Carbapenem resistance, inappropriate empiric treatment and outcomes among patients hospitalized with Enterobacteriaceae urinary tract infection, pneumonia and sepsis

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Abstract

Background: Drug resistance among gram-negative pathogens is a risk factor for inappropriate empiric treatment (IET), which in turn increases the risk for mortality. We explored the impact of carbapenem-resistant Enterobacteriaceae (CRE) on the risk of IET and of IET on outcomes in patients with Enterobacteriaceae infections.

Methods: We conducted a retrospective cohort study in Premier Perspective database (2009–2013) of 175 US hospitals. We included all adult patients with community-onset culture-positive urinary tract infection (UTI), pneumonia, or sepsis as a principal diagnosis, or as a secondary diagnosis in the setting of respiratory failure, treated with antibiotics within 2 days of admission. We employed regression modeling to compute adjusted association of presence of CRE with risk of receiving IET, and of IET on hospital mortality, length of stay (LOS) and costs.

Results: Among 40,137 patients presenting to the hospital with an Enterobacteriaceae UTI, pneumonia or sepsis, 1227 (3.1%) were CRE. In both groups, the majority of the cases were UTI (51.4% CRE and 54.3% non-CRE). Those with CRE were younger (66.6+/−15.3 vs. 69.1+/−15.9 years, p < 0.001), and more likely to be African-American (19.7% vs. 14.0%, p < 0.001) than those with non-CRE. Both chronic (Charlson score 2.0+/−2.0 vs. 1.9+/−2.1, p = 0.009) and acute (by day 2: ICU 56.3% vs. 30.4%, p < 0.001, and mechanical ventilation 35.8% vs. 11.7%, p < 0.001) illness burdens were higher among CRE than non-CRE subjects, respectively. CRE patients were 3× more likely to receive IET than non-CRE (46.5% vs. 11.8%, p < 0.001). In a regression model CRE was a strong predictor of receiving IET (adjusted relative risk ratio 3.95, 95% confidence interval 3.5 to 4.5, p < 0.001). In turn, IET was associated with an adjusted rise in mortality of 12% (95% confidence interval 3% to 23%), and an excess of 5.2 days (95% confidence interval 4.8, 5.6, p < 0.001) LOS and $10,312 (95% confidence interval $9497, $11,126, p < 0.001) in costs.

Conclusions: In this large US database, the prevalence of CRE among patients with Enterobacteriaceae UTI, pneumonia or sepsis was comparable to other national estimates. Infection with CRE was associated with a four-fold increased risk of receiving IET, which in turn increased mortality, LOS and costs.

Keywords: UTI, Pneumonia, Sepsis, Enterobacteriaceae, Antimicrobial resistance, Inappropriate empiric therapy, Hospital mortality, Hospital cost
Background

Initial antibiotic therapy affects outcomes in severe infection. For empiric therapy to have a benefit on patient outcomes, it must not only be given in a timely manner but must also be active in vitro against the infecting pathogen. Many studies indicate that either delaying antibiotic therapy or selecting a treatment to which the infecting pathogen is non-susceptible increases the risk for death 2–5-fold [1–13]. Therefore, clinicians must be aware of the common pathogens in specific infectious syndromes and of local antimicrobial susceptibility patterns in order to make appropriate choices for antimicrobial therapies. Unfortunately, rapidly rising rates of resistance and shifting resistance patterns render ensuring appropriate empiric coverage a challenge [14].

Recently, the Centers for Disease Control and Prevention have identified carbapenem-resistance among Enterobacteriaceae as an urgent threat in the US [15]. Though Enterobacteriaceae are common pathogens in pneumonia, urinary tract infections and sepsis and thus are often treated in most empiric coverage recommendations, the escalating frequency of carbapenem resistance in these pathogens makes ensuring initially appropriate antimicrobial treatment in areas where carbapenem-resistant Enterobacteriaceae (CRE) are prevalent nearly impossible [13, 14, 16–19]. Furthermore, administering broad-spectrum agents to all severely ill patients in order not to miss some individual with a rare highly resistant pathogen is not a sustainable practice, since the concerns for promoting further resistance may outweigh any potential benefit to patient-specific outcomes. In this way, the dilemma of CREs amplifies the tension between public (preservation of antimicrobial activity) and patient-level (optimizing clinical outcomes) health imperatives.

It remains unclear if the nexus between inappropriate therapy and outcomes seen with other pathogens exists in the case of infections due to CRE. Few analyses have specifically addressed this issue, while some that have attempted this lacked the ability to delineate the impact of inappropriate empiric therapy of CREs on attributable morbidity or on resources such as length of stay (LOS) [20, 21]. To understand better the relationship between carbapenem-resistance, choice of inappropriate empiric therapy (IET), and key hospital outcomes, we conducted a cohort study of patients admitted to the hospital with community-onset urinary tract infections (UTI), pneumonia and sepsis due to Enterobacteriaceae.

Methods

This was a multi-center retrospective cohort study of patients admitted to the hospital with pneumonia, sepsis and UTI (referred to from here on as “UTI”), or sepsis from another source in the Premier Research database in the years 2009–2013. We hypothesized that infection with a CRE phenotype increased the risk of receiving IET. In turn, we hypothesized that the receipt of IET is adversely associated with hospital mortality, LOS, and costs.

Because this study used already existing fully de-identified retrospective data, it was exempt from IRB review.

Since the data source was the same and methods utilized in this study were similar to those used in our previous study, please refer to that paper for details [22].

Patient population

Patients were included if they were adults (age ≥ 18 years) hospitalized with a UTI International Classification of Diseases, version 9, Clinical Modification (ICD-9-CM) codes (principal diagnosis 112.2, 590.1, 590.11, 590.2, 590.3, 590.8, 590.81, 595, 597, 599 or 996.64, or principal sepsis diagnosis [see below] with UTI as a secondary diagnosis), pneumonia ICD-9-CM codes (principal diagnosis 481–486, or respiratory failure codes [518.81 or 518.84] with pneumonia as a secondary diagnosis) or sepsis codes from another source (principal diagnosis 038, 038.9, 020.0, 790.7, 995.92 or 785.52, or respiratory failure codes [518.81 or 518.84] with sepsis coded as a secondary diagnosis) [23–27]. In order to eliminate confounding of the outcomes by pre-infection onset hospital events, only patients with infection present on admission, as evidenced by antibiotic treatment beginning within the first 2 days of hospitalization and continuing for at least 3 consecutive days, or until discharge, were included [24–26]. Patients were excluded if they were transferred from another acute care facility, if they were diagnosed with cystic fibrosis, or if their hospital length of stay (LOS) was 1 day or less. Those who met criteria for both UTI and sepsis or pneumonia and sepsis were included in the UTI or pneumonia group, respectively. Those with both UTI and pneumonia were analyzed with the pneumonia group. Patients were followed until death in or discharge from the hospital.

Data source

The data for the study derived from Premier Research database, an electronic laboratory, pharmacy and billing data repository, for years 2009 through 2013, which contains approximately 15% of all hospitalizations nationwide. For detailed description of the dataset, please, refer to citation #22.
Baseline variables
We classified each community-onset infection (UTI, pneumonia or sepsis) as healthcare-associated (HCA) if one or more of the following risk factors was present: 1) prior hospitalization within 90 days of the index hospitalization, 2) hemodialysis, 3) admission from a long-term care facility, 4) immune suppression [3, 6, 16, 23–26]. All other infections were considered to be community-acquired (CA). For other patient factors and hospital-level variables, please see citation #22.

