Epidemiology and outcomes of carbapenem resistance among patients with hospital-acquired and ventilator-associated pneumonia

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ABSTRACT

Background: Antimicrobial resistance increases the risk of exposure to inappropriate empiric treatment (IET), which adversely impacts hospital outcomes. Carbapenem resistance (CR) in particular is a growing concern in hospital-acquired (HAP) and ventilator-associated pneumonia (VAP). We developed a novel algorithm to identify HAP/VAP in administrative data and, using it, examined the epidemiology and outcomes of CR among Gram-negative (GN) pathogens in HAP/VAP.

Methods: We performed a retrospective cohort study within the Premier Research database (2009-2016) of 166 US hospitals. We included all hospitalized adult patients with a gram-negative organism in at least one respiratory culture, who fit our definition for HAP/VAP, and were treated with an antibiotic starting on the day of the index culture and continued for >3 days. CR was defined as any organism with an I or R in the susceptibility category to imipenem, meropenem, ertapenem, or doripenem.

Results: Among 8,969 patients with HAP/VAP, 1,059 (11.8%) were CR (10.5% HAP vs. 13.2% VAP, p<0.001). The median (IQR) hospital rate of CR was 9.8% (0%, 15.7%). Patients with CR were more likely female (41.4% vs. 33.2%, p<0.001) and medical (33.8% vs. 27.4%, p<0.001) than those with carbapenem-susceptible [CS] organisms. Patients with CR also had higher comorbidity burden than CS (median [IQR] Charlson Comorbidity Index 3 [1, 4] vs. 2 [1, 4], p<0.001). P. aeruginosa was the most common GN pathogen overall (24.9%) and among CS (23.5%) and second to S. maltophilia (44.0%) among CR (35.3 %). A. baumannii accounted for 11.8% of CR and 2.5% of CS (p<0.001). Patients with CR were more likely than CS to receive IET (25.8% vs. 10.0%, p<0.001). While the adjusted mortality did not differ (22.9% CR vs. 21.6% CS, p=0.223), CR was associated with an excess in length of stay (LOS) of 3.0 (95% CI 1.4, 4.6) days and costs of $8,921 (95% CI $3,864, $13,977).

Conclusions: Our novel algorithm identified pneumonia patients in administrative data at high risk for death, consistent with HAP/VAP. Among them, CR occurred in 12% of all cases and was associated with substantial excess in hospital LOS and costs.

BACKGROUND

- Nosocomial pneumonia (hospital-acquired [HAP] and ventilator-associated [VAP] pneumonias)
  - Common hospital-acquired infections
  - More likely than community-acquired to harbor a resistant pathogen (1)
    - Makes patients with HAP/VAP likely to receive inappropriate empiric treatment (IET)
- IET raises both the risk of hospital death and hospital costs (2-14)
  - Rising rates of antimicrobial resistance hobble clinicians' ability to choose appropriate empiric coverage
- Gram-negative pathogens common in HAP/VAP
  - *Pseudomonas aeruginosa* (PA) and *Acinetobacter baumannii* (AB): rising rates of carbapenem resistance (CR)
  - Enterobacteriaceae: increasingly frequent presence of ESBL and CR
  - Appropriate empiric treatment: opportunity to improve clinical and economic outcomes (15, 16)
- Challenge: no reliable rapid diagnostic strategy
  - Need probabilistic approaches to recognize likelihood of resistant pathogens

STUDY AIMS

- To derive an algorithm to identify HAP/VAP in an administrative data set
- To explore current epidemiology and outcomes of hospitalized patients with HAP/VAP due to PA, AB and Enterobacriaceae

METHODS

***Design*: multi-center retrospective cohort**

***Data source*: Premier Research database, years 2009-2016**

- 178 US institutions that submit microbiology data

***Population*: hospitalized patients with HAP/VAP**

Inclusion criteria:

- Adults (age ≥18 years), LOS ≥ 4 days, had a respiratory and/or blood culture positive for at least one gram-negative organism obtained on hospital day 3 or later for HAP, or on mechanical ventilation (MV) day 3 or later for VAP, AND
- Antibiotic treatment on the day index culture drawn and continued for ≥3 consecutive days
- HAP present if the hospitalization included pneumonia as a secondary and not as a principal or a present-on-admission (POA) ICD-9-CM code(s) 481-486, 997.31

Exclusion criteria:

- Transferred from another acute care facility
- HAP/VAP episode a repeat bout during the index hospitalization, as evidenced by a ≥3-day hiatus in antimicrobial regimen administration and a new positive culture.
- Complicated urinary tract infections (algorithm available upon request)
- Complicated intra-abdominal infections (algorithm available upon request)

