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Major Article

# Attributable mortality from extensively drug-resistant gram-negative infections using propensity-matched tracer antibiotic algorithms

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***Background:*** Tracer antibiotic algorithms using administrative data were investigated to estimate mortality attributable to extensively drug-resistant gram-negative infections (GNIs).

***Methods:*** Among adult inpatients coded for GNIs, colistin cases and 2 comparator cohorts (non-carbapenem $\beta$-lactams or carbapenems) treated for ≥4 consecutive days, or died while receiving the antibiotic, were separately propensity score-matched (1:2). Attributable mortality was the in-hospital mortality difference among propensity-matched groups. Infection characteristics and sepsis severity influences on attributable mortality were examined. Algorithm accuracy was assessed by chart review.

***Results:*** Of 232,834 GNIs between 2010 and 2013 at 79 hospitals, 1,023 per 3,350 (30.5%) colistin and 9,188 per 105,641 (8.7%) $\beta$-lactam (non-carbapenem) comparator cases died. Propensity-matched colistin and $\beta$-lactam case mortality was 29.2% and 16.6%, respectively, for an attributable mortality of 12.6% (95% confidence interval 10.8-14.4%). Attributable mortality varied from 11.0% (7.5%-14.7%) for urinary to 15.5% (12.6%-18.4%) for respiratory ($P < .0001$), and 4.6% (2.1%-7.4%) for early (≤4 days) to 16.6% (14.3%-18.9%) for late-onset infections ($P < .0001$). Attributable mortality decreased to 7.5% (5.6%-9.4%) using a carbapenem comparator cohort but increased 9-fold in patients coded for severe sepsis or septic shock ($P < .0001$). Our colistin algorithm had a positive predictive value of 60.4% and sensitivity of 65.3%.

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***Conclusions:*** Mortality attributable to treatment-limiting resistance during GNIs varied considerably by site, onset, and severity of infection.

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Antimicrobial resistance during gram-negative infections (GNIs) has been associated with non-survival. However, estimating mortality burden specific to resistance is challenging as patients often have competing risks for death. Attributable mortality, total mortality minus mortality expected from underlying diseases and conditions,[1] attempts to quantify the impact of resistance on survival. Several studies and meta-analyses have estimated mortality attributable to specific resistance profiles among GNIs such as carbapenem resistance,[2-9] despite limitations in sample size and or risk-adjustment. Notably, the attributable mortality rate of 6.5% used to estimate the annual burden of US deaths due to carbapenem-resistant *Enterobacteriaceae* was derived from a single-center analysis of all antibiotic-resistant hospital-onset infections.[10,11] A more recent study from over 100 Veterans Administration hospitals estimated the 30-day mortality risk attributable to multidrug-resistant (MDR; non-susceptibility to at least 1 agent in ≥3 categories) GNIs, combining sterile and non-sterile sites, at 4.9%.[12] Notably, strains classified as MDR, or even carbapenem-resistant, often retain susceptibility to other highly active agents, which might mitigate the impact of these resistance traits on attributable mortality.[13]

The term extensively drug resistant (XDR), first used for *Mycobacterium tuberculosis*, has been similarly applied to gram-negative bacteria.[14,15] The consensus definition for XDR is non-susceptibility to ≥1 agent in all but 2 or fewer categories.[16] As a practical and clinically meaningful alternative, we have proposed defining XDR in GNI as non-susceptibility to quinolones and all $\beta$-lactams including carbapenems.[17] Well-recognized among *Enterobacteriaceae*, *Pseudomonas aeruginosa*, and *Acinetobacter baumannii* isolates, such treatment-limiting resistance may include chromosomal gene mutations, but is often caused by the horizontal transfer of plasmids carrying multiple resistance traits,[18] rendering preferred antibiotic regimens inactive and increasing the risk of inadequate therapy and poor outcomes.[19] Although recently introduced $\beta$-lactam - $\beta$-lactamase inhibitors (ceftazidime-avibactam, ceftolozane-tazobactam, and meropenem-vaborbactam) have activity against a variety of XDR GNIs, de novo resistance on therapy has already emerged.[20,21] Accordingly, the precise contribution of XDR to non-survival in GNIs will likely continue to vary as bacterial resistance evolves and new antibiotics become available. Mining rapidly expanding sources of digital health care data at different levels of granularity is essential to navigate and harness this changing landscape.

Colistin, an antimicrobial agent originally used in the 1960s, has resurfaced over the last decade in response to the resistance crisis. Despite substantial nephrotoxicity, colistin has been administered with increasing frequency to treat XDR GNIs with limited therapeutic options. In a previous study, we showed that ≥4 consecutive days of, or death while receiving, intravenous colistin (defined as "colistin cases") was predictive of targeted therapy for XDR GNIs, and therefore, could function as a surrogate for these infections in large electronic health care databases.[17] Here, mortality attributable to XDR in GNIs was estimated by comparing outcomes between colistin cases and 2 propensity-matched comparator case cohorts (representative of non-XDR GNIs) that received targeted therapy with conventional active agents. In addition, site and period of onset of infection, and coding for sepsis or severe sepsis or septic shock were examined to identify factors that affect XDR-attributable mortality.

## METHODS

### *Primary data source*

A retrospective cohort study was performed using inpatient encounters admitted between January 2010 and December 2013 available in the Clinical Database/Resource Manager (CDB/RM) of Vizient Inc (Chicago, IL; formerly University HealthSystem Consortium), a health care company that includes a collaborative of 120 academic medical centers and 300 affiliated hospitals comprising >95% of US academic medical centers.[22] The CDB/RM includes administrative claim codes and specific charges for medications.

