Journal of Hospital Infection 102 (2019) 37–44

Available online at www.sciencedirect.com

Journal of Hospital Infection

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

Attributable clinical and economic burden of carbapenem-non-susceptible Gram-negative infections in patients hospitalized with complicated urinary tract infections

Y.P. Tabak [a], A.H. Sung [b], G. Ye [a], L. Vankeepuram [a], V. Gupta [a], E. McCann [b,*]

[a] Becton, Dickinson and Company, Franklin Lakes, NJ, USA
[b] Merck & Co., Inc., Kenilworth, NJ, USA

ARTICLE INFO

Article history:
Received 13 July 2018
Accepted 23 November 2018
Available online 29 November 2018

Keywords:
Gram-negative
Complicated urinary tract infection
Mortality
Length of stay
30-Day re-admission
Hospital cost

SUMMARY

Background: Gram-negative complicated urinary tract infections (cUTIs) can have serious consequences for patients and hospitals.

Aim: To examine the clinical and economic burden attributable to Gram-negative carbapenem-non-susceptible (C-NS; resistant/intermediate) infections compared with carbapenem-susceptible (C-S) infections in 78 US hospitals.

Methods: All non-duplicate C-NS and C-S urine source isolates were analysed. A subset had principal diagnosis ICD-9-CM codes denoting cUTI. Collection time (<3 vs ≥3 days after admission) determined isolate classification as community or hospital onset. Mortality, 30-day re-admissions, length of stay (LOS), hospital cost and net gain/loss in US dollars were determined for C-NS and C-S cases, with the C-NS-attributable burden estimated through propensity score matching. Three subgroups with adequate patient numbers were analysed: cUTI principal diagnosis, community onset; other principal diagnosis, community onset; and other principal diagnosis, hospital onset.

Findings: The C-NS-attributable mortality risk was significantly higher (58%) for the other principal diagnosis, hospital-onset subgroup alone (odds ratio 1.58, 95% confidence interval 1.14–2.20; $P < 0.01$). The C-NS-attributable risk for 30-day re-admission ranged from 29% to 55% (all $P < 0.05$). The average attributable economic impact of C-NS was 1.1–3.9 additional days LOS (all $P < 0.05$), US$1512–10,403 additional total cost (all $P < 0.001$) and US$1582–11,848 net loss (all $P < 0.01$); overall burden and C-NS-attributable burden were greatest in the other principal diagnosis, hospital-onset subgroup.

Conclusion: Greater clinical and economic burden was observed in propensity-score-matched patients with C-NS infections compared with C-S infections, regardless of whether cUTI was the principal diagnosis, and this burden was most severe in hospital-onset infections.

* Corresponding author. Address: Center for Observational and Real-World Evidence, Merck & Co., Inc., 2000 Galloping Hill Road, Kenilworth, NJ 07033, USA. Tel.: +1 732 594 7472.
E-mail address: eilish.mccann@merck.com (E. McCann).

https://doi.org/10.1016/j.jhin.2018.11.018
0195-6701/

Introduction

Urinary tract infections (UTIs) are among the most common healthcare-associated infections in the USA, with the majority of UTIs linked to the use of an indwelling catheter [1,2]. Complicated UTIs (cUTIs) are distinguished from UTIs based on the presence of structural or functional abnormalities of the urinary tract, or clinical manifestations such as pyelonephritis [3,4]. Gram-negative bacteria such as *Escherichia coli*, *Klebsiella* spp., *Pseudomonas* spp., *Enterobacter cloacae* and *Proteus mirabilis* are most commonly implicated in cUTIs [4–6]. Antimicrobial surveillance programmes indicate an increase in Gram-negative bacterial strains that are resistant to multiple antimicrobial agents, including aminoglycosides, cephalosporins, carbapenems, fluoroquinolones and penicillins, with adverse consequences associated with the loss of these treatment options [7–11].

