report format most useful for the clinician treating empirically (proportions) may not be as useful to the public health professional (rates) (Rempel and Laupland, 2009; Schwaber et al., 2004; Laxminarayan and Klugman, 2011; Monnet et al., 2001; Sanchez et al., 2013).

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http://dx.doi.org/10.1016/j.diagmicrobio.2014.09.017
0732-8893/Published by Elsevier Inc.

2. Methods

This study was undertaken as a quality improvement initiative authorized by policy memoranda 09-050, 11-035, 13-016, and IRB protocol number #1812.

2.1. Population and data collection

The DoD has a managed care system composed of 266 fixed location medical facilities throughout the United States and overseas. It is divided into 4 geographic regions: North, South, West, and Pacific. The surveillance population, all DoD beneficiaries who were eligible to receive care from January 2005 through December 2012, included patients of all ages and races. There were approximately 9.7 million beneficiaries in 2012 and an average of 9.5 million yearly, and the demographic details have been published previously (Landrum et al., 2012). The DoD uses electronic health records (EHR) for all clinical encounters. Methods used for extracting and aggregating microbiology data from EHR have been previously published (Landrum et al., 2012), as have methods for isolate collection and characterization (Waterman et al., 2012; Milillo et al., 2013).

Briefly, from all positive cultures, only unique/deduplicated isolates, defined as the first Enterobacteriaceae (*Escherichia coli*, *Enterobacter* spp., or *Klebsiella* spp.) isolate per patient per calendar year, were culled. From these, those nonsusceptible to imipenem, meropenem, and/or doripenem, based on the prevailing Food and Drug Administration (FDA) and the 2010 Clinical Laboratory Standards Institute (CLSI) (M100-S20-U) susceptibility breakpoint defined by an MIC of ≥4 μg/mL, were extracted to calculate incident rates and proportions of CRE. This breakpoint was used for all the years because the newest CLSI breakpoints released in 2012 (M100-S22) could not be universally adopted (across all years and all facilities) for this study. Workload tracking and billing location codes were used to determine if the culture originated from an inpatient or outpatient care area. Correlation tests were performed several ways: 1 set of tests used aggregate data from the entire DoD (system level); the second series of tests used data from US domestic facilities, stratified by geographic region (regional level); the third set of analyses focused on data from the 2 busiest and largest referral centers in the DoD, presumably where the most carbapenems and fluoroquinolones are prescribed and the resistance occurs (facility level). For system level data, we examined correlations between antibiotic usage and a) incidence rates, b) incident proportions, and c) absolute numbers of resistant isolates. These tests were performed for CREs as a whole as well as for *E. coli*, *Klebsiella* spp., and *Enterobacter* spp. separately. At the regional and facility levels, we measured correlations between antibiotic usage and incident proportions and between usage and absolute numbers of CR isolates.

For antibiotic consumption at the major referral facilities, the unit of measure was physician orders or prescriptions written for each antibiotic. For regional-level usage and usage across the entire system, doses given, and/or for outpatient usage, purchases invoiced were used. In terms of a defined daily dose (DDD), this unit would approximately equate to a fraction of the DDD depending on the average recommended daily dose based on normal renal function. For example, for a patient with normal creatinine clearance who received the antibiotic for a full 24-hour period, 1 unit would equate to 1/3 the usual meropenem, DDD, or ¼ the usual imipenem DDD. Meropenem is usually dosed every 8 hours, and imipenem every 6.

2.2. Statistics

Statistical tests were performed using the R version 2.14 software package (http://cran.us.r-project.org/). For analysis of variance (ANOVA) of US regional data, we used the *aov* and *TukeyHSD* functions. For data collected across the entire military health care system (US and overseas facilities), pairwise comparisons of rates and proportions were performed using Fisher's exact test, trends were analyzed using the chi-squared proportion trend test, and usage resistance relationships were analyzed using the Pearson correlation test. *P* values were adjusted for multiple testing using the Bonferroni correction.

3. Results

3.1. Overall burden of CR

During 2005–2012, there were 75,529,012 person-years of surveillance and 1,969,315 bacterial organisms identified from 1,823,030 clinical cultures. Those organisms included 667,004 Enterobacteriaceae, of which 368 were classified as CRE for an overall incident proportion of 0.487% (95% confidence interval [CI]: 0.439–0.540) (Table 1). Seventy-seven percent (284) were isolated in outpatient care areas, and 23% (84) were isolated from inpatient care areas. The mean annual incident rate of CRE for this period was 0.49 per 100,000 patient-years (Table 1).