### *Tracer antibiotic algorithms*

Colistin cases were defined as inpatient encounters receiving ≥4 consecutive days of intravenous colistin or died while receiving colistin.[17] Polymyxin-B was not included given that on an initial query, only 6 hospitals in the CDB/RM reported non-topical administration of polymyxin-B during the study period, all of which was for irrigation. The primary comparator group was similarly defined using non-carbapenem $\beta$-lactam antibiotics, namely $\beta$-lactam or- $\beta$-lactamase inhibitor combinations (piperacillin-tazobactam and ampicillin-sulbactam), antipseudomonal cephalosporins (ceftazidime and cefepime), or aztreonam (henceforth referred to as the $\beta$-lactam comparator). Cases with ≥4 consecutive days of or death while receiving intravenous carbapenems were analyzed separately as a secondary comparator group (ie, the carbapenem comparator). Among encounters with multiple qualifying episodes, the first tracer-specific episode was chosen; when encounters displayed multiple episode types qualifying under different tracers, the case was assigned using the following hierarchical order: colistin case > carbapenem case > other comparator. The XDR-type phenotype was defined as previously described,[13,17] that is, non-susceptibility to all $\beta$-lactams including carbapenems and to all fluoroquinolones tested. Colistin and comparator cases were used as pharmacologic surrogates for XDR and non-XDR GNIs, respectively. Only cases associated with ICD-9-CM diagnosis codes for GNIs were selected to enhance the likelihood of targeted therapy. Patients aged <18 years and those with cystic fibrosis, the latter has shown previously to represent a different risk set,[17] were excluded.

### *Outcomes*

Colistin cases were matched in a 1:2 ratio separately to both $\beta$-lactam and carbapenem comparator groups based on the propensity to be a colistin case. The primary outcome was mortality attributable to XDR calculated as the difference in percentage in in-hospital mortality between propensity-matched colistin and $\beta$-lactam comparators. Potential effect-modifiers were separately explored in 1 secondary and 3 sensitivity analyses to study attributable mortality stability: (1) use of carbapenems as the secondary comparator; (2) site of infection, classified by adapting previously defined site categories using ICD-9-CM diagnosis codes,[23] (3) time of GNI onset, dividing matched cases into early-onset (up to day 4 of hospital admission) and late-onset (thereafter), and (4) classification as sepsis or severe sepsis and septic shock using explicit ICD-9-CM diagnosis codes (excluding the code

"septicemia"). Analyses 2 and 4, described earlier, were limited to case pairs in which colistin cases were matched to either 1 or 2 comparators with the same site of infection or sepsis stratum, respectively. For analysis 3, the ≤4 vs >4 day cut-off was used to discriminate early versus late onset (in lieu of the typical ≤2 vs >2 day cut-off generally used to separate community- and hospital-onset of infection) to account for time from culture to the availability of in vitro susceptibility testing that could drive colistin use. The median direct cost attributable to XDR GNI was obtained by calculating the difference in median direct costs between matched colistin and non-colistin hospitalizations.

*Statistical analysis*

All analyses were conducted in R packages compareGroups, MatchIt, and exact 2 × 2 (R-project; Vienna, Austria). CompareGroups was used for baseline characteristic comparisons. *P* values for categorical variables were computed by the $\chi^2$ tests (or the Fisher exact test for n <5) and for continuous variables by t tests. Propensity score matching was used to arrive at 1:2 colistin:comparator pairs; matching variables included age, sex, Charlson Comorbidity Index, site of infection, and 3M (3M Health Information Systems, Salt Lake City, UT). All patients were refined as diagnosis related groups, severity of illness, and risk of mortality assignments,[24] discharge year, transfer status on admission, and day of initial antibiotic administration. We reduced standardized biases from unmatched to matched so that they were within −10%-10%. Matched colistin-comparator pairs were bootstrap sampled 10,000 times to calculate confidence intervals. In-hospital mortality was averaged for the 2 comparator cases in each pair, that is, if 1 died and 1 survived their outcome contribution would be 0.5. Differences between the binary outcome for colistin cases and the average of comparator cases were calculated for each pair. Omnibus permutation tests were conducted on the subset analyses for infection site and sepsis respectively in which a *P* value <.05 indicates significant variation. Attributable direct costs were calculated as the difference in median direct cost between propensity-matched case-groups; medians were adjusted by re-ranking patients who died as if they incurred greater than the maximum direct cost identified in the overall cohort.

*Validation of tracer antibiotic algorithm accuracy*

After institutional review board approval, chart review was performed at 3 centers in the primary cohort: Georgetown University Hospital (GUH), Washington District of Columbia; Barnes Jewish Hospital (BJH), St. Louis, Missouri; and University of Maryland Medical System (UMMS), Baltimore, Maryland. For chart review 1, center-specific colistin cases were 1:1 propensity-matched to overall comparators (ie, β-lactam and carbapenems comparators combined) within each institution using all the matching variables used for the primary analysis described earlier except for discharge year, Charlson Comorbidity Index, and site of infection given the limited sample size at each institution. Microbiology and pharmacy data were manually reviewed for matched cases to compute the positive predictive value of tracer-antibiotic algorithms. Furthermore, the tri-institutional XDR-attributable mortality was calculated as the difference in mortality between all reviewed colistin cases identified as having true XDR GNI and all reviewed non-colistin cases identified as having true non-XDR infections. Chart review 2, beginning with XDR GNI of the bloodstream identified in microbiology records, enabled calculation of algorithm sensitivity, that is, the proportion of XDR GNI of the bloodstream that met colistin case criteria against a gold-standard for true gram-negative infection. These data have been previously reported for GUH and BJH.[17] Colistin administrations charged as intravenous were manually reviewed to determine the frequency of misclassifying inhaled or nebulized doses.

