Tracking Colistin-Treated Patients to Monitor the Incidence and Outcome of Carbapenem-Resistant Gram-Negative Infections

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Background. Existing surveillance mechanisms may underestimate the incidence of carbapenem-resistant gram-negative infections (CRGNIs). Although carbapenem resistance increases the risk of death, the trend in mortality over time is unknown.

Methods. A retrospective cohort study was conducted at 40 academic medical centers using a discharge database to identify adult hospital admissions without cystic fibrosis in 2006–2012 and received intravenous colistin for >3 consecutive days or died during therapy (termed colistin cases). The primary outcomes were the number of colistin cases per 100 000 admissions per year and change in the hospital mortality rate over time compared with the rate of discharges to home. Secondary outcomes included median overall and intensive care unit lengths of stay.

Results. From 2006 to 2012, a total of 5011 unique patients were identified as colistin cases. The number per 100 000 admissions per year increased from 35.56 to 92.98 during the 7-year study (P < .001). The odds of in-hospital death among colistin cases (compared with discharge to home) decreased by a mean of 5.2%/y (P = .04), whereas discharge to an institution (P = .24) or hospice (P = .89) remained steady over time. The median overall and intensive care unit lengths of stay decreased by 7.5 and 6 days, respectively (P < .001). In a 4-hospital chart review, 81.6% of colistin cases were found to have culture-positive CRGNIs. Conversely, 53% of extensively drug-resistant bloodstream CRGNIs at 2 of these hospitals met colistin case criteria.

Conclusions. Colistin cases represent a severely ill population with a high probability of having culture-confirmed CRGNIs. Colistin tracking is a novel strategy for monitoring the incidence and mortality of CRGNIs, particularly those caused by extensively drug-resistant bacteria. Although the incidence of colistin cases nearly tripled within 7 years, more of these patients are surviving hospitalization and going home.

Keywords. colistin; carbapenem resistance; gram-negative infection; extensively drug resistant; surveillance.

Infections caused by multidrug-resistant and extensively drug-resistant gram-negative organisms may be the greatest emerging threat to critically ill patients worldwide. According to recent estimates, 63% of Acinetobacter isolates, 13% of Pseudomonas isolates, and 11% of Klebsiella isolates causing healthcare-associated infections in the United States are multidrug resistant [1]. In particular, the emergence and dissemination of resistance to carbapenems, a β-lactam antibiotic class effective against extended-spectrum β-lactamase producers, have profoundly limited treatment options [2, 3]. During the past decade, carbapenem-resistant Enterobacteriaceae have spread at an alarming rate and have now been identified in at least 44 US states [4]. Although the Centers for Disease Control and...
Prevention have been vital to identifying the threat posed by carbapenem-resistant gram-negative infections (CRGNIs), available surveillance tools have been limited by sample size and reporting bias [1]. New surveillance strategies are clearly needed to clarify the true burden and clinical consequences of these infections [5].

Patients with CRGNIs are thought to carry mortality rates ranging from 35% to 60%, and resistance has been shown to be an independent risk factor for death [6–11]. Delay in the administration of effective antibiotics (especially after the onset of septic shock) [12], serious comorbid conditions in affected patient populations [13], and toxicity from alternative drug regimens probably contribute to excess mortality in CRGNIs. With the recent emergence of widespread carbapenem resistance among gram-negative pathogens, colistin use has surged in US hospitals, requiring clinicians to become reacquainted with this toxic drug [14, 15] of limited efficacy. Administration of colistin intravenously for >72 hours has been used as an inclusion criterion in studies evaluating colistin dosage and outcomes and offers a reasonable indication of nonempiric postantibiogram therapy [16–18].

Despite recognition of excess mortality rates associated with CRGNIs and evolving management strategies [10, 13, 19, 20], mortality trends over time have not yet been investigated. In the current study, we used a unique surveillance strategy to track colistin cases among hospitalized adults at 40 US academic medical centers (AMCs). Seven-year trends in mortality and length of stay were investigated, and the association of colistin cases with CRGNIs was examined by means of chart review in a subset of patients.