The Centers for Disease Control and Prevention has declared the rise of carbapenem-resistant Enterobacteriaceae (CRE) to be an urgent public health threat; similarly, the World Health Organization identified these pathogens as a critical priority to address and for which new antibiotics are needed [12,13]. In a recent retrospective cohort study, an Enterobacteriaceae was the infecting organism in approximately 17% of patients hospitalized for UTI, pneumonia or sepsis [14]. The majority (54%) of Enterobacteriaceae infections occurred in patients with UTI, and 2.9% of these infections were resistant to carbapenem antibiotics [14]. In another retrospective study of hospitalized patients with cUTI, antimicrobial resistance was also detected in *P. aeruginosa* and *Acinetobacter baumannii*, with observed carbapenem resistance rates of 11.7% and 42.0%, respectively [15].

Recent studies have indicated that carbapenem-non-susceptible (C-NS) Gram-negative pathogens can be associated with prolonged hospital length of stay (LOS), increased costs and increased mortality compared with carbapenem-susceptible (C-S) bacteria in various infection types [5,15,16]. This multi-centre study compared C-NS and C-S Gram-negative urinary-tract-sourced isolates from a large sample of >40 000 isolates from 78 US hospitals, and assessed the C-NS-attributable clinical and economic burden according to principal diagnosis and infection-onset period.

Methods

Data source

This study used electronically captured and de-identified patient-level microbiological and administrative data from the BD Insights Research Database (Becton, Dickinson and Company, Franklin Lakes, NJ, USA) [17–19]. The data set included microbiological data (specimen collection time, source, and culture and susceptibility results), hospital location data and postdischarge administrative data (principal diagnosis, discharge disposition, payer, hospital LOS, total cost and payment received). Financial data were captured in the hospital's financial system. The net gain/loss was defined as the total payment received minus total cost, with a negative value indicating net loss.

Study population

The study population consisted of adult inpatients at 78 US acute care hospitals in the BD Insights Research Database from 1st January 2013 to 30th September 2015. Isolates obtained from patients were included if they were tested for carbapenem susceptibility and if they were non-duplicate (the first isolate obtained from a patient per 30-day period), Gram-negative and from a urinary tract source. The 30-day non-duplicate criterion is the same definition used by the Centers for Disease Control and Prevention National Healthcare Safety Network [20]. The study protocol was approved by the New England Institutional Review Board (Wellesley, MA, USA).

Definitions

Carbapenem-non-susceptible vs carbapenem-susceptible cases

Non-duplicate, Gram-negative isolates from a urinary tract source that tested as 'resistant' or 'intermediate' to imipenem or meropenem for *P. aeruginosa* and *A. baumannii* (as ertapenem is intrinsically not active against these pathogens), or 'resistant' or 'intermediate' to ertapenem, imipenem or meropenem for Enterobacteriaceae (*E. coli, Klebsiella pneumoniae, P. mirabilis, E. cloacae, Enterobacter aerogenes, Serratia marcescens, Citrobacter freundii, Morganella morganii*) were classified as C-NS; otherwise, isolates were classified as C-S. 'Resistant' and 'intermediate' were based on the hospital's interpretation of susceptibility test results reported in the clinical laboratory information system.

Principal diagnosis

All patients included in the analysis had isolates obtained from a urine source. A principal diagnosis of International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes that denoted cUTI (when viewed in conjunction with a positive urine culture) was identified in a subset of patients (see Table A1, online supplementary material).

Infection-onset period

Isolates were classified as community onset or hospital onset based on the specimen collection time (<3 vs ≥3 days after admission, respectively).

Statistical analysis

Propensity score matching

Using C-NS and C-S as a binary variable, propensity score models were developed within four subgroups, thereby permitting adjustment of potential confounders. Subgroups were based on: (1) principal diagnosis (cUTI vs other principal diagnosis) and (2) infection onset (community onset vs hospital onset). Subgroups were as follows: Group 1, cUTI principal diagnosis, community onset; Group 2, cUTI principal diagnosis, hospital onset; Group 3, other principal diagnosis, community onset; and Group 4, other principal diagnosis, hospital onset.