## RESULTS

*Baseline characteristics*

We identified 232,834 unique GNI encounters among adult inpatients between 2010 and 2013 at 79 hospitals in Vizient CDB/RM. Of these, 3,350 colistin and 105,641 β-lactam (non-carbapenem) comparator cases were found. Among these, 3,099 colistin cases from 76 hospitals were 1:2 matched to 6,198 β-lactam comparator pairs from 79 hospitals (Fig 1; Table 1). Of these, only 154 (5%) colistin cases and 211 (3.4%) comparator cases were included owing to death occurring within 3 days of initiation of the tracer antibiotic. Prior to matching, a

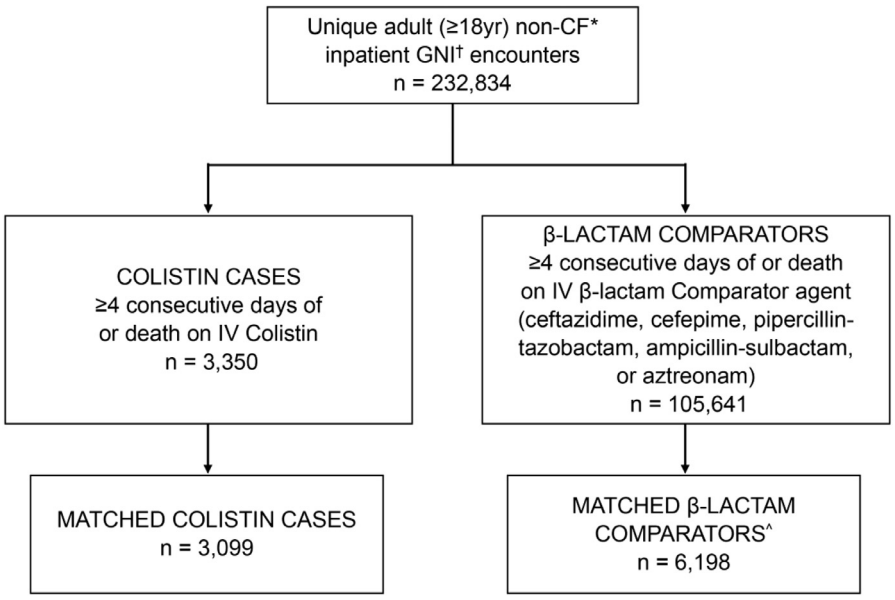



**Fig 1.** Case selection flowchart. Encounters with ICD-9-CM codes for GNI who received ≥4 consecutive days of colistin (colistin case) or ≥4 consecutive days of a β-lactam (non-carbapenem) comparator antibiotic were propensity matched in a 1:2 ratio. *CF*, cystic fibrosis; *GNI*, gram-negative infections; *IV*, intravenous. *Based on ICD-9-CM code 277-0 (CF). †Based on ICD-9-CM GNI codes (ICD-9 008.46-47, 038.3-038.49, 041.3-041.49, 041.7, 041.84-85, 320.81-82, 482.0, 482.81-83). ^Non-carbapenem.

**Table 1**
Baseline characteristics of colistin and β-lactam (non-carbapenem) comparator cases before and after propensity matching

| Variable | Matched colistin cases N = 3,099* | Unmatched comparator cases N = 105,641 | *P* value | Matched comparator cases N = 6,198 | *P* values |
|---|---|---|---|---|---|
| Death | 905 (29.2) | 9,188 (8.7) | <.001 | 1,029 (16.6) | <.001 |
| Age categories (y) | | | <.001 | | .895 |
| 18-44 | 729 (23.5) | 17,154 (16.2) | | 1,433 (23.1) | |
| 45-59 | 959 (30.9) | 27,577 (26.1) | | 1,932 (31.2) | |
| 60-74 | 1,044 (33.7) | 334,977 (33.1) | | 2,122 (34.2) | |
| 74+ | 367 (11.8) | 25,933 (24.5) | | 711 (11.5) | |
| Sex | | | <.001 | | 1.000 |
| Male | 1,873 (60.4) | 55,392 (52.4) | | 3,747 (60.5) | |
| Female | 1,226 (39.6) | 50,247 (47.6) | | 2,451 (39.5) | |
| Charlson Comorbidity Index categories | | | <.001 | | .686 |
| 0-3 | 820 (26.5) | 25,458 (24.1) | | 1,688 (27.2) | |
| 4-5 | 793 (25.6) | 26,509 (25.1) | | 1,525 (24.6) | |
| 6-7 | 736 (23.7) | 24,533 (23.2) | | 1,457 (23.5) | |
| 8+ | 750 (24.2) | 29,141 (27.6) | | 1,528 (24.7) | |
| 3M APR DRG severity of illness assignment | | | <.001 | | .260 |
| 1 (mild) | 32 (1.03) | 3,147 (2.98) | | 72 (1.16) | |
| 2 (moderate) | 169 (5.45) | 18,081 (17.1) | | 399 (6.44) | |
| 3 (severe) | 851 (27.5) | 49,687 (47.0) | | 1,705 (27.5) | |
| 4 (extreme) | 2,047 (66.1) | 34,726 (32.9) | | 4,022 (64.9) | |
| 3M APR DRG risk of mortality assignment | | | <.001 | | .195 |
| 1 (mild) | 140 (4.52) | 14,794 (14.0) | | 324 (5.23) | |
| 2 (moderate) | 562 (18.1) | 30,297 (28.7) | | 1,199 (19.3) | |
| 3 (severe) | 1,192 (38.5) | 37,873 (35.9) | | 2,331 (37.6) | |
| 4 (extreme) | 1,205 (38.9) | 22,677 (21.5) | | 2,344 (37.8) | |
| Admission source | | | <.001 | | .994 |
| Institution | 1,194 (38.5) | 25,588 (24.2) | | 2,386 (38.5) | |
| Non-institution | 1,905 (61.5) | 80,053 (75.8) | | 3,812 (61.5) | |
| Infection site | | | | | |
| Abdominal | 622 (20.1) | 13,162 (12.5) | <.001 | 1,258 (20.3) | .819 |
| Bacteremia | 274 (8.84) | 12,190 (11.5) | <.001 | 562 (9.07) | .749 |
| Cellulitis | 349 (11.3) | 12,200 (11.5) | .643 | 708 (11.4) | .844 |
| Respiratory | 1,745 (56.3) | 30,379 (28.8) | <.001 | 3,397 (54.8) | .177 |
| Urinary | 1,202 (38.8) | 49,564 (46.9) | <.001 | 2,521 (40.7) | .084 |
| Site known | 715 (23.1) | 16,244 (15.4) | <.001 | 1,341 (21.6) | .122 |
| Site unspecified | 2,107 (68.0) | 45,775 (43.3) | <.001 | 4,022 (64.9) | .003 |
| Discharge year | | | <.001 | | .853 |
| 2010 | 840 (27.1) | 24,108 (22.8) | | 1,631 (26.3) | |
| 2011 | 782 (25.2) | 25,161 (23.8) | | 1,567 (25.3) | |
| 2012 | 774 (25.0) | 27,408 (25.9) | | 1,584 (25.6) | |
| 2013 | 703 (22.7) | 28,964 (27.4) | | 1,416 (22.8) | |
| Late onset of infection† | 2,062 (66.5) | 28,667 (27.1) | <.001 | 4,124 (66.5) | 1.00 |
| Mean d from admission to initiation of tracer antibiotic | 10 (3, 24) | 1 (0, 5) | <.001 | 10 (3, 24) | 1.00 |