**MATERIALS AND METHODS**

**Study Design**

A multicenter, retrospective, observational cohort study was conducted within the University HealthSystem Consortium to identify colistin cases as representative units of CRGNIs. Trends in yearly incidence and in-hospital mortality rates were examined for a 7-year period (calendar years 2006–2012). A colistin case patient was defined as any adult (aged ≥18 years) admission receiving intravenous colistin for >3 consecutive days or dying within 3 days after starting intravenous colistin therapy.

The University HealthSystem Consortium is a collaboration of 120 AMCs and 300 affiliated hospitals comprising >90% of the nation’s nonprofit AMCs. Data are compiled using billing records for quality improvement and research purposes. Additional details can be found in the Supplementary Data.

Patients with cystic fibrosis (CF) were excluded a priori from the primary analysis. In CF, colistin is usually administered by inhalation to manage colonization by multidrug-resistant *Pseudomonas aeruginosa* [21–25]. A sensitivity analysis was performed to confirm that patients with CF are epidemiologically distinct and have a lower mortality risk.

Demographic variables, comorbid conditions, and data related to site of infection were based on International Classification of Diseases, Ninth Revision, diagnosis related groups and diagnostic and procedure codes (Supplementary Table 1). Discharge destinations (Supplementary Table 2), use of critical care services, antibiotic administration, and the corresponding route of administration were obtained from the Clinical Database/Resource Manager. For severity stratification, we used the 3M™ All Patient Refined Diagnosis Related Groups classification system with 4 severity of illness levels, based on comorbid conditions, age, procedures, and principal diagnosis [26].

The primary outcomes were colistin cases per 100 000 admissions per year and change in the in-hospital mortality rate over time compared with the rate of discharges to home. Secondary outcomes included change over time in discharge to hospice or institution compared with discharge to home and in median overall and intensive care unit (ICU) lengths of stay.

Chart reviews (with institutional review board approval) were performed at 4 hospitals (Brigham and Women’s Hospital, Massachusetts General Hospital, Barnes Jewish Hospital, and Georgetown University Hospital) to determine the positive predictive value of colistin case criteria for tracking true CRGNIs. In a reverse analysis performed at 2 centers (Barnes Jewish Hospital and Georgetown University Hospital), patients with bloodstream CRGNIs were identified though the microbiology laboratories to determine what proportion became colistin cases. See the Supplementary Data for methodological details and carbapenem susceptibility breakpoints used at the 4 centers during the study period (Supplementary Table 3).

**Statistical Methods**

Patient characteristics for the first and last years (2006 and 2012) are presented as frequencies and percentages or medians and interquartile ranges and compared using χ^2 or Wilcoxon tests, as appropriate for categorical and continuous variables. The incidence of colistin cases was compared during the 7 years of the study using a χ^2 trend test. Multinomial logistic regression analysis was used to test the effect of time on the probability of in-hospital death or discharge to home, an institution, or hospice.

Discharge to home was selected as the reference category so that all odds ratios (ORs) represented a comparison against this subgroup of patients (denominator). This model allowed us to examine whether there was a time trend for the rate of in-hospital mortality compared with discharge to home, as well as separate time trends in discharge to institutional care or to another hospital, each compared with discharge to home. Sensitivity analyses were performed on patients with CF otherwise meeting
the colistin case definition as well as the subsets with respiratory and nonrespiratory site of infection. The following variables were included in the model based on an a priori clinical concern about confounding: age, sex, geographic region, diabetes, malignancy, neutropenia, mechanical ventilation, vasopressor use, ICU admission, severity of illness scale, and chronic kidney disease (CKD). For the remaining covariates, we calculated the correlation with time, and any covariate that showed a significant correlation with time (at $P < .05$) was considered a potential confounder and also included in the model.

Relationships between discharge year and median overall and ICU length of stay, respectively, were tested using median regression, because length of stay was right skewed. The models were adjusted for the same covariates as the mortality models, and resampling was used to calculate confidence intervals (CIs) [27]. The QUANTREG procedure in the SAS statistical package was used to fit the median regression model, and the RESAMPLING option was chosen to enable bootstrapping to provide repeat estimates of model coefficients from which variability and CIs could be calculated. Time was included in the models initially as a linear term to simplify the presentation but later as a categorical indicator to assess the linearity assumption.