Microbiology and treatment variables and definitions
Urinary, blood and respiratory cultures had to be obtained within the first 2 days of hospitalization.

The following organisms were defined as Enterobacteriaceae of interest:

1. *Escherichia coli*
2. *Klebsiella pneumoniae*
3. *Klebsiella oxytoca*
4. *Enterobacter cloacae*
5. *Enterobacter aerogenes*
6. *Proteus mirabilis*
7. *Proteus spp.*
8. *Serratia marcescens*
9. *Citrobacter freundii*
10. *Morganella morganii*
11. *Providencia spp.*

Premier database receives organism susceptibility reports from individual institutions’ laboratories as S (susceptible), I (intermediate) or R (resistant). Although no MIC data are available in the database, all microbiology testing was performed locally at the institutions contributing the data and conformed to the CLSI standards. Carbapenem-resistant Enterobacteriaceae were defined as one of the above organisms where susceptibility testing yielded an I or R result to at least one of the four carbapenems: imipenem, meropenem, ertapenem or doripenem.

IET was present if the antibiotic administered for the infection did not cover the organism or if appropriate coverage did not start within 2 days of the positive culture being obtained.

Statistical analyses
We compared characteristics of patients infected with CRE to those infected with carbapenem-susceptible Enterobacteriaceae (CSE) and those treated with IET to those treated with non-IET. All unadjusted comparisons were done using standard methods described in detail in citation #22.

We developed a generalized logistic regression model to explore the relationship between CRE and the risk of IET. Covariates in the model were identical to those in citation #22. We calculated the relative risk ratio with 95% confidence intervals of receiving IET for CRE vs. CSE based on Huber-White robust standard errors clustered at the hospital level [28]. Consistent with our prior study, we confirmed our results in a non-parse model and a propensity matched model with propensity for CRE derived from a logistic regression model using the non-parse model’s predictors [22]. To explore the impact of IET on hospital mortality, LOS and costs, we developed hierarchical regression models with hospitals as random effects along with confirmatory propensity-matched models.

All tests were two-tailed, and a *p* value < 0.05 was deemed a priori to represent statistical significance. All analyses were performed in Stata/MP 13.1 for Windows (StataCorp LP, College Station, TX).

Results
Among 230,086 patients presenting to the hospital with a UTI, pneumonia or sepsis, 40,137 (17.4%) met the inclusion criteria for Enterobacteriaceae of which the majority were UTI (54.2%), with the remainder either pneumonia (13.1%) or sepsis (32.7%). Among all patients with Enterobacteriaceae, 1227 (3.1%) had 1938 CRE organisms (Table 1). The prevalence of CRE among the Enterobacteriaceae ranged from 2.9% in UTI to 3.6% in pneumonia. Notably, over 85% of patients in both the

| CRE organism name | CRE organism Count | % of Total CRE | % of the Total patientsa | % of Total CRE (N = 1938) | % of the Total patientsa (N = 1227) |
|-------------------|--------------------|----------------|-------------------------|--------------------------|-----------------------------------|
| Klebsiella pneumoniae | 724 | 37.4% | 59.0% |
| Proteus mirabilis | 370 | 19.1% | 30.2% |
| Escherichia coli | 294 | 15.2% | 24.0% |
| Enterobacter cloacae | 128 | 6.6% | 10.4% |
| Providencia spp | 94 | 4.9% | 7.7% |
| Serratia marcescens | 87 | 4.5% | 7.1% |
| Morganella morganii | 87 | 4.5% | 7.1% |
| Enterobacter aerogenes | 40 | 2.1% | 3.3% |
| Proteus spp. | 27 | 1.4% | 2.2% |
| Citrobacter freundii | 27 | 1.4% | 2.2% |
| Klebsiella oxytoca | 22 | 1.1% | 1.8% |
| Enterobacter other | 13 | 0.7% | 1.1% |
| Citrobacter other | 14 | 0.7% | 1.1% |
| Serratia other | 6 | 0.3% | 0.5% |
| Klebsiella other | 5 | 0.3% | 0.4% |

aSum adds up to >100%, as some patients had >1 CRE organism
Table 2 Baseline characteristics

|                        | CSE (%, N = 38,910) | CRE (%, N = 1227) | P-value |
|------------------------|---------------------|-------------------|---------|
| **Mean age, years (SD)** | 69.1 (15.9)         | 66.6 (15.3)       | <0.001  |
| **Gender: male**       | 41.8% (16,273)      | 52.3% (642)       | <0.001  |
| **Race**               |                     |                   |         |
| White                  | 72.7% (28,295)      | 66.9% (821)       | <0.001  |
| Black                  | 14.0% (5464)        | 19.7% (242)       |         |
| Hispanic               | 2.7% (1069)         | 2.6% (32)         |         |
| Other                  | 10.5% (4082)        | 10.8% (132)       |         |
| **Admission Source**   |                     |                   |         |
| Non-healthcare facility (including from home) | 65.7% (25,559) | 63.2% (776) | <0.001 |
| Clinic                 | 3.3% (1285)         | 2.2% (27)         |         |
| Transfer from ECF      | 9.5% (3697)         | 21.7% (266)       |         |
| Transfer from another non-acute care facility | 1.2% (473)  | 1.8% (22)        |         |
| Emergency Department   | 20.0% (7766)        | 10.8% (132)       |         |
| Other                  | 0.3% (130)          | 0.3% (4)          |         |
| **Elixhauser Comorbidities** |                 |                   |         |
| Congestive heart failure | 24.7% (9623)      | 26.8% (329)       | 0.096   |
| Valvular disease       | 8.0% (3112)         | 7.8% (96)         | 0.825   |
| Pulmonary circulation disease | 6.0% (2323)   | 7.6% (93)         | 0.020   |
| Peripheral vascular disease | 11.0% (4285) | 13.8% (169)       | 0.002   |
| Paralysis              | 10.5% (4085)        | 22.1% (271)       | <0.001  |
| Other neurological disorders | 22.3% (8668) | 28.4% (348)       | <0.001  |
| Chronic pulmonary disease | 28.4% (11,035)  | 30.2% (371)       | 0.151   |
| Diabetes without chronic complications | 29.9% (11,616) | 34.2% (420)       | 0.001   |
| Diabetes with chronic complications | 9.8% (3809)  | 11.5% (141)       | 0.049   |
| Hypothyroidism         | 17.4% (6764)        | 18.3% (224)       | 0.428   |
| Renal failure          | 27.8% (10,810)      | 36.3% (446)       | <0.001  |
| Liver disease          | 5.4% (2084)         | 5.3% (65)         | 0.929   |
| Peptic ulcer disease with bleeding | 0.0% (17)      | 0.1% (1)          | 0.428   |
| AIDS                   | 0.0% (12)           | 0.0% (0)          | 1.000   |
| Lymphoma               | 1.6% (604)          | 1.7% (21)         | 0.657   |
| Metastatic cancer      | 4.6% (1787)         | 3.3% (40)         | 0.027   |
| Solid tumor without metastasis | 4.0% (1569)  | 2.8% (34)         | 0.026   |
| Rheumatoid arthritis/collagen vascular | 4.4% (1721) | 3.7% (45)         | 0.204   |
| Coagulopathy           | 13.7% (5350)        | 11.3% (139)       | 0.015   |
| Obesity                | 15.7% (6095)        | 15.6% (191)       | 0.926   |
| Weight loss            | 17.6% (6855)        | 27.7% (340)       | <0.001  |
| Fluid and electrolyte disorders | 54.8% (21,332) | 30.8% (378)       | 0.764   |
| Chronic blood loss anemia | 1.4% (545)     | 2.0% (24)         | 0.105   |
| Deficiency anemia      | 38.9% (15,154)      | 48.7% (598)       | <0.001  |
| Alcohol abuse          | 3.5% (1367)         | 2.7% (33)         | 0.122   |
| Drug abuse             | 2.4% (923)          | 2.9% (35)         | 0.278   |
| Psychosis              | 6.1% (2358)         | 6.6% (81)         | 0.435   |
| Depression             | 15.0% (5854)        | 14.2% (174)       | 0.404   |
CRE and CSE groups had a sepsis diagnosis code at some point during the hospitalization.