*APR*, all patients refined; *DRG*, diagnosis related groups.
*Only matched colistin cases shown for simplicity; 8% (n=251) colistin cases were unmatched.
†Consecutive days of antibiotics initiated after 4 days of admission.

greater percentage of colistin cases versus β-lactam comparators were male patients, younger, sicker at baseline by severity of illness and risk of mortality criteria, and presented from a health care facility. After matching, the balance of variables between colistin and β-lactam comparators improved considerably (Table 1). The 6,198 matched β-lactam comparators predominantly received either piperacillin-tazobactam (n = 3086; 50%) or cefepime (n = 2311; 37%). Among 6,198 separately matched carbapenem comparators, 3348 (54%) received meropenem, 1170 (19%) received imipenem, 979 (16%) received ertapenem, and 701 (11%) received doripenem.

### *Outcome*

Crude mortality among all unmatched colistin cases was 30.5% (1,023 per 3,350) and among all unmatched β-lactam comparators was 8.7% (9,188 per 105,641). Mortality among propensity-matched colistin cases and β-lactam comparators was 29.2% (95% confidence interval 27.6%-30.8%) and 16.6% (15.7%-17.6%), respectively, resulting in an attributable mortality of 12.6% (10.8%-14.4%) (Fig 2). The use of carbapenem comparators instead of β-lactam comparators reduced the proxy XDR-attributable mortality rate by over one-third to 7.5% (5.6%-9.4%) (Fig 2). This lower estimate for XDR-attributable mortality resulted from the substantially higher mortality among propensity-matched carbapenem comparators of 21.7% (20.6%-22.8%), relative to 16.6% (15.7%-17.6%) observed among β-lactam comparators.

Mortality among propensity-matched cohorts demonstrated a consistent hierarchical pattern (colistin case mortality > β-lactam comparator mortality) across all infection sites (Fig 3A). Colistin cases specified as respiratory and abdominal sources demonstrated the highest mortality, 35.4% (33.1%-37.6%) and 33.9% (30.2%-37.8%), respectively. Attributable mortality was highest in patients with a respiratory source at 15.5% (12.3%-18.4%) and lowest in those with a urinary source at 11% (7.5%-14.7%; $P < .001$). Mortality attributable to XDR was 4.6% (2.1%-7.4%) in patients with early-onset and 16.6% (14.3%-18.9%) in those with late-onset GNIs. A hierarchical increase in attributable mortality was also observed for the presence and severity of sepsis (Fig 3B). Notably, XDR-attributable mortality among cases without any coding for sepsis syndromes was only 1.5% (0.56%-3.6%), whereas it was 3-fold higher at 4.6% (2.3%-11.6%) among cases coded for sepsis and 9-fold higher at 13.4% (9.6%-17.2%) among cases coded for severe sepsis and or septic shock ($P < .001$).