All statistical analyses were performed using SAS software (version 9.3; SAS Institute). Differences were considered statistically significant at $P < .05$ (2 sided). Bonferroni corrections were not applied because our primary interest focused on in-hospital death compared with discharge to home. Discharge to a hospice or institution, length of stay, and the effects of the covariates are reported but are considered secondary findings.

**RESULTS**

**Comparison of Baseline Characteristics (2006 and 2012)**

For the 7-year period, we identified a total of 20 338 adult encounters with any intravenous colistin administration, which included 5288 colistin cases among 5011 patients (see Figure 1 for a stepwise description of colistin case patient selection). Demographic and clinical variables for 2006 and 2012 are presented in Table 1. The median age was higher in 2012 than in 2006 (56.9 vs 54.9 years; $P = .02$), and the proportion of men was higher in 2006 (61.2% vs 59.8% in 2012; $P = .65$). The
The proportion of patients with neutropenia among colistin cases remained low but more than doubled during the 7-year periods (from 2.5% to 5.6%; \(P = .02\)). The proportion who were diabetic nearly doubled, from 20.3% to 37.8% (\(P < .001\)) and the proportion with CKD rose from 25.8% to 38.5% (\(P < .001\)).

Concomitant tigecycline use with colistin more than doubled from 2006 to 2012 (from 8.3% to 17.5%; \(P < .001\)), but concomitant intravenous aminoglycoside use declined significantly (from 34.5% to 28.1%; \(P = .03\)). Although the rate of respiratory tract infections decreased (\(P < .002\)), the respiratory tract remained the most common site. The incidence of bacteremia remained low (8.3% in 2006 and 7.5% in 2012), but this incidence was probably underestimated owing to inadequate coding of this entity. Nearly 88% of all colistin cases were classified as having severe illness (ie, severity of illness level IV). More than two-thirds had acute respiratory failure requiring mechanical ventilation, and shock developed in a similar proportion, requiring vasopressors; these proportions remained relatively constant in 2006 and 2012.

### 7-Year Time Trends

#### Incidence

The number of colistin cases in the 40-AMC cohort rose from 325 in 2006 to 905 in 2012 (\(P < .001\)). This represented a 178.5%