Those with CRE were younger (66.6+/-15.3 vs. 69.1+/-15.9 years, \( p < 0.001 \)) and more likely to be African-American (19.7% vs. 14.0%, \( p < 0.001 \)) than those with CSE. Many of the individual chronic conditions were more prevalent in the CRE than CSE group, and the mean Charlson comorbidity index reflected this (2.0+/-2.0 vs. 1.9+/-2.1, \( p = 0.009 \)) (Table 2). CRE was more common than CSE in the West and the Northeast, in urban hospitals, in those of medium size (200–499 beds) and in teaching hospitals (\( p < 0.001 \) for each comparison) (Table 2). Large hospitals (500+ beds) were less likely to have CRE than CSE (Table 2).

In both the CRE and CSE groups, over one-half the patients had the diagnosis of UTI, with the remaining divided between sepsis (33.3% CRE vs. 32.7% CSE) and pneumonia (15.2% CRE vs. 13.0% CSE) (Table 2). Patients infected with CRE were more likely to have a HCA infection (58.5% vs. 35.4%, \( p < 0.001 \)) along with a greater illness severity by day 2 of admission (ICU 56.0% vs. 40.8%, \( p < 0.001 \); mechanical ventilation 35.6% vs. 15.7%, \( p < 0.001 \); though not vasopressors 16.7% vs. 14.9%, \( p = 0.081 \)) than CSE patients (Table 3). Although among the CRE group there was a higher prevalence of empiric use of carbapenems, aminoglycosides and polymyxins than in those eventually found to be infected with a CSE, those with CRE infections were also significantly more likely to receive IET (52.8% vs. 11.1%, \( p < 0.001 \)). Unadjusted hospital mortality median LOS and costs among CRE were also significantly greater than CSE, and these differences held across all infection types (Table 3).

Comparing the cohort of 37,694 patients (93.9% of all patients with Enterobacteriaceae) with valid antimicrobial treatment data, 32,710 (86.8%) received appropriate therapy (Table 4). While patients receiving appropriate empiric therapy were more likely to have UTI or sepsis than those in the IET group, the frequency of pneumonia was higher among patients on IET (20.0%) than those on appropriate treatment (12.0%) (\( p < 0.001 \)) (Table 4). As for the unadjusted hospital outcomes, mortality was higher in patients receiving IET than appropriate therapy (12.2% vs. 9.9%, \( p < 0.001 \)). Both LOS and costs were

| Table 2 Baseline characteristics (Continued) |
|--------------------------------------------|
| Hypertension                                | 24,938 | 64.1% | 781 | 63.7% | 0.752 |
| Charlson Comorbidity Score                  |        |       |     |       |       |
| 0                                          | 12,010 | 30.9% | 334 | 27.2% | <0.001|
| 1                                          | 7855   | 20.2% | 230 | 18.7% |       |
| 2                                          | 7902   | 20.3% | 244 | 19.9% |       |
| 3                                          | 5118   | 13.2% | 180 | 14.7% |       |
| 4                                          | 2897   | 7.4%  | 146 | 11.9% |       |
| 5+                                         | 3128   | 8.0%  | 93  | 7.6%  |       |
| Mean (SD)                                  | 1.9 (2.1) | 2.0 (2.0) |       | 0.009 |
| Median [IQR]                               | 1 [0,3] | 2 [0,3] |       | <0.001|
| Hospital Characteristics                    |        |       |     |       |       |
| Census region                              |        |       |     |       |       |
| Midwest                                    | 10,531 | 27.1% | 288 | 23.5% | <0.001|
| Northeast                                  | 5297   | 13.6% | 336 | 27.4% |       |
| South                                      | 16,203 | 41.6% | 310 | 25.3% |       |
| West                                       | 6879   | 17.7% | 293 | 23.9% |       |
| Number of Beds                             |        |       |     |       |       |
| < 200                                      | 6589   | 16.9% | 192 | 15.6% | <0.001|
| 200 to 299                                 | 8779   | 22.6% | 338 | 27.5% |       |
| 300 to 499                                 | 12,691 | 32.6% | 421 | 34.3% |       |
| 500+                                       | 10,851 | 27.9% | 276 | 22.5% |       |
| Teaching                                   | 14,609 | 37.5% | 566 | 46.1% | <0.001|
| Urban                                      | 35,079 | 90.2% | 1167| 95.1% | <0.001|

CSE carbapenem sensitive Enterobacteriaceae, CRE carbapenem resistant Enterobacteriaceae, SD standard deviation, ECF extended care facility, AIDS acquired immune deficiency syndrome, IQR interquartile range
### Table 3 Infection characteristics, treatment and outcomes

|                         | CSE        | %          | CRE        | %          | P-value   |
|-------------------------|------------|------------|------------|------------|-----------|
| Infection characteristics|            |            |            |            |           |
| Sepsis                  | 12,726     | 32.7%      | 409        | 33.3%      | 0.039     |
| Pneumonia               | 5060       | 13.0%      | 187        | 15.2%      |           |
| UTI                     | 21,124     | 54.3%      | 631        | 51.4%      |           |
| HCA                     | 13,782     | 35.4%      | 718        | 58.5%      | <0.001    |
| Illness severity measures by day 2 |          |            |            |            |           |
| ICU admission           | 15,876     | 40.8%      | 687        | 56.0%      | <0.001    |
| Mechanical ventilation  | 6092       | 15.7%      | 437        | 35.6%      | <0.001    |
| Vasopressors            | 5798       | 14.9%      | 205        | 16.7%      | 0.081     |
| Antibiotics administered by day 2 |    |            |            |            |           |
| Aminoglycosides         | 3843       | 9.9%       | 242        | 19.7%      | <0.001    |
| Antipseudomonal penicillins | 6403     | 16.5%      | 313        | 25.5%      | <0.001    |
| Antipseudomonal floquinolones | 18,468    | 47.5%      | 406        | 33.1%      | <0.001    |
| Antipseudomonal penicillins with beta-lactamase inhibitors | 19,727 | 50.7% | 617 | 50.3% | 0.775 |
| Extended spectrum cephalosporins | 13,327 | 34.3% | 415 | 33.8% | 0.755 |
| Folate pathway inhibitors | 251       | 0.6%       | 12         | 1.0%       | 0.155     |
| Penicillins with beta-lactamase inhibitors | 854 | 2.2% | 26 | 2.1% | 0.837 |
| Polymyxins              | 126        | 0.3%       | 24         | 2.0%       | <0.001    |
| Tetracyclines           | 248        | 0.6%       | 6          | 0.5%       | 0.519     |
| Tigecycline             | 586        | 1.5%       | 86         | 7.0%       | <0.001    |
| Aztreonam               | 1740       | 4.5%       | 56         | 4.6%       | 0.878     |
| Empiric treatment appropriateness |          |            |            |            |           |
| Non-IET                 | 32,197     | 82.7%      | 513        | 41.8%      | <0.001    |
| IET                     | 4336       | 11.1%      | 648        | 52.8%      |           |
| Indeterminate           | 2337       | 6.0%       | 66         | 5.4%       |           |
| Hospital outcomes       |            |            |            |            |           |
| Mortality               | 3958       | 10.2%      | 178        | 14.5%      | <0.001    |
| Mean (SD) LOS, days     | 9.6 (10.7) |            | 15.6 (17.4)|            | <0.001    |
| Median [IQR] LOS, days  | 7 [4, 11]  |            | 10 [6, 18] |            | <0.001    |
| Mean (SD) costs, $      | 20,601     |            | 38,494     |            | <0.001    |
| Median [IQR] costs, $   | 13,020     |            | 22,909     |            | <0.001    |