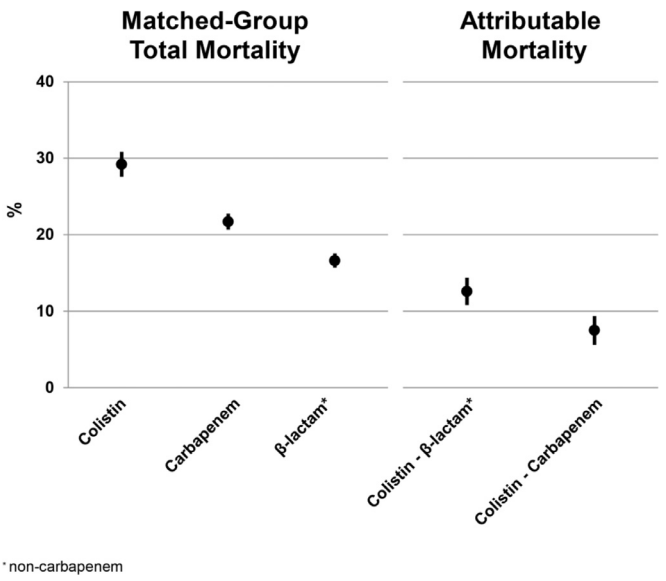
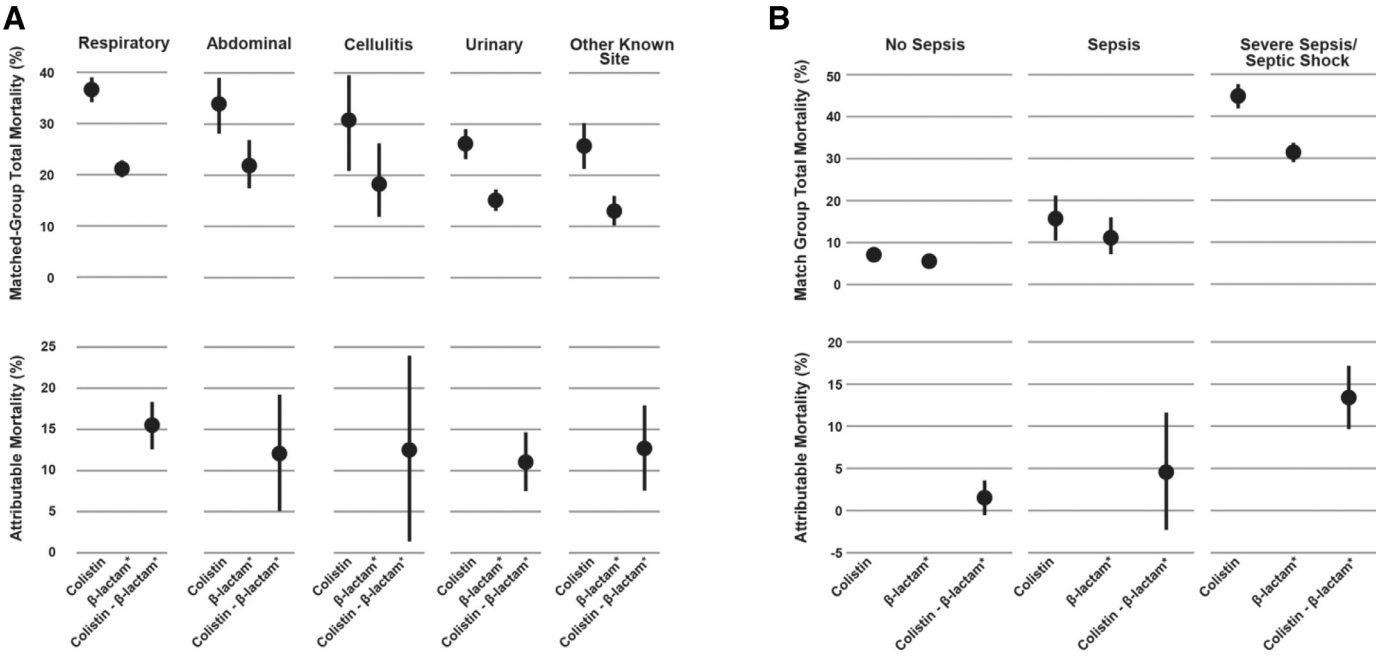



**Fig 2.** Impact of comparator antibiotic tracer type on attributable mortality from extensively drug-resistant gram-negative infection. Crude mortality of the respective propensity matched cohorts were subtracted from each other to determine the attributable mortality of colistin versus $\beta$-lactam comparator and colistin versus carbapenem comparator. A step-wise decrease is noted in the crude mortality rate from the colistin, to carbapenem, to $\beta$-lactam (non-carbapenem) cases. Dots represent mortality estimates and vertical lines represent 95% bootstrapped confidence intervals.

The median direct cost (adjusted for maximum cost assigned to cases that died in hospital) for matched colistin cases was $101,190 and for matched $\beta$-lactam comparators cases was $65,334, therefore, the XDR-attributable, median direct cost per GNI hospitalization was estimated at $35,856 (Fig 4).

*Validation analysis*

At 3 institutions, 263 patient-pairs were reviewed: 65 at GUH, 98 at BJH, and 100 at UMMS (Table 2). One case each at GUH and BJH, and 6 cases at UMMS were not assessable because of missing data. In chart review 1, cases could not be matched for taxa: 76% of colistin and 25% of comparator GNI cases were due to *Acinetobacter* spp and other non-lactose fermenters, whereas 18.4% of colistin and 45.9% of comparator GNI cases were due to *Enterobacteriaceae* (Table 3). Among the 101 (39.6 %) colistin cases that did not meet the XDR definition, 86 (85.1%) were non-XDR GNIs, whereas 15 (14.9%) were either culture-negative (n = 6) or represented potential colonization (n = 9). Colistin cases representing true XDR GNIs (154 of 255) yielded a positive predictive value of 60.4% (ranging from 51.5%-70.3% by institution). However, the positive predictive value rose to 68.2% for true intravenous colistin cases and was only 39.1% for inhaled colistin cases misidentified as intravenous. This misidentification varied considerably across the 3 institutions undergoing chart review, ranging from 0-57.7%. The 3-center average of misclassified inhaled cases was 27.1% among all colistin cases and 21.1% among those found to




*non-carbapenem

Note: Infection site categories displayed in the figure are not mutually exclusive

| | Respiratory | Abdominal | Cellulitis | Urinary | Other Known Site |
|---|---|---|---|---|---|
| Colistin | N=1515 | N=274 | N=91 | N=830 | N=381 |
| β-lactam* | N=2395 | N=320 | N=104 | N=1185 | N=491 |