The confounding factors included in the propensity score models were age, sex, intensive care unit (ICU) admission status, exposure risk [defined as number of days from admission to onset of infections (for hospital-onset subgroups only)], type of Gram-negative organism(s), principal-diagnosis-based

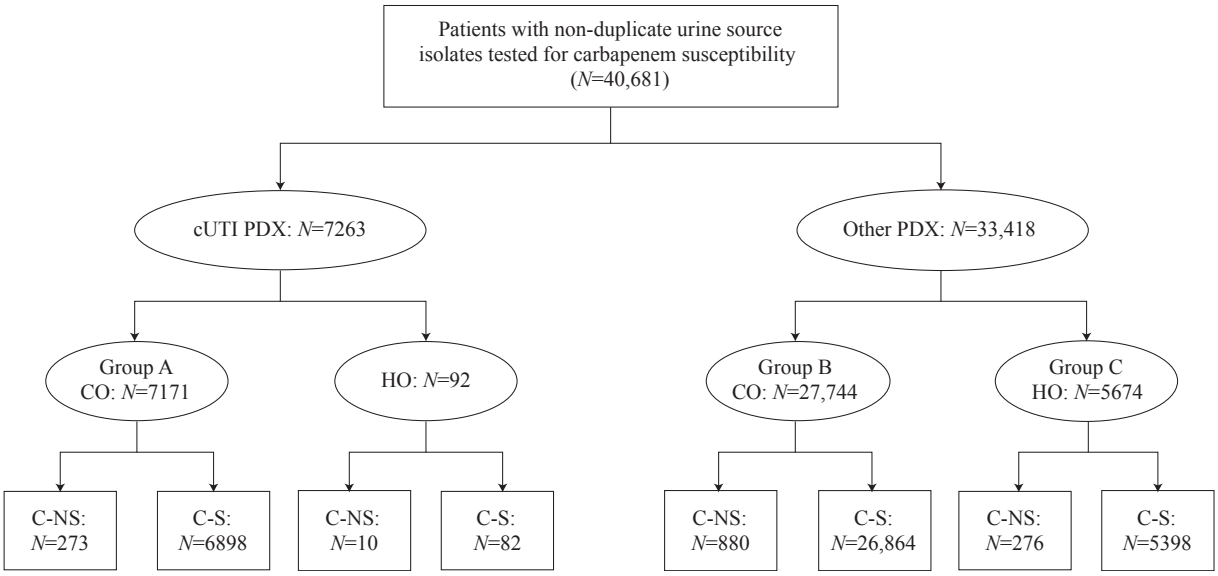

Figure 1. Study population case tree. C-NS, carbapenem non-susceptible; C-S, carbapenem susceptible; CO, community onset; cUTI, complicated urinary tract infection; HO, hospital onset; PDX, principal diagnosis.

disease groups [Clinical Classification Software (CCS); for other principal diagnosis subgroups only] [21], number of hospital admissions in the 90 days prior to the index admission, payer and hospital characteristics [teaching status, size (number of beds) and geographical location]. An aggregated measure of clinical severity using a published Acute Laboratory Risk of Mortality Score (ALaRMS) was included [22]. ALaRMS assesses the probability of in-hospital mortality based on patient demographic data and numeric values from 23 laboratory tests. The laboratory results included arterial blood gas (partial pressure of carbon dioxide, partial pressure of oxygen and pH value), cardiac markers (brain natriuretic peptide, creatine phosphokinase-MB, pro-brain natriuretic peptide, and troponin I or troponin T), haematology and coagulation parameters (bands, haemoglobin, partial thromboplastin time, prothrombin time international normalized ratio, platelets and white blood cell count), and serum chemistry (albumin, aspartate transaminase, alkaline phosphatase, blood urea nitrogen, calcium, creatinine, glucose, potassium, sodium and total bilirubin).