**Hospital outcomes stratified by infection type**

**UTI**

| Mortality               | 1873       | 8.9%       | 78         | 12.4%      | 0.002     |
| Mean (SD) LOS, days     | 9.0 (9.4)  |            | 14.6 (15.9)|            | <0.001    |
| Median [IQR] LOS, days  | 7 [4, 11]  |            | 10 [6, 17] |            | <0.001    |
| Mean (SD) costs, $      | 19,036     |            | 33,400     |            | <0.001    |
| Median [IQR] costs, $   | 12,082     |            | 21,154     |            | <0.001    |

**Sepsis**

| Mortality               | 1660       | 13.0%      | 81         | 19.8%      | <0.001    |
| Mean (SD) LOS, days     | 10.9 (12.6)|            | 18.0 (20.8)|            | <0.001    |
| Median [IQR] LOS, days  | 7 [4, 13]  |            | 11 [7, 21] |            | <0.001    |
| Mean (SD) costs, $      | 26,793     |            | 50,038     |            | <0.001    |
significantly higher in the IET group than in the group receiving non-IET (Table 4). These relationships generally held irrespective of the infection type (Table 4).

In a parse generalized regression model exploring the impact of CRE on the risk of IET, resistance was the single strongest predictor of receiving IET (adjusted relative risk ratio 3.95, 95% confidence interval 3.51, 4.46, \( p < 0.001 \)) (Table 5). The confirmatory analyses produced similar risk ratios (Table 5).

In a hierarchical regression model adjusting for all confounders (demographics, comorbidities, severity of illness measures, hospital characteristics) IET was associated with an increased risk of in-hospital mortality (adjusted relative risk ratio 1.12; 95% confidence interval 1.03, 1.23, \( p = 0.013 \)) (Table 5). In other hierarchical models, the excess LOS and costs associated with IET exposure were 5.2 days (95% confidence interval 4.8, 5.6, \( p < 0.001 \)) and $10,312 (95% confidence interval $9497, $11,126, \( p < 0.001 \)). Propensity-matched analyses produced similar estimates (Table 5).

An interaction term suggested a greater impact on mortality of IET in the setting of sepsis, which prompted a sensitivity analysis in the group whose organisms were cultured from blood. In this set of analyses, including 12,807 patients (186 CRE, 1.5%), the impact of IET on mortality was indeed greater (relative risk ratio 1.55, 95% confidence interval 1.18 to 2.03) than in the overall cohort.

Multiple studies have noted an increase in the prevalence of CRE among patients with serious infections in the hospital. A recent US surveillance study reported the annual population incidence of CRE infections to be nearly 3 cases per 100,000 population [28]. A US Centers for Disease Control and Prevention study noted a rise in CRE prevalence from 1.2% in 2001 to 4.2% in 2011 [29]. The same study analyzing a different database, however, noted an increase in CRE from 0 in 2001 to 1.4% in 2010, echoing findings of other investigators [19, 30, 31]. Our findings are generally in agreement with these numbers. Although CRE incidence and prevalence are far lower than such common pathogens as methicillin-resistant Staphylococcus aureus or Clostridium difficile, there are few treatment alternatives for CRE, which underscores the need for more precise information about the epidemiology and outcomes related to CRE infections [32, 33]. Consequently, this study helps to address this need for more granular information regarding this pathogen. In addition we confirm that at this point, CRE is encountered most often as a urinary pathogen, which may mediate the otherwise high mortality rate associated with CRE infections. Despite this, the increasing frequency of this organism as a cause of sepsis indicates that CRE is poised to become a major contributor to infectious disease related mortality in the US.

Though thought of mostly as healthcare-associated pathogens, our data suggest that this may be too narrow a view. Namely, in our cohort, over 40% of patients with CRE did not have an identifiable exposure to the healthcare system. There are several potential sources for misclassifying this burden, one of which may be the 90-day period for prior hospitalization as a risk factor for HCA infection. Though it remains unclear how long the impact of prior hospitalization persists on the risk of resistance, and 90 days is a standard interval used in many other studies, in some investigations this period is longer [34]. Although a probable overestimate due to misclassification and because of limitations in the patient records, our data

### Table 3 Infection characteristics, treatment and outcomes (Continued)

|                | Median (IQR) costs, $ | Median (IQR) LOS, days | Mean (SD) LOS, days | Mean (SD) costs, $ |
|----------------|----------------------|------------------------|--------------------|-------------------|
| Pneumonia      | 27,264 [14,581, 57,825] | 19 [1.2] | 13.4 (13.0) | 30,432 (35,089) |
| Mortality      | 425 [8584, 30,317] | 8.4% [1.1, 19] | 10.2% (0.36) | 19,820 [12,220, 35,713] |
| Mean (SD) LOS, days | 7 [4, 10] | 9 [6, 16] | <0.001 | <0.001 |
| Mean (SD) costs, $ | 19,250 (25,743) | 30,432 (35,089) | <0.001 | <0.001 |

|                | Median (IQR) costs, $ | Median (IQR) LOS, days | Mean (SD) LOS, days | Mean (SD) costs, $ |
|----------------|----------------------|------------------------|--------------------|-------------------|
| CSE carabepenem sensitive Enterobacteriaceae, CRE carabepenem resistant Enterobacteriaceae, UTI urinary tract infection, HCA healthcare-associated, ICU intensive care unit, IET inappropriate empiric therapy |  