*non-carbapenem

| | No Sepsis | Sepsis | Severe Sepsis/ Septic Shock |
|---|---|---|---|
| Colistin | N=892 | N=173 | N=1142 |
| β-lactam* | N=1419 | N=208 | N=1540 |

**Fig 3.** Attributable mortality from extensively drug-resistant gram-negative infections by (A) site and (B) coding for sepsis or severe sepsis/septic shock. Dots represent mortality estimates and vertical lines represent 95% bootstrapped confidence intervals. The *P* value for the Omnibus Permutation Test was <.001 suggesting significant variation between groups. Analysis was limited to matched case pairs with coding for the same site of infection or with the same sepsis code assignment. In subfigure A, attributable mortality was lowest for infections coded as urinary and highest for those coded as respiratory infections. In subfigure B, a step-wise increase in attributable mortality is noted as the overall severity of sepsis increased. ICD-9-CM codes for sites adapted from[17,23]. ICD-9-CM codes signifying severe sepsis and septic shock were combined into 1 category. *Infection site categories displayed are not mutually exclusive.

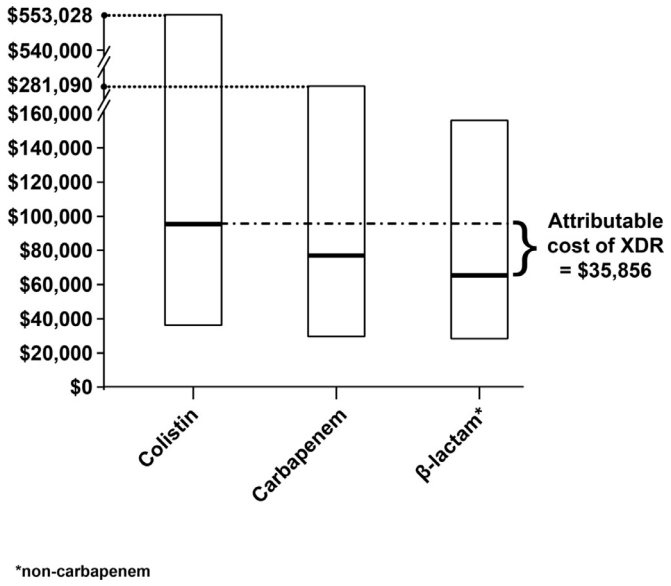



**Fig 4.** Adjusted median direct hospitalization cost for colistin cases and comparators. The difference in median direct hospitalization costs between colistin cases and $\beta$-lactam comparators provides the estimate of XDR gram-negative infection hospitalization costs attributable to XDR. Y Axis: Median direct hospitalization cost in 2014 US Dollars adjusted for patients who died and were assigned a direct cost that was greater than the maximum observed direct cost among survivors. Of note, the proportion of patients represented by colistin cases that died exceeded the size of upper quartile (upper 25%) for that group. Therefore, in the figure, 70% ($553,028) was used in lieu of the upper quartile for colistin cases. X Axis: Represents case cohorts identified by respective tracer antibiotic algorithms. *XDR*, extensively drug resistant.

represent true XDR GNI. For the 2 hospitals in which inhaled colistin cases were misclassified as intravenous, crude mortality was 37% (34 of 92) in cases that received intravenous colistin and 24.6% (17 of 69) in cases that only received inhaled colistin.

Overall, comparator cases (which included 84 carbapenems cases in chart review 1) had a cross-institutional positive predictive value for non-XDR infection of 76.1% with 194 of 255 meeting the definition. Of the 61 cases that failed to have microbiologically confirmed non-XDR GNIs, 38 were culture negative (62.3%), 13 only appeared colonized (21.3%), and 10 (16.4%) met criteria for XDR GNIs, for an XDR prevalence of only 4% (10 of 255).

Across the 3 centers where chart review was performed, mortality in colistin-cases identified as having true XDR GNIs was 30.5% (47 of 154) and in non-colistin cases identified as having true non-XDR GNIs was 15.9% (31 of 194), yielding a tri-institutional XDR-attributable mortality of 30.5% − 15.9% = 14.6%. In chart review 2, using microbiology data from the 3 institutions, 81 of 124 XDR-GNI of the bloodstream met the colistin case definition, for a sensitivity of 65.3% (range: 46%-80%).

## DISCUSSION

Our pharmacoepidemiologic analysis sought to estimate the attributable mortality and economic burden resulting from co-resistance that renders all routine therapeutic options for GNIs inactive. This scenario, implied by the sustained use of colistin, seemed likely to adversely affect mortality, a hypothesis that is supported by our findings. In a large administrative database of academic medical centers, patients coded for GNIs and administered ≥4 consecutive days of intravenous colistin, or who died within 4 days of initiating this therapy (collectively termed colistin cases), had an excess mortality of 12.6% (for an excess mortality fraction of 43.1%) compared with propensity-matched comparators who similarly received (or died receiving) first-line non-carbapenem $\beta$-lactam agents targeting gram-negative bacterial pathogens. Using colistin cases and $\beta$-lactam comparators as surrogates for XDR and non-XDR GNIs, respectively, and propensity matching to mitigate confounding by indication, XDR-attributable mortality was estimated at 12.6% using tracer antibiotic algorithms at 76 academic medical centers. Although less-stringently matched owing to fewer patients, chart review at 3 of these centers similarly returned an attributable mortality estimate of 14.6% when restricted to only true XDR and true non-XDR cases. In the overall cohort analysis, attributable health care cost of XDR was estimated to be $35,856 per XDR inpatient admission.