***Main exposure*: CR among gram-negative pathogens associated with HAP/VAP**

Microbiology and antimicrobial treatment variables and definitions

- Included if had at least one respiratory or blood organisms below:
  - *Pseudomonas aeruginosa*
  - *Acinetobacter bamannii*
  - *Stenotrophomonas maltophilia* (assumed 100% CR)
  - Enterobacteriaceae
    - *Escherishia coli*
    - *Klebsiella pneumoniae*
    - *Klebsiella oxytoca*
    - *Enterobacter cloacae*
    - *Enterobacter aerogenes*
    - *Proteus mirabilis*
    - *Proteus spp.*
    - *Serratia marcescens*
    - *Citrobacter freundii*
    - *Morganella morganii*
    - *Providencia spp.*
- First detection of a CR organism served as the index culture
  - If no CR organism detected, then first culture growing out one of the organisms of interest served as the index culture
- Empiric antibiotic treatment appropriate if patients received coverage that included the corresponding organism within two days of the culture being obtained
  - All other regimens considered IET

Outcomes

- Primary outcome: hospital mortality
- Secondary endpoints
  - Hospital LOS (both total and CR infection-related)
  - Hospital costs (both total and CR infection-attributable)
  - 30-day readmissio

Statistical analyses

- Descriptive statistics comparing CR with non-CR groups
- Logistic regression modeling to examine association of CR with mortality and 30-day readmissions
- Generalized linear modeling to examine associations of CR with costs and LOS
- Statistical significance set at alpha = 0.05

RESULTS

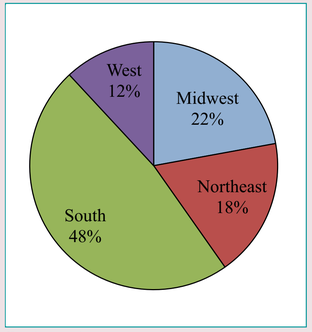
Total cohort N = 8,969

- HAP (50.8%) and VAP (49.2%)
- 1,059 (11.8%) had a CR organism
  - 10.5% in HAP vs. 13.2% in VAP, p<0.001
- Median (IQR) hospital rate of CR 9.8% (0%, 15.7%)

Geographic distribution:

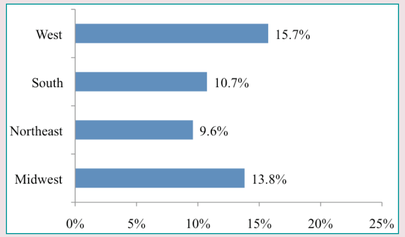
- Plurality of the cohort from the South (47.8%) (Figure 1a)
- Highest CR rate in Western census region (15.7%) (Figure 1b)

Figure 1a Geographic distribution of the cohort



CR = carbapenem resistance

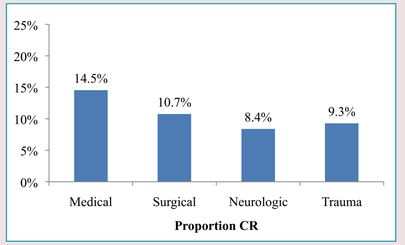
Figure 1b Proportion CR by census region



Patient type

- Majority (56.4%) cared for on a surgical service
- Medical patients highest (14.5%) and neurologic the lowest (8.4%) prevalence of CR (p<0.001) (Figure 2)

Figure 2 Proportion CR by patient type



CR more likely than CS among

- Females (41.4% vs. 33.2%, p<0.001)
- Those admitted from an extended care facility (ECF, 7.2% vs. 4.6%, p=0.014)

CR higher comorbidity burden than CS

- Median [IQR] Charlson Comorbidity Index (3 [1, 4] vs. 2 [1, 4], p<0.001).

Microbiology and empiric treatment (Table 1)