**Discussion**

We demonstrate in this large multicenter observational cohort that among patients admitted from the community with a UTI, sepsis or pneumonia, over 17% have an infection with Enterobacteriaceae, of which approximately 3% are CRE. Although infrequent, the presence of CRE increases the risk of receiving IET substantially. In turn, receiving IET is associated with a rise in hospital mortality, LOS and costs, a rise particularly pronounced in patients with sepsis.
### Table 4 Characteristics of the cohort based on the receipt of inappropriate empiric treatment

| Characteristic                              | Non-IET  | %     | IET     | %     | P-value |
|---------------------------------------------|----------|-------|---------|-------|---------|
| **Baseline characteristics**               |          |       |         |       |         |
| Mean age, years (SD)                        | 69.0 (16.0) | 69.4 (15.3) | 0.094  |       |         |
| Gender: male                                | 13,680   | 41.8% | 2169    | 43.5% | 0.024   |
| Race                                        |          |       |         |       |         |
| White                                       | 23,921   | 73.1% | 3443    | 69.1% | <0.001  |
| Black                                       | 4384     | 13.4% | 862     | 17.3% |         |
| Hispanic                                    | 919      | 2.8%  | 163     | 3.3%  |         |
| Other                                       | 3486     | 10.7% | 516     | 10.4% |         |
| **Admission Source**                        |          |       |         |       |         |
| Non-healthcare facility (including from home) | 21,450   | 65.6% | 3034    | 60.9% | <0.001  |
| Clinic                                      | 1093     | 3.3%  | 138     | 2.8%  |         |
| Transfer from ECF                          | 2996     | 9.2%  | 759     | 15.2% |         |
| Transfer from another non-acute care facility | 379      | 1.2%  | 77      | 1.5%  |         |
| Emergency Department                        | 6688     | 20.4% | 959     | 19.2% |         |
| Other                                       | 104      | 0.3%  | 17      | 0.3%  |         |
| **Elixhauser Comorbidities**                |          |       |         |       |         |
| Congestive heart failure                    | 7836     | 24.0% | 1509    | 30.3% | <0.001  |
| Valvular disease                            | 2594     | 7.9%  | 425     | 8.5%  | 0.148   |
| Pulmonary circulation disease               | 1912     | 5.8%  | 358     | 7.2%  | <0.001  |
| Peripheral vascular disease                 | 3564     | 10.9% | 577     | 11.6% | 0.152   |
| Paralysis                                   | 3289     | 10.1% | 770     | 15.4% | <0.001  |
| Other neurological disorders                | 7227     | 22.1% | 1269    | 25.5% | <0.001  |
| Chronic pulmonary disease                   | 9079     | 27.8% | 1663    | 33.4% | <0.001  |
| Diabetes without chronic complications       | 9695     | 29.6% | 1623    | 32.6% | <0.001  |
| Diabetes with chronic complications         | 3152     | 9.6%  | 524     | 10.5% | 0.052   |
| Hypothyroidism                              | 5645     | 17.3% | 942     | 18.9% | 0.004   |
| Renal failure                               | 9024     | 27.6% | 1540    | 30.9% | <0.001  |
| Liver disease                               | 1774     | 5.4%  | 245     | 4.9%  | 0.138   |
| Peptic ulcer disease with bleeding          | 15       | 0.0%  | 2       | 0.0%  | 1.000   |
| AIDS                                        | 8        | 0.0%  | 4       | 0.1%  | 0.063   |
| Lymphoma                                    | 508      | 1.6%  | 74      | 1.5%  | 0.716   |
| Metastatic cancer                           | 1543     | 4.7%  | 182     | 3.7%  | 0.001   |
| Solid tumor without metastasis              | 1335     | 4.1%  | 163     | 3.3%  | 0.006   |
| Rheumatoid arthritis/collagen vascular      | 1422     | 4.3%  | 215     | 4.3%  | 0.914   |
| Coagulopathy                                | 4626     | 14.1% | 540     | 10.8% | <0.001  |
| Obesity                                     | 5079     | 15.5% | 822     | 16.5% | 0.081   |
| Weight loss                                 | 5583     | 17.1% | 1117    | 22.4% | <0.001  |
| Fluid and electrolyte disorders             | 17,961   | 54.9% | 2702    | 54.2% | 0.357   |
| Chronic blood loss anemia                   | 459      | 1.4%  | 79      | 1.6%  | 0.313   |
| Deficiency Anemia                           | 12,735   | 38.9% | 2096    | 42.1% | <0.001  |
| Alcohol abuse                               | 1139     | 3.5%  | 163     | 3.3%  | 0.446   |
| Drug abuse                                  | 789      | 2.4%  | 103     | 2.1%  | 0.135   |
| Psychosis                                   | 1979     | 6.1%  | 294     | 5.9%  | 0.676   |
**Table 4** Characteristics of the cohort based on the receipt of inappropriate empiric treatment (Continued)

| Characteristic                             | Group 1 | Group 2 | p-value  |
|--------------------------------------------|---------|---------|----------|
| Depression                                | 4859    | 806     | 16.2%    | 0.018    |
| Hypertension                               | 20,987  | 3154    | 63.3%    | 0.229    |
| Charlson Comoribidity Score               |         |         |          |          |
| 0                                          | 10,353  | 1239    | 24.9%    | <0.001   |
| 1                                          | 6517    | 1072    | 21.5%    |          |
| 2                                          | 6595    | 1047    | 21.0%    |          |
| 3                                          | 4223    | 757     | 15.2%    |          |
| 4                                          | 2400    | 465     | 9.3%     |          |
| 5+                                         | 2622    | 404     | 8.1%     |          |
| Mean (SD)                                  | 1.9 (2.1)| 2.0 (2.0)|         | <0.001   |
| Median [IQR]                               | 1 [0, 3] | 2 [1, 3] |         | <0.001   |

**Infection characteristics and treatment**

**Infection characteristics**

| Infection                     | Group 1 | Group 2 | p-value |
|-------------------------------|---------|---------|---------|
| Sepsis                        | 10,736  | 1468    | 29.5%   | <0.001  |
| Pneumonia                     | 3936    | 995     | 20.0%   |         |
| UTI                           | 18,038  | 2521    | 50.6%   |         |
| HCA                           | 11,413  | 2221    | 44.6%   | <0.001  |
| CRE                           | 513     | 648     | 13.0%   | <0.001  |

**Illness severity**

| Illness                      | Group 1 | Group 2 | p-value |
|------------------------------|---------|---------|---------|
| ICU admission                | 13,524  | 2074    | 41.6%   | 0.720   |
| Mechanical ventilation       | 5064    | 1062    | 21.3%   | <0.001  |
| Vasopressors                 | 4929    | 709     | 14.2%   | 0.111   |

**Antibiotics administered**

| Antibiotics administered     | Group 1 | Group 2 | p-value |
|------------------------------|---------|---------|---------|
| Aminoglycosides              | 3694    | 351     | 7.0%    | <0.001  |
| Antipseudomonal penicillins  | 6199    | 347     | 7.0%    | <0.001  |
| Antipseudomonal floroquinolones | 15,995  | 2480    | 49.8%   | 0.258   |
| Antipseudomonal penicillins with beta-lactamase inhibitors | 16,874 | 2008 | 40.3% | <0.001 |
| Extended spectrum cephalosporins | 12,174 | 1134 | 22.8% | <0.001 |
| Folate pathway inhibitors    | 225     | 36      | 0.7%    | 0.809   |
| Penicillins with beta-lactamase inhibitors | 681 | 147 | 2.9% | 0.005 |
| Polymyxins                   | 102     | 32      | 0.6%    | <0.001  |
| Tetracyclines                | 210     | 15      | 0.3%    | 0.004   |
| Tigecycline                  | 485     | 110     | 2.2%    | <0.001  |
| Aztreonam                    | 1319    | 258     | 5.2%    | <0.001  |