### Table 1. Baseline Characteristics of Colistin Cases in 2006 and 2012

<table>
<thead>
<tr>
<th>Variable</th>
<th>2006 (n = 325)</th>
<th>2012 (n = 905)</th>
<th>(P) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median (IQR), y</td>
<td>54.9 (44–66)</td>
<td>56.9 (47–68)</td>
<td>.02</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td>.65(^{c})</td>
</tr>
<tr>
<td>Male</td>
<td>199 (61.2)</td>
<td>541 (59.8)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>126 (39.8)</td>
<td>364 (40.2)</td>
<td></td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td>.001(^{c})</td>
</tr>
<tr>
<td>White</td>
<td>185 (56.9)</td>
<td>507 (56.0)</td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td>15 (4.6)</td>
<td>50 (5.5)</td>
<td></td>
</tr>
<tr>
<td>African American</td>
<td>78 (24.0)</td>
<td>242 (26.7)</td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>7 (2.2)</td>
<td>13 (1.4)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>40 (12.3)</td>
<td>93 (10.3)</td>
<td></td>
</tr>
<tr>
<td>Region(^{d})</td>
<td></td>
<td></td>
<td>&lt;.001(^{c})</td>
</tr>
<tr>
<td>Northeast</td>
<td>32.8 (26.1)</td>
<td>115.5 (28.9)</td>
<td></td>
</tr>
<tr>
<td>South</td>
<td>33.6 (26.7)</td>
<td>182.7 (45.7)</td>
<td></td>
</tr>
<tr>
<td>Midwest</td>
<td>40.2 (40.0)</td>
<td>53.6 (13.4)</td>
<td></td>
</tr>
<tr>
<td>West</td>
<td>19.1 (15.2)</td>
<td>47.6 (11.9)</td>
<td></td>
</tr>
<tr>
<td>Comorbid condition(^{e})</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>66 (20.3)</td>
<td>342 (37.8)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Malignancy</td>
<td>23 (7.1)</td>
<td>57 (6.3)</td>
<td>.62</td>
</tr>
<tr>
<td>Organ or alogeneic hematopoietic transplantation</td>
<td>16 (4.9)</td>
<td>44 (4.9)</td>
<td>.96</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>8 (2.5)</td>
<td>51 (6.6)</td>
<td>.02</td>
</tr>
<tr>
<td>Tracheostomy/ chronic mechanical ventilation</td>
<td>80 (24.6)</td>
<td>217 (24.0)</td>
<td>.82</td>
</tr>
<tr>
<td>CKD</td>
<td>84 (25.8)</td>
<td>348 (38.5)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Dialysis status (receiving dialysis before admission)</td>
<td>NA</td>
<td>89 (9.8)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Presumed site of infection(^{f})</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Respiratory</td>
<td>219 (67.4)</td>
<td>522 (57.7)</td>
<td>.002</td>
</tr>
<tr>
<td>Abdominal</td>
<td>54 (16.6)</td>
<td>189 (20.9)</td>
<td>.10</td>
</tr>
<tr>
<td>Urinary</td>
<td>113 (34.8)</td>
<td>316 (34.9)</td>
<td>.96</td>
</tr>
<tr>
<td>Skin and soft tissue</td>
<td>31 (9.5)</td>
<td>79 (8.7)</td>
<td>.66</td>
</tr>
<tr>
<td>Bacteremia(^{g})</td>
<td>27 (8.3)</td>
<td>68 (7.5)</td>
<td>.65</td>
</tr>
<tr>
<td>Central venous catheter(^{h})</td>
<td>NA</td>
<td>64 (7.1)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Other known site</td>
<td>99 (30.5)</td>
<td>206 (22.8)</td>
<td>.006</td>
</tr>
<tr>
<td>Other unknown site</td>
<td>213 (65.5)</td>
<td>602 (66.5)</td>
<td>.78</td>
</tr>
<tr>
<td>Concomitant intravenous antimicrobial use(^{i})</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tigecycline and colistin</td>
<td>27 (8.3)</td>
<td>158 (17.5)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Aminoglycosides and colistin</td>
<td>112 (34.5)</td>
<td>254 (28.1)</td>
<td>.03</td>
</tr>
<tr>
<td>Tigecycline, aminoglycoside, and colistin</td>
<td>7 (2.2)</td>
<td>56 (6.2)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>APR DRG SOI level(^{j})</td>
<td></td>
<td></td>
<td>.12(^{c})</td>
</tr>
<tr>
<td>Minor</td>
<td>1 (0.3)</td>
<td>1 (0.1)</td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>11 (3.4)</td>
<td>15 (1.7)</td>
<td></td>
</tr>
<tr>
<td>Major</td>
<td>26 (8.0)</td>
<td>98 (10.8)</td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td>287 (88.3)</td>
<td>791 (87.4)</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: APR DRG, All Patient Refined Diagnosis Related Group; CKD, chronic kidney disease; ICU, intensive care unit; IQR, interquartile range; NA, not available; SOI, severity of illness.

* See Supplementary Data for the list of International Classification of Diseases, Ninth Revision (ICD-9) codes used to populate this table.

\(^{c}\) Unless otherwise indicated, data represent No. (%) of colistin cases.

\(^{d}\) \(P\) value based on a multiple-degree-of-freedom \(\chi^2\) test across all categories of the variable.

\(^{e}\) Numbers represent colistin cases per 100,000 discharges and percentages represent relative proportions by region.

\(^{f}\) ICD-9 codes for all comorbid conditions were present at admission except where reported as NA.

\(^{g}\) Not mutually exclusive. For instance, a patient may be coded as having more than one site of infection (eg, both abdominal AND respiratory).

\(^{h}\) Potentially underestimated due to under coding.

\(^{i}\) There was no ICD-9 diagnosis code for central line–associated bloodstream infection before October 2008.

\(^{j}\) The 3 categories represented are not mutually exclusive.