Notably, however, secondary analyses demonstrated that one-size-fits-all, aggregate attributable mortality estimates obscure important heterogeneity among GNIs that modify the effect of resistance on outcome. XDR-attributable mortality was substantially affected by the choice of comparator groups, the site and time of onset of infection, as well as the presence and severity of sepsis. For example, late-onset GNIs had a 4-fold higher XDR-attributable mortality compared to onset within 4 days of hospitalization. Coding for sepsis had 3-fold higher and severe sepsis or septic shock a 9-fold higher XDR-attributable mortality, indicating that a higher baseline risk of death potentially amplifies the effect of XDR on infection outcome. Chart review revealed that the accuracy of colistin cases as a pharmacologic surrogate for XDR was only moderate and varied considerably among institutions.

The impact of antimicrobial resistance on survival has been difficult to estimate and remains controversial. Although the interplay among resistance, fitness costs, and virulence are incompletely understood,[25,26] patients with underlying diseases and other comorbidities tend to acquire pathogens with higher levels of resistance.[2,27,28] The proliferation of plasmid-mediated co-resistance has complicated efforts to quantify monospecific relationships between individual resistance traits and outcome. However, it is therapeutically challenging co-resistance for which the impact of resistance on outcome is likely to be most pronounced.[13] Understanding this relationship and tracking it overtime, as resistance traits evolve and antibiotic practices change, is pivotal to national and international public health efforts to confront and mitigate the resistance crisis.[29,30] Despite the relatively low prevalence of XDR phenotypes among GNIs,[13] documenting their high mortality, propensity for outbreaks, and global spread are important to heighten awareness. The development of new tools for analyzing well-established, large administrative databases, as well as studies from the growing availability of more detailed electronic medical record repositories offer an opportunity to better define the clinical and economic consequences of XDR infections. Surveillance of prevalence, treatment patterns, and mortality attributable to XDR over time on a large scale in multicenter repositories will better inform antibiotic use and development,[31] as well as rapid diagnostics, stewardship, and infection-control measures.

The economic burden of resistance encompasses costs not limited to expensive antibiotics, longer hospital stays, management of sepsis sequelae, and isolation procedures.[32] Previous reports of health care costs attributable to MDR have ranged between $10,000 and $40,000 per patient affected.[33] The health care cost attributed to our surrogate marker for XDR reported here represents a conservative estimate and certain postdischarge factors such as greater rehabilitation costs and loss of productivity are not accounted for. However, it highlights the fact that extreme gram-negative resistance profiles pose a substantial financial burden for patients, health care systems and third party payers.

In studies quantifying the impact of resistance, the choice of comparison or control group has been recognized as an important determinant of attributable outcome.[34] For instance, comparing the outcome associated with methicillin-susceptible versus methicillin-resistant

**Table 2**
PPV and sensitivity of tracer antibiotic algorithms for detecting XDR GNIs (2010-2013)

| | GUH (2010-2013) | BJH (2010-2013) | UMMS (2010-2013) | Total (2010-2013) |
|---|---|---|---|---|
| Chart review 1 | | | | |
| Colistin cases PPV | | | | |
| Total number of colistin cases reviewed | 64* | 97* | 94† | 255 |
| Colistin cases meeting XDR GNI definition | 45/64 | 50/97 | 59/94 | 154/255 |
| PPV (%): | | | | |
| Among overall colistin cases | 45/64 (70.3%) | 50/97 (51.5%) | 59/94 (62.8%) | 154/255 (60.4%) |
| Among colistin cases that received IV colistin | 38/51 (74.5%) | 30/41 (73.2%) | 59/94 (62.8%) | 127/186 (68.2%) |
| Among colistin cases that received colistin only in inhaled form | 7/13 (53.8%) | 20/56 (35.7%) | 0 (0%) | 27/69 (39.1%) |
| Reason for exclusion from XDR GNI definition: | | | | |
| Microbiologically non-XDR GNI | 13 | 45 | 28 | 86 |
| Colonization | 5 | 0 | 4 | 9 |
| No gram-negative isolated‡ | 1 | 2 | 3 | 6 |
| Colistin cases only receiving inhaled form (%): | | | | |
| Total inhaled/all colistin cases | 13/64 (20.3%) | 56/97 (57.7%) | 0/94 (0%) | 69/255 (27.1%) |
| Inhaled meeting XDR GNI definition/all inhaled | 7/13 (53.8%) | 20/56 (35.7%) | 0/0 (0%) | 27/69 (39.1%) |
| Inhaled meeting XDR GNI definition/all XDR GNIs | 7/45 (15.6%) | 20/50 (40%) | 0/59 (0%) | 27/154 (17.5%) |
| Comparator§ cases PPV | | | | |
| Total number of comparator cases reviewed | 64* | 97* | 94† | 255 |
| Comparator cases meeting definition of non-XDR GNI | 57/64 | 70/97 | 67/94 | 194/255 |
| PPV (%) | 89.1% | 72.2% | 71.2% | 76.1% |
| Reason for exclusion from non-XDR GNI definition: | | | | |
| Microbiologically XDR GNI | 2 | 6 | 2 | 10 |
| Colonization | 0 | 3 | 10 | 13 |
| No gram-negative isolated‡ | 5 | 18 | 15 | 38 |
| Mortality among reviewed cases:‖ | | | | |
| A. Mortality among all colistin cases with true XDR GNIs | 16/45 | 15/50 | 15/59 | 47/154 (30.5%) |
| B. Mortality among all comparator§ cases with true non-XDR GNIs | 9/57 | 15/70 | 7/67 | 31/194 (15.9%) |
| Tri-institutional XDR-attributable mortality (A minus B) | - | - | - | 14.6% |
| Chart review 2 | | | | |
| Sensitivity of colistin case definition among XDR GNI of the bloodstream | | | | |
| Total XDR GNI of the bloodstream | 26 | 28 | 70 | 124 |
| Total XDR GNI of the bloodstream meeting colistin case definition | 12 | 13 | 56 | 81 |
| % of XDR GNI of the bloodstream meeting colistin case definition | 46% | 46.4% | 80.0% | 65.3% |