**Hospital Characteristics**

| Area                          | Group 1 | Group 2 | p-value |
|-------------------------------|---------|---------|---------|
| Midwest                       | 8848    | 1133    | 22.7%   | <0.001  |
| Northeast                     | 4397    | 950     | 19.1%   |         |
| South                        | 13,579  | 1951    | 39.1%   |         |
| West                         | 5886    | 950     | 19.1%   |         |

| Number of Beds                | Group 1 | Group 2 | p-value |
|-------------------------------|---------|---------|---------|
| < 200                         | 5597    | 744     | 14.9%   | <0.001  |
| 200 to 299                    | 7508    | 1171    | 23.5%   |         |
| 300 to 499                    | 10,540  | 1781    | 35.7%   |         |
| 500+                          | 9065    | 1288    | 25.8%   |         |
are not the first to bring into question this assumption in a US population. In the surveillance study of CRE by Guh et al., 2/3 of the cultures derived from the outpatient setting [35]. More importantly, 8% lacked any markers of healthcare exposure [35]. In an additional small study by Tang et al., community-acquired CRE accounted for 30% of all CRE infections [36]. Though higher in our study, the fact remains that persons with no ongoing relevant exposure to the healthcare system may still contract an infection with this organism. This finding is troubling in that it parallels what has been observed with extended-spectrum beta-lactamase carrying pathogens and their increasing prevalence in community-acquired infections [37–40].

There is mounting evidence to demonstrate that rising antimicrobial resistance impedes clinical efforts at instituting appropriate empiric treatment [14]. We confirm the important role resistance plays in thwarting the ability to choose appropriately, whereby the risk of receiving IET in the setting of CRE rose 4-fold compared to CSE. In turn, though modest, IET’s adverse impact on hospital mortality is consistent with what has been reported in other infections [1–13]. The more pronounced impact of IET on hospital LOS (~5 excess days) and costs (~additional $10,000) is a novel finding for infections with CRE, and provides a sound rationale for investing in technologies that identify patients at risk for CRE more rapidly, particularly given that this is approximately double the attributable burden reported in infections caused by other resistant organisms [41]. Moreover, having a precise estimate of the attributable costs of these infections helps put into perspective the potential value of various prevention and treatment paradigms. It is methodologically challenging to estimate the attributable impact of carbapenem resistance on cost

### Table 4 Characteristics of the cohort based on the receipt of inappropriate empiric treatment (Continued)

| Category                  | IET | SD | CSE | p-value |
|---------------------------|-----|----|-----|---------|
| Teaching                  | 12,096 | 37.0% | 1988 | 39.9% | 0.217 |
| Urban                     | 29,418 | 89.9% | 4574 | 91.8% | <0.001 |
| **Hospital outcomes**     |     |    |     |         |
| Mortality                 | 3234 | 9.9% | 607 | 12.2% | <0.001 |
| Mean (SD) LOS, days       | 9.0 (8.5) | 14.7 (19.4) |       | <0.001 |
| Median (IQR) LOS, days    | 7 [4, 11] | 9 [5, 16] |       | <0.001 |
| Mean (SD) costs, $        | 20,227 (25,616) | 33,216 (49,567) |       | <0.001 |
| Median (IQR) costs, $     | 12,719 [7401, 23,275] | 17,386 [9255, 35,625] |       | <0.001 |

**Hospital outcomes stratified by infection type**

| Category | IET | SD | CSE | p-value |
|----------|-----|----|-----|---------|
| UTI      | 1548 | 8.6% | 267 | 10.6% | <0.001 |
| Mean (SD) LOS, days | 8.5 (7.8) | 13.3 (17.1) |       | <0.001 |
| Median (IQR) LOS, days | 6 [4, 10] | 9 [5, 15] |       | <0.001 |
| Mean (SD) costs, $ | 18,103 (21,440) | 28,069 (40,490) |       | <0.001 |
| Median (IQR) costs, $ | 11,862 [7015, 21,222] | 16,209 [8828, 31,535] |       | <0.001 |
| Sepsis    | 1356 | 12.6% | 260 | 17.7% | <0.001 |
| Mean (SD) LOS, days | 9.9 (9.9) | 18.9 (23.3) |       | <0.001 |
| Median (IQR) LOS, days | 7 [4, 12] | 12 [6, 22] |       | <0.001 |
| Mean (SD) costs, $ | 24,532 (32,043) | 47,881 (64,812) |       | <0.001 |
| Median (IQR) costs, $ | 15,048 [8312, 28,558] | 25,121 [12,382, 55,529] |       | <0.001 |
| Pneumonia | 330  | 8.4% | 80  | 8.0% | 0.726 |
| Mean (SD) LOS, days | 8.5 (7.6) | 12.0 (17.6) |       | <0.001 |
| Median (IQR) LOS, days | 7 [4, 10] | 7 [4, 13] |       | <0.001 |
| Mean (SD) costs, $ | 18,220 (21,710) | 24,623 (38,753) |       | <0.001 |
| Median (IQR) costs, $ | 11,742 [7125, 20,561] | 13,040 [7393, 26,339] |       | <0.001 |

IET inappropriate empiric therapy, SD standard deviation, ECF extended care facility, AIDS acquired immune deficiency syndrome, IQR interquartile range, HCA healthcare-associated, CSE carbapenem sensitive Enterobacteriaceae, CRE carbapenem resistant Enterobacteriaceae, UTI urinary tract infection, ICU intensive care unit, IQR interquartile range 25–75%
and LOS in nosocomial CRE infections since those outcomes are confounded by the cause of the initial hospitalization. Therefore, our findings help clarify this issue.

Our study has a number of strengths and limitations. The limitations that are common to both the current and previous studies are discussed in citation #22. Specific to the current analysis, a potential source of misclassification is a relatively high prevalence of Proteus mirabilis as a pathogen, as this microbe may have naturally occurring higher MICs for imipenem (Table 1) [42, 43]. Since susceptibility data in Premier are reported not by the MIC, but by susceptibility designation (S, I, R, see above in Methods), for the purpose of this analysis we had to presume that clinical adjudication occurred at each individual institution. However, this type of misclassification, if present, is likely to lead to an underestimate of the impact of CRE on outcomes, thus suggesting that in fact, CRE, when determined without this potential misclassification, may have an even greater effect on the risk of IET exposure.

Conclusions
In summary, CRE is an uncommon but important pathogen in community-onset UTI, pneumonia and sepsis. We confirm that, similar to other resistant organisms, it evades appropriate empiric treatment and exposure to IET worsens both clinical and economic outcomes. Although the true extent of the problem requires further study, our data confirm that a substantial proportion of CRE may be acquired in the community irrespective of exposure to the healthcare system. In sum, our study provides compelling evidence to hasten development of rapid identification methods and new antibiotic treatments in order to optimize empiric therapy among hospitalized patients with serious infections.

Abbreviations
CA: Community-acquired; CRE: Carbapenem-resistant Enterobacteriaceae; CSE: Carbapenem-sensitive Enterobacteriaceae; HCA: Healthcare-associated; ICU: Intensive care unit; IET: Inappropriate empiric therapy; LOS: Length of stay; UTI: Urinary tract infection

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Availability of data and material
The data that support the findings of this study are available from Premier, Inc., but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available.