TABLE 1 Organisms and empiric treatment

	CR	*%*	*CS*	*%*	*P-value*
	N =1059		*N =7910*		
Organism					
Klebsiella pneumoniae	95	8.97%	1742	22.02%	<0.001
Proteus mirabilis	27	2.55%	321	4.06%	0.017
Escherichia coli	37	3.49%	1544	19.52%	<0.001
Enterobacter cloacae	65	6.14%	708	8.95%	0.002
Providencia spp	3	0.28%	23	0.29%	1.000
Serratia marcescens	32	3.02%	690	8.72%	<0.001
Morganella morganii	2	0.19%	88	1.11%	0.005
Enterobacter aerogenes	22	2.08%	467	5.90%	<0.001
Proteus spp.	27	2.55%	334	4.22%	0.009
Citrobacter freundii	6	0.57%	100	1.26%	0.049
Klebsiella oxytoca	17	1.61%	419	5.30%	<0.001
Enterobacter other	28	2.64%	549	6.94%	<0.001
Citrobacter other	4	0.38%	163	2.06%	<0.001
Serratia other	1	0.09%	32	0.40%	0.117
Klebsiella other	0	0.00%	31	0.39%	0.044
PA	374	35.32%	1859	23.50%	<0.001
AB	125	11.80%	198	2.50%	<0.001
Stenotrophomonas maltophilia	466	44.00%	0	0.00%	<0.001
Empiric antibiotic (by day 2 from index culture)					
Antipseudomonal penicillins with beta-lactamase inhibitor	471	44.48%	4038	51.05%	<0.001
Extended spectrum cephalosporins	257	24.27%	2342	29.61%	<0.001
Antipseudomonal floroquinolones	307	28.99%	2125	26.86%	0.144
Antipseudomonal carbapenems	294	27.76%	1210	15.30%	<0.001
Aminoglycosides	72	6.80%	271	3.43%	<0.001
Penicillins with beta-lactamase inhibitors	31	2.93%	433	5.47%	<0.001
Tetracyclines	25	2.36%	104	1.31%	0.007
Folate pathway inhibitors	57	5.38%	96	1.21%	<0.001
Polymyxins	10	0.94%	17	0.21%	<0.001
Antipseudomonal cephalosporins	203	19.17%	1682	21.26%	0.116
Aztreonam	42	3.97%	275	3.48%	0.418
Fosfomycin	0	0.00%	0	0.00%	1.000
Tygecycline	68	6.42%	135	1.71%	<0.001
3rd generation cephalosporin	94	8.88%	1133	14.32%	<0.001

CR = carbapenem resistant; CS = carbapenem susceptible; PA = *Pseudomonas aeruginosa*; AB = *Acinetobacter baumannii*

- *P. aeruginosa* most common GN pathogen overall (24.9%)
  - Among CS (23.5%) and second to *S. maltophilia* (44.0%) among CR (35.3 %)
- *A. baumannii* accounted for 11.8% of CR and 2.5% of CS (p<0.001)
- Antipseudomonal penicillins with beta-lactamase inhibitor most common antimicrobial class in both CR and CS groups
- Antipseudomonal carbapenems administered to the CR group at nearly twice the rate in CS (27.8% vs. 15.3%, p<0.001)
- Patients with CR more likely than CS to receive IET (25.8% vs. 10.0%, p<0.001)

Unadjusted outcomes

- Mortality 21.7% (CR 25.5% vs. CS 21.2%, p = 0.002)
- 30-day readmission among survivors 23.7% (CR 24.0% vs. CS 23.7%, p = 0.867)

Adjusted outcomes shown in Table 2

- Neither mortality nor 30-day readmission risk differed between the two groups
- Relative to CS, CR associated with excess in
  - LOS of 3.0 days
  - Costs of nearly $9,000

TABLE 2 Adjusted outcomes (CR vs. CS)

	Point estimate	*95% CI*
Mortality	OR 1.09	0.95, 1.27
30-day readmissio n	OR 1.01	0.84, 1.23
Excess costs, $	$8,921	$3,864, $13,977
Excess LOS, days	3.0	1.4, 4.6

CR = carbapenem resistant; CS = carbapenem susceptible; OR = odds ratio; CI = confidence interval; LOS = length of stay

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STRENGTHS AND LIMITATIONS

- Generalizability
  - Large multicenter cohort representative of US institutions
    - Broadly generalizable
- Selection bias
  - Reduced by setting a priori enrollment criteria and definitions for exposures and outcomes
- Misclassification
  - Our HAP/VAP algorithm designed to maximize specificity
  - Outcomes of interest minimally susceptible to misclassification
  - At least in some cases positive cultures might have represented colonization, not infection
    - Such misclassification would dilute effects of CR on the outcomes
- Confounding
  - Attempted to eliminate through regression analyses using a large number of potentially confounding variables
  - Possibility of residual confounding remains

CONCLUSIONS

- Novel algorithm identified pneumonia patients in administrative data at high risk for death (over 20%), consistent with HAP/VAP
  - Microbiology supports this
- Among them, high prevalence of CR (12%)
- CR associated with substantial excess in hospital LOS (3 days) and costs ($9,000)

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