Using the propensity score models described above, C-NS cases were matched with C-S cases at a 1:5 ratio within each subgroup using the Greedy nearest-neighbour matching method. Within each subgroup, outcomes were compared for the matched C-NS and C-S cases.

Estimating attributable clinical and economic burden

Attributable burdens were estimated using the generalized linear mixed model (GLMM) method on the propensity-score-matched C-NS and C-S cases within each subgroup. The GLMM approach accounts for skewed distributions and variations among hospitals. Categorical outcomes (e.g. mortality, readmission) were modelled using a random intercept logistic regression model, and continuous outcomes (e.g. LOS, total cost and net gain/loss, defined as total payment received minus total cost) were modelled using GLMM with 'hospital' as the random effect. A gamma distribution with a log link function via the ILINK option in Statistical Analysis Software Version 9.4 (SAS Institute, Cary, NC, USA) GLIMMIX procedure was used. $P < 0.05$ was considered to indicate statistical significance.

Results

Patient characteristics

Among 40,681 admissions with non-duplicate, Gram-negative isolates from a urinary tract source that were tested for carbapenem susceptibility, 7263 (17.9%) had a principal diagnosis of cUTI [Group 1: 7171 (17.6%) community onset; Group 2: 92 (0.2%) hospital onset] and 33,418 (82.1%) had another diagnosis as the principal diagnosis [Group 3: 27,744 (68.2%) community onset; Group 4: 5674 (13.9%) hospital onset; Figure 1]. Due to the small number of cUTI principal diagnosis, hospital-onset cases ($N = 92$, 10 of which were C-NS), no further analysis was conducted for this subgroup. The remaining subgroups with sufficient numbers were reordered and presented as Group A: cUTI principal diagnosis, community onset; Group B: other principal diagnosis, community onset; and Group C: other principal diagnosis, hospital onset.

Table I presents the baseline characteristics after propensity score matching for C-NS and C-S cases in each subgroup. After 1:5 matching, the numbers in each subgroup were Group A: C-NS 273, C-S 1365; Group B: C-NS 880, C-S 4400; and Group C: C-NS 276, C-S 1380. The potential confounding factors were mostly balanced within each of the three subgroups (see Table I and pre- vs post-matching comparison in Table A2, online supplementary material). The majority of patients in the overall matched cohort were aged ≥65 years, had an ALaRMS value in the third or fourth quartile, and were recipients of Medicare. In Group A, approximately 40% of infections were catheter associated; for Groups B and C, 'infectious and parasitic diseases' and 'all other CCS' were the most frequently observed CCS disease categories, respectively. Most patients were not admitted to the ICU during their hospitalization, but a higher proportion of ICU admissions was observed in Group C