Table 5 Adjusted risk of inappropriate empiric therapy, hospital mortality, excess LOS and costs

|                                   | Marginal effect, CSE | Marginal effect, CRE | Adjusted relative risk ratio/excess days or costs (95% confidence interval) | P-value |
|-----------------------------------|----------------------|----------------------|-----------------------------------------------------------------------------|---------|
| Risk of IET                       |                       |                      |                                                                             |         |
| Parse Model                       | 11.8%                | 47.7%               | 3.95 (3.51, 4.46)                                                          | <0.001  |
| Propensity score (based on 100% CRE cases matched to CSE 1:1) | 13.1%                | 55.8%               | 4.27 (3.64, 5.00)                                                          | <0.001  |
| Non-parse model                   | 11.9%                | 47.7%               | 4.00 (3.48, 4.59)                                                          | <0.001  |
| Risk of death                     |                       |                      |                                                                             |         |
| Hierarchical model                | 9.8%                 | 11.0%               | 1.12 (1.03, 1.23)                                                          | 0.013   |
| Propensity score (based on 96.4% IET cases matched to non-IET 1:1) | 10.5%                | 11.9%               | 1.13 (1.01, 1.27)                                                          | 0.030   |
| Length of stay (days)             |                       |                      |                                                                             |         |
| Hierarchical model                | 8.2                  | 13.4                 | 5.2 (4.8, 5.6)                                                             | <0.001  |
| Propensity score (based on 96.4% IET cases matched to non-IET 1:1) | 9.6                  | 14.6                 | 5.0 (4.4, 5.6)                                                             | <0.001  |
| Hospital costs                    |                       |                      |                                                                             |         |
| Hierarchical model                | $20,508              | $30,819              | $10,312 ($9497, $11,126)                                                   | <0.001  |
| Propensity score (based on 96.4% IET cases matched to non-IET 1:1) | $22,005              | $32,837              | $10,831 ($9254, $12,409)                                                   | <0.001  |

IET inappropriate empiric therapy, CSE carbapenem sensitive Enterobacteriaceae, CRE carbapenem resistant Enterobacteriaceae
Authors' contributions
MDZ contributed substantially to the study design, data interpretation, and the writing of the manuscript. BHN contributed substantially to the study design, data interpretation, and the writing of the manuscript. He had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. KS contributed substantially to the study design, data interpretation, and the writing of the manuscript. WF contributed substantially to the study design, data interpretation, and the writing of the manuscript. AFS contributed substantially to the study design, data interpretation, and the writing of the manuscript. He had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. MDZ contributed substantially to the study design, data interpretation, and the writing of the manuscript. He had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. WF contributed substantially to the study design, data interpretation, and the writing of the manuscript. BHN contributed substantially to the study design, data interpretation, and the writing of the manuscript. Ms. Fan and Ms. Sulham are employees of and stockholders in The Medicines Company. Dr. Shorr is a consultant and has received research grant support from The Medicines Company. Drs. Zilberberg and Shorr have received grant support from The Medicines Company. The study was supported by The Medicines Company.

Competing interests
This study was supported by The Medicines Company. Dr. Zilberberg is a consultant to The Medicines Company. Her employer, EvIMed Research Group, LLC, has received research grant support from The Medicines Company. Dr. Nathanson is an employee of OptiStatim, LLC, who received grant support from EvIMed Research Group, LLC, for conducting this study. Ms. Fan and Ms. Sulham are employees of and stockholders in The Medicines Company. Dr. Shorr is a consultant and has received research grant support from The Medicines Company. Ms. Fan and Ms. Sulham are employees of and stockholders in The Medicines Company. Dr. Shorr is a consultant to Pfizer, Merck, Inc., Tetraphase, Melinta, Asahi Kasei, Shionogi, Archazogen and Theravance.

Consent for publication
Not applicable.

Ethics approval and consent to participate
The study was a retrospective analysis of a de-identified database. As such, it is not considered human subject research.

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References
1. National Nosocomial Infections Surveillance (NNIS) System Report. Am J Infect Control. 2004;32:470. https://www.cdc.gov/nhsn/pdfs/datasheet/nnis_2004.pdf.
2. Obstetric MD, Fish DN, MacLaren R, Jung R. National surveillance of antimicrobial resistance in Pseudomonas aeruginosa isolates obtained from intensive care unit patients from 1993 to 2002. Antimicrob Agents Chemother. 2004;48:4606–10.
3. Micek ST, Kollef KE, Reichley RM, et al. Health care-associated pneumonia and community-acquired pneumonia: a single-center experience. Antimicrob Agents Chemother. 2007;51:3568–73.
4. Iregui M, Ward S, Sherman G, et al. Clinical importance of delays in the initiation of appropriate antibiotic treatment for ventilator-associated pneumonia. Chest. 2002;122:262–8.
5. Alvarez-Lerma F. ICU-acquired Pneumonia Study Group. Modification of empiric antibiotic treatment in patients with pneumonia acquired in the intensive care unit. Intensive Care Med. 1996;22:387–94.
6. Zilberberg MD, Shorr AF, Micek MT, Mody SH, Kollef MH. Antimicrobial therapy escalation and hospital mortality among patients with HCAP: a single center experience. Chest. 2008;134:963–8.
7. Dellinger RP, Levy MM, Carlet JM, Bion J, Blon J, Parker MM, Jaeschke R, Reinhard K, Angus DC,-Brun-Buisson C, Beale R, Calandra T, Dhainaut JF, Gerlach H, Harvey M, Mari M, Marshall J, Ranieri M, Ramsay G, Seviansky J, Thompson BT, Townsend S, Vender J, Zimmerman JL, Vincent JL. Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock: 2008. Crit Care Med. 2008;36:296–327.
8. Shorr AF, Micek ST, Welch EC, Doherty JA, Reichley RM, Kollef MH. Inappropriate antibiotic therapy in gram-negative sepsis increases hospital length of stay. Crit Care Med. 2011;39:46–51.
9. Kollef MH, Sherman G, Ward S, Fraser VJ. Inadequate antimicrobial treatment of infections: a risk factor for hospital mortality among critically ill patients. Chest. 1999;115:462–74.
10. Garnacho-Montero J, Garcia-Garmendia JL, Barrero-Almodovar A, Jimenez-Jimenez FJ, Perez-Paredes C, Ortiz-Leyba C. Impact of adequate empirical antibiotic therapy on the outcome of patients admitted to the intensive care unit with sepsis. Crit Care Med. 2003;31:2742–51.
11. Harbath S, Garbinio J, Pugin J, Romand JA, Liew D, Pittet D. Inappropriate initial antimicrobial therapy and its effect on survival in a clinical trial of immuno-modulating therapy for severe sepsis. Am J Med. 2005;115:529–35.
12. Ferrer R, Artigas A, Suarez D, Palencia E, Levy MM, Arenzana A, Perez X, Sient JM. Effectiveness of treatments for severe sepsis in a prospective, multicenter observational study. Am J Respir Crit Care Med. 2009;180:861–6.
13. Silver D, Ricks P, Edwards JR, Schneider A, Patel J, Srinivasan A, Kallen A, Limbago B, Fridkin S, National Healthcare Safety Network (NHSN) Team and Participating NHSN Facilities. Antimicrobial-resistant pathogens associated with healthcare-associated infections: summary of data reported to the National Healthcare Safety Network at the Centers for Disease Control and Prevention, 2009–2010. Infect Control Hosp Epidemiol. 2013;34:1–14.
14. Zilberberg MD, Shorr AF, Micek ST, Vazquez-Guillamet C, Kollef MH. Multidrug resistance, inappropriate initial antibiotic therapy and mortality in gram-negative severe sepsis and septic shock: a retrospective cohort study. Crit Care. 2014;18(6):596.
15. Centers for Disease Control and Prevention. Antibiotic Resistance Threats in the United States, 2013. Available at https://www.cdc.gov/drugresistance/threat-report-2013/pdf/ar-threats-2013-508.pdf. Accessed 29 May 2014.
16. Kollef MH, Shorr A, Tabak YP, et al. Epidemiology and outcomes of healthcare-associated pneumonia: results from a large US database of culture-positive pneumonia. Chest. 2005;128:3854–56.
17. Hospital-Acquired Pneumonia Guideline Committee of the American Thoracic Society and Infectious Diseases Society of America. Guidelines for the management of adults with hospital-acquired pneumonia, ventilator-associated pneumonia, and healthcare-associated pneumonia. Am J Respir Crit Care Med. 2005;171:388–416.
18. Dellinger RP, Levy MM, Rhodes A, et al. Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock 2012. Crit Care Med. 2013;41:60–3.
19. Zilberberg MD, Shorr AF. Secular trends in gram-negative resistance among urinary tract infection hospitalizations in the United States, 2000–2009. Infect Control Hosp Epidemiol. 2013;34:940–6.
20. Daikos GL, Perikiosis P, Psichogios M, Kosmidis C, Vryonis E, Skoulitis A, Georgoussi K, Tsouvelakis LS, Tassios PT, Bamia C, Petrikos G. Prospective observational study of the impact of VIM-1 metallo-beta-lactamase on the outcome of patients with Klebsiella Pneumoniae bloodstream infections. Antimicrob Agents Chemother. 2009;53:1868–73.
21. Ben-David D, Kordevani R, Keller N, Tal I, Marzel A, Gal-Mor O, Maor Y, Rahav G. Outcome of carbapenem resistant Klebsiella pneumoniae bloodstream infections. Clin Microbiol Infect. 2012;18:54–60.
22. Zilberberg MD, Nathanson BH, Sulham K, Fan W, Shorr AF. Multidrug resistance, inappropriate empiric therapy, and hospital mortality in Acinetobacter baumannii pneumonia and sepsis. Crit Care Med. 2014;15;416.
23. Dellinger RP, Levy MM, Rhodes A, et al. Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock 2012. Crit Care Med. 2013;41:580–637.
24. Zilberberg MD, Shorr AF. Secular trends in gram-negative resistance among urinary tract infection hospitalizations in the United States, 2000–2009. Infect Control Hosp Epidemiol. 2013;34:940–6.
25. Rothberg MB, Haessler S, Lagu T, Lindenuer PK, Pekow PS, Priya A, Skiest D, Zilberberg MD. Outcomes of patients with healthcare-associated pneumonia: worse disease or sicker patients? Infect Control Hosp Epidemiol. 2014;35(Suppl 3):S107–15.