3.2. Proportions

The proportion of all Enterobacteriaceae that were carbapenem resistant rose from 0.033% in 2005 to 0.052% in 2012 ($P = 0.053$) (Fig. 1). Combining all species and using 2005 as the reference year, incidence proportions of CRE increased significantly in 3 of 7 subsequent surveillance years, with the most significant increase occurring in 2010 ($P < 0.0001$) (Fig. 1). Considering species separately, CR in *E. coli* also showed a statistically significant increase in 3 of 7 surveillance years compared to the baseline in 2005. CR in *Klebsiella* spp. (*Klebsiella pneumoniae* and *Klebsiella oxytoca*) reached a maximum in 2010 ($P = 0.035$). CR in *Enterobacter* spp. (*Enterobacter cloacae* and *Enterobacter aerogenes*) fluctuated the most and showed no significant trend (Fig. 1). The lowest proportion of incident resistance (0.020%) was seen in *E. coli* in 2005, and the highest (0.243%) was seen in *Enterobacter* spp. during 2012. The decrease in the proportion of all CRE from the peak year of 2010 to 2012 was significant ($P = 0.048$). Among Enterobacteriaceae, *Klebsiella* spp. showed the fastest increase in the proportion resistant to carbapenems, as measured by linear regression (Online Supplemental Fig. 1).

3.3. Rates

Incidence rates of all CRE combined varied from a low of 0.335 per 100,000 person-years in 2005 to a high of 0.672 in 2010 ($P = 0.001$) (Table 1). Relative to 2005, the reference year, rates of CR in *E. coli* were significantly higher in 2009 and 2010 (Fig. 2). The lowest rate (0.043) was seen in *Enterobacter* spp. in 2008, and the highest rate was seen in *E. coli* (0.455) in 2010. *E. coli* had the fastest increase in CR rate from 2005 to 2012 (Online Supplemental Fig. 2).

3.4. Factors affecting the likelihood of CR

To see which variables were associated with the probability that an organism was carbapenem resistant, we performed ANOVA on the regional data set. The analysis was performed 2 ways: a) the correlation of year, region, and organism to incident proportion was examined individually; b) all variables were examined together, sequentially controlling for organism, then region, then year. Region and organism were highly significant factors ($P < 0.0001$). The year of isolation showed a lesser, though statistically significant association, after controlling for region and organisms (data not shown).

Tuke's highly significant difference test was used to discover which specific pairs of regions, organisms, and years had significantly different incidence proportions. Examination of CR incident proportion by species revealed significant differences between *E. coli* and *Enterobacter* spp. ($P < 0.001$) and *E. coli* and *Klebsiella* spp. ($P < 0.001$) but not between *Enterobacter* and *Klebsiella* ($P = 0.06$) (Fig. 3 and other data not shown). When we analyzed the relationship between geographical region and CR, we found CR proportions differed significantly between every pair of regions except between West and Pacific (Fig. 3). The South had the highest incidence of resistance; the West and Pacific had the lowest. Examining CR incidence proportions by year showed that overall CR incidence in 2010 was significantly higher than in 2005 and 2008. No other difference in annual incident proportions was statistically significant (Fig. 3).

We next asked whether differences in regional incident proportions remained significant after controlling for species differences. CR incidence in *Klebsiella* varied the least between geographical regions, and *E. coli* differed the most (data not shown). A similar analysis demonstrated statistically significantly yearly variation in *E. coli* CR incidence (data not shown).

3.5. Antibiotic consumption

The earliest year for which system-level (enterprise wide) antibiotic usage data were available is 2008 (Supplemental Table 1A and B). Carbapenem consumption ranged from a low of 8023 units in 2009 to a high of 12,965 units in 2011. Between 2008 and 2012, carbapenem consumption increased by 32%. Fluoroquinolone consumption ranged from a low of 158,145 units in 2011 to a high of 245,765 units in 2012. From 2008 to 2012 fluoroquinolone consumption within the DoD increased by 17%. For the major referral centers in the North and South regions, we further stratified carbapenem and fluoroquinolone usage into inpatient and outpatient doses (Supplemental Fig. 3). Peak consumption in