Table I
Patient characteristics after 1–5 propensity score matching

Variables, *N* (%)	Group A: cUTI PDX, CO		Group B: Other PDX, CO		Group C: Other PDX, HO	
	C-NS (*N* = 273)	C-S (*N* = 1365)	C-NS (*N* = 880)	C-S (*N* = 4400)	C-NS (*N* = 276)	C-S (*N* = 1380)
Sex						
Female	136 (49.8)	688 (50.4)	463 (52.6)	2655 (60.3)	142 (51.4)	865 (62.7)
Male	137 (50.2)	677 (49.6)	417 (47.4)	1745 (39.7)	134 (48.6)	515 (37.3)
Age group (years)						
18–34	15 (5.5)	65 (4.8)	30 (3.4)	152 (3.5)	18 (6.5)	73 (5.3)
35–44	18 (6.6)	82 (6.0)	42 (4.8)	180 (4.1)	15 (5.4)	60 (4.3)
45–54	27 (9.9)	124 (9.1)	61 (6.9)	292 (6.6)	30 (10.9)	122 (8.8)
55–64	48 (17.6)	196 (14.4)	143 (16.3)	664 (15.1)	53 (19.2)	244 (17.7)
65–74	35 (12.8)	233 (17.1)	211 (24.0)	1053 (23.9)	65 (23.6)	361 (26.2)
75–84	71 (26.0)	350 (25.6)	213 (24.2)	1167 (26.5)	62 (22.5)	347 (25.1)
≥85	59 (21.6)	315 (23.1)	180 (20.5)	892 (20.3)	33 (12.0)	173 (12.5)
Payer						
Medicare	178 (65.2)	928 (68.0)	636 (72.3)	3235 (73.5)	179 (64.9)	910 (65.9)
Medicaid	18 (6.6)	72 (5.3)	62 (7.0)	221 (5.0)	23 (8.3)	79 (5.7)
Private	60 (22.0)	279 (20.4)	150 (17.0)	784 (17.8)	63 (22.8)	339 (24.6)
All other	17 (6.2)	86 (6.3)	32 (3.6)	160 (3.6)	11 (4.0)	52 (3.8)
ALaRMS[a]						
Missing	2 (0.7)	4 (0.3)	23 (2.6)	96 (2.2)	23 (8.3)	106 (7.7)
First quartile	57 (20.9)	284 (20.8)	133 (15.1)	720 (16.4)	58 (21.0)	306 (22.2)
Second quartile	55 (20.1)	282 (20.7)	192 (21.8)	904 (20.5)	53 (19.2)	270 (19.6)
Third quartile	68 (24.9)	338 (24.8)	199 (22.6)	1092 (24.8)	54 (19.6)	314 (22.8)
Fourth quartile	91 (33.3)	457 (33.5)	333 (37.8)	1588 (36.1)	88 (31.9)	384 (27.8)
Number of hospital admissions in the 90 days prior to index hospitalization						
0	146 (53.5)	855 (62.6)	515 (58.5)	2846 (64.7)	181 (65.6)	1020 (73.9)
1	73 (26.7)	337 (24.7)	214 (24.3)	976 (22.2)	59 (21.4)	242 (17.5)
>1	54 (19.8)	173 (12.7)	151 (17.2)	578 (13.1)	36 (13.0)	118 (8.6)
Intensive care unit admission status						
No	256 (93.8)	1336 (97.9)	780 (88.6)	4077 (92.7)	229 (83.0)	1188 (86.1)
Yes	17 (6.2)	29 (2.1)	100 (11.4)	323 (7.3)	47 (17.0)	192 (13.9)
Exposure risk (number of days from admission to onset of infections)						
First quartile	-	-	-	-	74 (26.8)	369 (26.7)
Second quartile	-	-	-	-	33 (12.0)	215 (15.6)
Third quartile	-	-	-	-	53 (19.2)	279 (20.2)
Fourth quartile	-	-	-	-	116 (42.0)	517 (37.5)
Type of Gram-negative organism						
Escherichia coli	10 (3.7)	325 (23.8)	36 (4.1)	1110 (25.2)	15 (5.4)	386 (28.0)
Pseudomonas aeruginosa	112 (41.0)	285 (20.9)	322 (36.6)	704 (16.0)	108 (39.1)	238 (17.2)
Polymicrobial	46 (16.8)	187 (13.7)	154 (17.5)	501 (11.4)	40 (14.5)	146 (10.6)
Other Gram-negative	105 (38.5)	568 (41.6)	368 (41.8)	2085 (47.4)	113 (40.9)	610 (44.2)
PDX-based CCS disease category[b]						
Catheter-associated UTI	109 (39.9)	541 (39.6)	-	-	-	-
Other cUTI	164 (60.1)	824 (60.4)	-	-	-	-
Diseases of the genitourinary system	-	-	45 (5.1)	243 (5.5)	12 (4.3)	40 (2.9)
Injury and poisoning	-	-	98 (11.1)	419 (9.5)	35 (12.7)	174 (12.6)
Diseases of the circulatory system	-	-	92 (10.5)	520 (11.8)	44 (15.9)	306 (22.2)
Diseases of the digestive system	-	-	57 (6.5)	308 (7.0)	33 (12.0)	138 (10.0)
Diseases of the respiratory system	-	-	71 (8.1)	340 (7.7)	20 (7.2)	62 (4.5)
Endocrine, nutritional and metabolic diseases and immunity disorders	-	-	35 (4.0)	152 (3.5)	7 (2.5)	23 (1.7)
Neoplasms	-	-	21 (2.4)	78 (1.8)	15 (5.4)	80 (5.8)
Infectious and parasitic diseases	-	-	280 (31.8)	1382 (31.4)	24 (8.7)	88 (6.4)
All other CCS	-	-	181 (20.6)	958 (21.8)	86 (31.2)	469 (34.0)
Hospital teaching status						
Non-teaching	209 (76.6)	1122 (82.2)	653 (74.2)	3460 (78.6)	186 (67.4)	966 (70.0)
Teaching	64 (23.4)	243 (17.8)	227 (25.8)	940 (21.4)	90 (32.6)	414 (30.0)