26. Rothberg MB, Zilberberg MD, Pekow PS, Priya A, Haessler S, Belfort R, Skiest D, Lagu T, Higgins TL, Lindenuer PK. Association of guideline-based antimicrobial therapy and outcomes in healthcare-associated pneumonia. J Antimicrob Chemother 2015 Jan 3. pii: dku 533. [Epub ahead of print]

27. Martin GS, Mannino DM, Eaton S, Moss M. The epidemiology of sepsis in the United States from 1979 through 2000. N Engl J Med. 2003;348:1546–54.

28. Williams RL. A note on robust variance estimation for cluster-correlated data. Biometrics. 2000;56:645–6.

29. Centers for Disease Control and Prevention (CDC). Vital signs: carbapenem-resistant enterobacteriaceae. MMWR Morb Mortal Wkly Rep. 2013;62:165–70.

30. Braykov NP, Eber MR, Klein EY, Morgan DJ, Laxminarayan R. Trends in resistance to carbapenems and third-generation cephalosporins among clinical isolates of Klebsiella pneumoniae in the United States, 1999–2010. Infect Control Hosp Epidemiol. 2013;34:259–68.

31. Zilberberg MD, Shorr AF. Prevalence of multidrug-resistant Pseudomonas aeruginosa and carbapenem-resistant Enterobacteriaceae among specimens from hospitalized patients with pneumonia and bloodstream infections in the United States from 2000 to 2009. J Hosp Med. 2013;8:559–63.

32. Dantes R, Mu Y, Belflower R, et al. Emerging infections program active bacterial Core surveillance MRSA surveillance investigators. National burden of invasive methicillin-resistant Staphylococcus aureus infections, United States, 2011. JAMA Intern Med. 2013;173:1970–8.

33. Lessa FC, Mu Y, Bamborg WM, et al. Burden of Clostridium difficile infection in the United States. N Engl J Med. 2015;372:825–34.

34. Herold BC, Immelgluck LC, MAranan MC, Lauderdale DS, Gaskin RE, Boyle-Vavra S, Leitch CD, Daum RS. Community-acquired methicillin-resistant Staphylococcus Aureus in children with no identified predisposing risk. JAMA. 1998;279:593–8.

35. Guh AY, Bulens SN, Mu Y, et al. Epidemiology of Carbapenem-resistant Enterobacteriaceae in 7 US communities, 2012-2013. JAMA. 2015;314:1479–87.

36. Tang HJ, Hsieh CF, Chang PC, Chen JJ, Lin YH, Lai CC, Chao CM, Chuang YC. Clinical significance of community- and healthcare-acquired Carbapenem-resistant Enterobacteriaceae isolates. PLoS One. 2016;11(3):e0151897.

37. Doi Y, Park YS, Rivera JI, et al. Community-associated extended-spectrum β-lactamase-producing Escherichia coli infection in the United States. Clin Infect Dis. 2013;56:641–8.

38. Pitout JD, Nordmann P, Laupland KB, Poirel L. Emergence of Enterobacteriaceae producing extended-spectrum beta-lactamases (ESBLs) in the community. J Antimicrob Chemother. 2005;56:52–9.

39. Rodríguez-Baño J, Alcalá J, Alcalá J, Cisneros JM, et al. Escherichia coli producing SHV-type extended-spectrum beta-lactamase is a significant cause of community-acquired infection. J Antimicrob Chemother. 2009;63:781–4.

40. Banerjee R, Strahilevitz J, Johnson JR, et al. Predictors and molecular epidemiology of community-onset extended-spectrum β-lactamase-producing Escherichia coli infection in a Midwestern community. Infect Control Hosp Epidemiol. 2013;34:947–53.

41. Shorr AF, Miccek ST, Kellf M. Inappropriate therapy for methicillin-resistant Staphylococcus Aureus: resource utilization and cost implications. Crit Care Med. 2008;36:2335–40.

42. Bouchillon SK, Badal RE, Hoban DJ, Hawser SP. Antimicrobial susceptibility of inpatient urinary tract isolates of gram-negative bacilli in the United States: results from the study for monitoring antimicrobial resistance trends (SMART) program: 2009–2011. Clin Ther. 2013;35:872–7.

43. Hawser SP, Badal RE, Bouchillon SK, Hoban DJ, Hackel MA, Biedenbach DJ, Goff DA. Susceptibility of gram-negative aerobic bacilli from intra-abdominal pathogens to antimicrobial agents collected in the United States during 2011. J Inf Secur. 2014;48:71–6.