\(^{k}\) Classification system developed by 3M™ Health Information Systems.
increase compared with a 6.5% increase in overall admissions to the same hospitals (from 913,866 to 973,331; Table 2 and Figure 2). The incidence of colistin cases increased from 35.56 to 92.98 per 100,000 admissions per year (\(P < .001\)). Interestingly, the incidence plateaued in 2009 and fell in 2012 relative to 2011.

The distribution of increase by region during the 7-year period revealed the highest increase in the South (444%), followed by the Northeast (252%), West (170%), and Midwest (33.3%). The median duration of intravenous colistin use fell from 19 days in 2006 to 16 days in 2012 (\(P = .01\)).

### In-Hospital Death

Of the 5011 patients included in the multinomial logistic regression model (Table 3), 1811 (36.1%) died in the hospital, 979 (19.5%) were discharged to home, 2094 (41.8%) were discharged to an institution, and 127 (2.5%) were discharged to either inpatient or home hospice. In the multinomial logistic regression model, the odds of in-hospital death among colistin cases, compared with discharge to home, decreased by a mean of 5.2%/y (Figure 3A), and this difference was statistically significant (\(P = .04\)).

Among demographic variables, age >65 years (OR, 2.16; 95% CI, 1.75–2.66) and Northeast region compared with the West (OR, 1.73; 95% CI, 1.24–2.41) were independently associated with in-hospital death. Among comorbid conditions, independent associations with mortality were seen among colistin cases with diabetes (OR, 1.28; 95% CI, 1.05–1.57), malignancy (OR, 1.53; 1.09–2.15), or CKD (OR, 1.36; 1.10–1.68). The odds of dying (compared with being discharged home) in colistin cases increased 4.37-fold (95% CI, 2.90–6.61) per stratum increase in the severity of illness level, 1.43-fold (1.05–1.95) with admission to the ICU, 4.02-fold (3.18–5.08) with mechanical ventilation, and 5.40-fold (4.23–6.89) if vasopressor-dependent shock ensued. Simultaneous administration of any aminoglycoside with intravenous colistin was also independently associated with in-hospital death (OR, 1.38; 95% CI, 1.13–1.70), whereas a similar

### Table 2. Colistin Cases: Incidence, Increase, In-Hospital Mortality Rate, and Median Overall and ICU Lengths of Stay at 40 US Academic Medical Centers (2006–2012)

<table>
<thead>
<tr>
<th>Year</th>
<th>All Admissions</th>
<th>Colistin Cases</th>
<th>LOS, Median, d</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>No.</td>
<td>Overall</td>
</tr>
<tr>
<td>2006</td>
<td>913,866</td>
<td>325</td>
<td>35.56</td>
</tr>
<tr>
<td>2007</td>
<td>929,041</td>
<td>503</td>
<td>54.14</td>
</tr>
<tr>
<td>2008</td>
<td>940,914</td>
<td>715</td>
<td>75.99</td>
</tr>
<tr>
<td>2009</td>
<td>947,584</td>
<td>904</td>
<td>95.40</td>
</tr>
<tr>
<td>2010</td>
<td>958,767</td>
<td>976</td>
<td>101.80</td>
</tr>
<tr>
<td>2011</td>
<td>970,350</td>
<td>960</td>
<td>98.93</td>
</tr>
<tr>
<td>2012</td>
<td>973,331</td>
<td>905</td>
<td>92.98</td>
</tr>
</tbody>
</table>

Abbreviations: ICU, intensive care unit; LOS, length of stay.

a Data represent all admissions and colistin cases from 40 academic medical centers that subscribe to the Clinical Database/Resource Manager of the University Health Systems Consortium and reported continuous pharmacy data between 2006 and 2012. The number of colistin cases per 100,000 admissions increased significantly over time (\(P < .001\)).

b Inpatient adult encounters among patients not carrying a diagnosis of cystic fibrosis who received intravenous colistin for >3 consecutive days or died while receiving intravenous colistin, regardless of the duration of administration.

c Unadjusted proportions (see Figure 3 for adjusted in-hospital mortality rate over time).

d Adjusted values using categorical changes over time (\(P < .001\)).

e Adjusted values using categorical changes over time (\(P < .001\)).