Table I (*continued*)

Variables, *N* (%)	Group A: cUTI PDX, CO		Group B: Other PDX, CO		Group C: Other PDX, HO	
	C-NS (*N* = 273)	C-S (*N* = 1365)	C-NS (*N* = 880)	C-S (*N* = 4400)	C-NS (*N* = 276)	C-S (*N* = 1380)
Hospital size (number of beds)						
≤300	96 (35.2)	495 (36.3)	299 (34.0)	1562 (35.5)	61 (22.1)	369 (26.7)
>300	177 (64.8)	870 (63.7)	581 (66.0)	2838 (64.5)	215 (77.9)	1011 (73.3)
Geographical location (region)						
Midwest	77 (28.2)	379 (27.8)	228 (25.9)	1145 (26.0)	57 (20.7)	277 (20.1)
Northeast	7 (2.6)	14 (1.0)	41 (4.7)	57 (1.3)	5 (1.8)	12 (0.9)
South	169 (61.9)	881 (64.5)	527 (59.9)	2912 (66.2)	195 (70.7)	1037 (75.1)
West	20 (7.3)	91 (6.7)	84 (9.5)	286 (6.5)	19 (6.9)	54 (3.9)

ALaRMS, Acute Laboratory Risk for Mortality Score; C-NS, carbapenem non-susceptible; C-S, carbapenem susceptible; CCS, Clinical Classification Software; CO, community onset; cUTI, complicated urinary tract infection; HO, hospital onset; PDX, principal diagnosis; UTI, urinary tract infection.
[a] ALaRMS quartile cut-off was based on the distribution within each of the three subgroups before propensity score matching.
[b] As determined by CCS.

than in Groups A or B (13.9% for C-S, 17.0% for C-NS). For C-NS infections, *P. aeruginosa* and 'other Gram-negative' pathogens accounted for most of the infections (ranging from 36.6% to 41.0% and from 38.5% to 41.8%, respectively); for C-S infections, 'other Gram-negative' pathogens accounted for a similarly high proportion, although *P. aeruginosa* was replaced by *E. coli* as the most common individual pathogen (23.8–28.0%).

Propensity-score-matched results

In the propensity-score-matched C-NS and C-S cohorts, mortality rates ranged from 1.2% to 6.0% for all C-S cases, and from 2.2% to 9.1% for all C-NS cases (Figure 2A). The highest mortality rate for C-NS cases was observed in Group C (other principal diagnosis, hospital-onset subgroup). The C-NS-attributable mortality risk was significantly higher in this subgroup alone [C-NS: 9.1% vs C-S: 5.3%; odds ratio (OR) 1.58, 95% confidence interval (CI) 1.14–2.20; $P < 0.01$]. Mortality was also higher for C-NS cases compared with C-S cases in Group A (C-NS: 2.2% vs C-S: 1.2%), although this was not statistically significant.