*BJH*, Barnes Jewish Hospital; *GNI*, gram-negative infections; *GUH*, Georgetown University Hospital; *IV*, intravenous; *PPV*, positive predictive value; *UMMS*, University of Maryland Medical Center; *XDR*, extensively drug resistant.
*1 patient removed from analysis because of missing data in medical records.
†6 patients removed from analysis because of missing data in medical records.
‡Includes culture-negative and gram-positive growth in culture.
§Includes carbapenem and non-carbapenem comparators in chart review cohort.
‖All cases reviewed were analyzed (not just those matched pairs of colistin and comparator cases that displayed XDR and non-XDR GNI, respectively).

**Table 3**
Chart review 1: cases stratified by organism

| | Colistin cases n = 255 | Comparator cases* n = 255 |
|---|---|---|
| Non-lactose fermenter | 194 | 63 |
| Acinetobacter | 73 | 10 |
| Pseudomonas | 115 | 50 |
| Stenotrophomonas | 3 | 3 |
| Other (Achromobacter, Brevundimonas, Burkholderia) | 3 | 0 |
| Enterobacteriaceae | 47 | 117 |
| Klebsiella | 35 | 40 |
| Escherichia coli | 4 | 53 |
| Enterobacter | 3 | 12 |
| Citrobacter | 1 | 3 |
| Proteus | 3 | 4 |
| Other (Aeromonas, Edwardsiella, Providencia, Serratia) | 1 | 5 |
| Polymicrobial | 8 | 33 |
| Other (Bacteroides, Bordetella, Pasteurella) | 0 | 4 |
| No gram-negative isolated | 6 | 38 |

Note: At the chart review level, colistin and comparator cases were not matched on site of infection. All 255 cases included in each chart review were assessed and grouped based on the gram-negative organism that was isolated.
*Comparators at the chart review level includes carbapenem and non-carbapenem comparators.

*Staphylococcus aureus* infections will generate a lower attributable mortality than comparing the outcomes of patients with methicillin-resistant *S aureus* versus no infection. Similarly, use of 2 comparators representing therapy targeting different degrees of implied resistance generated different estimates of attributable mortality in our study. Carbapenem cases were excluded from the $\beta$-lactam comparator group analysis because carbapenem use variably enriches for specific resistance phenotypes such as extended-spectrum cephalosporin resistance (eg, secondary to extended-spectrum $\beta$-lactamase or Amp C expression). In our secondary analysis, propensity-matched carbapenem comparators had higher mortality rates and therefore generated lower attributable mortality estimates compared to $\beta$-lactam non-carbapenem-based comparators. This supports the notion that carbapenem cases capture a different risk group of GNIs than non-carbapenem, $\beta$-lactam comparators.

Important limitations require mention. We only evaluated XDR-attributable mortality among actively treated cases. Administrative data are subject to a variety of biases. Explicit diagnosis codes for sepsis have been previously shown to be poorly sensitive in capturing true cases.[35] In addition to GNI diagnosis codes, our unit of analysis also included individual antibiotic charges, reducing the risk of false-positive GNIs. We hypothesized that colistin cases represented XDR GNIs. However, chart review found that this assumption was only true two-thirds of the time with variable accuracy across hospitals, possibly because of differences in case mix, resistance patterns, and

antibiotic prescribing practices. Our tracer algorithm-based study design naturally portrays a simplification of reality. Most antibiotic-based studies that use electronic algorithms often encounter similar limitations,[36] however provide useful insights that inform practice and the design of future studies. Our administrative data algorithms lack the granularity found in clinical data. Although propensity scores are excellent tools to minimize confounding by indication, this technique cannot account for unknown or unmeasured confounding. Therefore, the extent to which differences in adequacy of source control and empiric therapy, baseline severity of acute illness, drug toxicity including antimicrobials as well as isolate taxa and virulence affect our estimates remains unknown.

About one-fourth of colistin cases were found to represent inhaled-only administrations, which varied considerably across the 3 hospitals reviewed. Cases that only received nebulized colistin displayed lower, but still substantial, crude mortality rates compared to those who received the drug intravenously. As such, the true proportion of such misclassifications in the overall study cohort and its impact on our attributable mortality estimates remains unknown. Notably, filtering out inhaled cases improved the positive predictive value of colistin cases for XDR GNIs. Our study calls attention to the need to identify and correct for administration route misclassification in studies that rely on administrative data. Billing codes for sepsis syndromes and site-of-infection are encounter specific (not date stamped) and may not necessarily represent the GNI episodes that we identified using antibiotic tracer algorithms. Coding for bacteremia has poor sensitivity, which may have been the reason for the relatively low prevalence of primary bacteremia cases in our cohort that precluded its inclusion as an analyzable site of infection.

## CONCLUSIONS

In a large cohort of patients coded for GNIs, those who received ≥4 days of intravenous colistin, or who died on therapy, demonstrated an excess mortality of 12.6% over those who similarly received, or died, while receiving non-carbapenem $\beta$-lactam agents with activity against similar gram-negative bacteria. This tracer antibiotic algorithm-based estimate of XDR-attributable mortality varied considerably by choice of comparator agents, site and onset of infection, and the presence or severity of sepsis. Accounting for these and other important modifiers are likely to generate truer, situation-specific estimates of the outcome burden attributable to antimicrobial resistance.

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