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**Figure 2.** Incidence trends at 40 academic medical centers in the United States. From 2006 to 2012, the number colistin cases per 100,000 admissions per year increased by 178.5%, while overall admissions rose by only 6.5% (\(P < .001\)).
association with tigecycline trended toward but did not reach significance (OR, 1.27; 99–1.62).

**Discharge to an Institution or Hospice and Median Overall and ICU Lengths of Stay**

The odds of discharge to an institution compared with discharge to home decreased by 2.8%/y, which was not statistically significant (P = .24). The odds of discharge to hospice compared with discharge to home decreased by 0.8%/y, which was also not statistically significant (P = .89).

In the multivariate median regression models, the median overall length of stay was reduced significantly by 1.25 days each year (P < .001) to 28 days in 2012, and the median ICU length of stay was reduced significantly by 1 day each year (P < .001) to 21 days in 2012 (Supplementary Figure 1). For further details, see the sensitivity analyses (Figure 3B and Supplementary Data: Results) and effects of secondary covariates on discharge to an institution or hospice (Results in Supplementary Data and Supplementary Table 4) and on median overall and ICU lengths of stay (Results in Supplementary Data).

**Colistin Cases and CRGNI Association**

Of the 277 colistin cases examined in the 4-center chart review, 226 (81.6%) had both ≥1 positive culture (regardless of sampling site) for carbapenem-resistant gram-negative bacteria and evidence of an active infection (Supplementary Table 5). The organisms identified among the 226 colistin cases with documented CRGNIs included *Pseudomonas* spp. in 97 (42.9%), *Acinetobacter* spp. in 90 (39.8%), *Klebsiella pneumoniae* in 29 (12.8%), and other organisms in 10 (4.4%). In the complementary analysis of unique cases of bloodstream CRGNIs, data from Barnes Jewish Hospital demonstrated that colistin cases were almost entirely restricted (97%) to extensively drug-resistant CRGNIs (26 of 29 blood isolates and isolates from nonblood sites in 2 patients; see Supplementary Data for definition and Supplementary Table 6). Focusing only on extensively drug-resistant bloodstream CRGNIs, 53% overall (54% at Barnes Jewish Hospital and 50% at Georgetown University Hospital) met the criteria for a colistin case. Therefore colistin tracking missed nearly half of all extensively drug-resistant bloodstream CRGNIs.

**DISCUSSION**

The World Health Organization has recommended the monitoring of antimicrobial use at the health systems level and linking these findings to resistance surveillance as part of a global strategy [28]. Our retrospective cohort study of 40 US AMCs adopted this approach and revealed a substantial increase over time in adult patients receiving intravenous colistin for >3 consecutive days or dying during therapy. Notably, our definition of colistin cases captured acutely ill patients with serious comorbid conditions. The 7-year trend in colistin case incidence reflects the parallel increase in serious CRGNIs at these centers. Despite the successful control of local outbreaks [29], our findings and those of the Centers for Disease Control and Prevention [3] indicate that the CRGNI crisis has not been controlled on a national level. This is the first multicenter, large-scale study reporting temporal trends within in-hospital mortality rates among CRGNIs in the United States. Notably, more patients with these infections (as represented by colistin cases) survived to hospital discharge, and more improved enough to go home rather than be discharged to institutions or hospice. In addition, after illness severity and other temporal confounders were controlled for, colistin cases have had shorter hospital and ICU stays each year.

Observed decreases in hospital mortality rates among colistin cases may be explained by increased awareness of CRGNIs, earlier initiation of intravenous colistin, national trends in sepsis outcomes [30], changes in supportive care [31], improved awareness and management of colistin-related toxic effects, and improvements in treating underlying diseases over...
time. Most secondary covariates identified here as independent risk factors for mortality are plausible and supported by studies of more general populations with severe sepsis [32]. Interestingly, patients in the Northeast had worse outcomes. One might speculate that this finding was influenced by the K. pneumoniae carbapenemase–producing subgroup of CRGNIs, because initial outbreaks followed by endemicity were clustered in the Northeast starting in 2005. By December 2010, however, 36 US states, Washington, DC, and Puerto Rico reported the presence of K. pneumoniae carbapenemase–producing isolates [33]. An increasing proportion of colistin cases with CKD suggests increased colonization with extensively drug-resistant gram-negative bacteria and growing familiarity with colistin in this population. High mortality in the presence of CKD may reflect a greater risk for colistin toxicity [18] or just a higher risk of death from sepsis in these patients. Recently available pharmacokinetic/pharmacodynamic data for colistin [34, 35] and evidence of improved efficacy using higher-dose colistin regimens [16–18] may have contributed to overall improved outcomes.

Our study was not designed to evaluate the efficacy of monotherapy versus combination therapy. In a previous observational study, tigecycline combined with colistin was associated with worse microbiological outcomes [18]. In the current study, mortality rates were higher when colistin was combined with either tigecycline or aminoglycoside, but this difference reached significance only for aminoglycoside. The practice of administering empiric aminoglycoside in patients whose condition is deteriorating may explain this association, at least in part. However, evidence of efficacy [35] and even robust comparisons between monotherapy and combination therapy [10, 36] are currently lacking.

Our study has several limitations. The results are representative only of AMCs. Mortality data beyond discharge were not available. Nationwide trends toward increased postdischarge institutionalization [37] may contribute to the observed in-hospital mortality rate reductions. Among colistin cases in our study, the rates of discharge to institutions remained unchanged over time. Another limitation of all administrative databases relates to variability in coding practices, which can be mitigated only partially by adequate sample size and validating substudies. Carbapenem susceptibility breakpoints for Enterobacteriaceae from the Clinical and Laboratory Standards Institute [38] have been lowered based on emerging carbapenem pharmacokinetic/pharmacodynamic data, poor capture of carbapenemase–producers, and suboptimal implementation of the modified Hodge test. Temporal changes in breakpoints and inconsistency in their implementation across laboratories could confound attempts to track colistin use as a marker for quantifying the burden of CRGNIs. Notwithstanding, the impact of breakpoint variance may be minimized by our large sample of patients and centers. Moreover, the trajectory for colistin case incidence was seen to rise before the new cutoffs were widely implemented (Supplementary Table 3). Subjects that died while receiving colistin were included regardless of the duration of administration. These patients may have had a lower incidence of CRGNI, but their proportion in our cohort was small (1.1%).

Significant heterogeneity in susceptibility to other agents among carbapenem-resistant gram-negative isolates makes colistin cases a less sensitive means for tracking these infections. The colistin case definition almost exclusively captures CRGNIs that are extensively drug-resistant, an important subset owing to severely limited treatment options. Extensively drug-resistant organisms caused 90% of bloodstream CRGNIs that met...
colistin case criteria. Including concomitant nonblood infections, 97% of these colistin cases had extensively drug-resistant gram-negative infections. Notably, colistin case tracking missed nearly half of all patients with extensively drug-resistant gram-negative bacteremia. Although some of these patients were treated with aminoglycosides or source control alone, almost half died or transitioned to hospice before final susceptibility results were available. Other reasons colistin tracking may underestimate the burden of disease include lack of colistin availability or familiarity and under sampling (eg, pneumonia). In addition, organisms with constitutive or emerging resistance to colistin cannot be monitored using this strategy.

Patients with CF were excluded a priori from our definition of colistin cases. Inhaled colistin is commonly prescribed for these patients, and these doses may sometimes be misrepresented as intravenous. Further justifying the exclusion of this group, colistin use in the CF population remained constant over time, and mortality rates were low and unchanging, findings substantially different from those among colistin cases without CF (Figure 3).

These data on the rising incidence of CRGNIs, especially those that are extensively drug-resistant, underscore the need to bolster antibiotic stewardship, prevent the spread of resistant organisms, and develop new agents with novel mechanisms of action and more favorable toxicity profiles. Although mortality rates improved modestly, the sharply rising incidence indicates that the absolute mortality burden is increasing. Further studies (particularly in a community hospital cohort) should focus on identifying pathogen-, host-, and practice-related factors that might explain current and future trends in mortality. Despite the limitations stated above, we used a unique strategy to track the incidence and outcome of CRGNIs at a time when no single perfect system exists to survey the true burden of this crisis.

Supplementary Data

Supplementary materials are available at Clinical Infectious Diseases online (http://cid.oxfordjournals.org). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyrighted. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

Notes

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References


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