Thirty-day re-admission rates ranged from 16.5% to 24.0% for C-S cases and from 23.3% to 28.3% for C-NS cases, with the highest rates observed in Group C (C-NS: 28.3% vs C-S: 24.0%; Figure 2B). Re-admission rates were higher for C-NS cases compared with C-S cases in each subgroup, and the C-NS-attributable risk for 30-day re-admission was significant for all three subgroups, with ORs of 1.55 (95% CI 1.11–2.16), 1.36 (95% CI 1.11–1.68) and 1.29 (95% CI 1.04–1.61) for Groups A, B and C, respectively (all $P < 0.05$).

C-NS cases had significantly longer hospital LOS compared with C-S cases across all three subgroups (LOS ranged from 6.0 days to 20.5 days for C-S cases, and from 7.2 days to 24.4 days for C-NS cases), with the highest LOS observed in Group C (C-NS: 24.4 days vs C-S: 20.5 days; Figure 2C). The C-NS-attributable excess LOS ranged from 1.1 days to 3.9 days (all $P < 0.05$). Similar to LOS, total costs were greater for C-NS cases compared with C-S cases in all three subgroups, with the highest total cost observed in Group C (C-NS: US$51,024 vs C-S: US$40,621; Figure 3A). The attributable cost burden per case ranged from US$1512 to US$10,403 (all $P < 0.001$). The attributable net loss per case ranged from US$1582 to US$11,848 (all $P < 0.01$; Figure 3B).

Discussion

For the primary comparison of C-NS vs C-S, C-NS cases were found to be associated with significantly higher 30-day re-admission rates, LOS, total cost and total net loss compared with C-S cases, irrespective of whether cUTI was the principal diagnosis or not, or in the case of other principal diagnosis cases, whether the infection was community onset or hospital onset. These findings appear to be consistent with previously published studies that reported poorer patient outcomes for C-NS infections [23–25]. Strengths of this study include the large sample of urinary tract isolates (>40,000) that were considered in the analysis, the large number of hospitals from which data were collected, and the capture of pathogen and infection-onset information. This study considered patient demographics, clinical severity (as measured by objective laboratory test results), underlying clinical conditions, comorbidities and time prior to the onset of infections for hospital-onset cUTI cases, with all of these factors being included in the propensity-score-matching approach. These potential confounders are known risk factors, and their inclusion in the propensity score matching enhances the clinical validity and robustness of the study. Furthermore, this study compared outcomes in propensity-score-matched C-NS cases vs C-S cases within each subgroup of patients to ensure a fair comparison across all subgroups.

The 30-day re-admission rates for C-NS and C-S cUTIs observed in the present analysis may point to the difficulty of treating cUTIs to a successful outcome. Indeed, a multi-centre, retrospective study by Alexander *et al.* found that 25.3% of patients with cUTI or acute pyelonephritis due to CRE did not meet the definition of a clinical cure after treatment, and 38.7% did not have complete bacterial eradication from the site of infection [5].

The mean LOS observed in this study was similar to the LOS reported in other retrospective studies (8.2 days for C-NS cUTIs and 19.5 days for C-NS *K. pneumoniae* infections of any type) [5,26]. The far-greater LOS in hospital-onset cases (Group C) compared with community-onset cases (Groups A and B) translated to substantially increased total adjusted estimated costs, highlighting the substantial investment of healthcare resources that is required for patients with hospital-onset infections. Not surprisingly, operating losses were also substantially higher for hospital-onset cases. The poorer outcomes observed for hospital-onset cases (compared with community-onset cases), regardless of carbapenem susceptibility, underscore the need

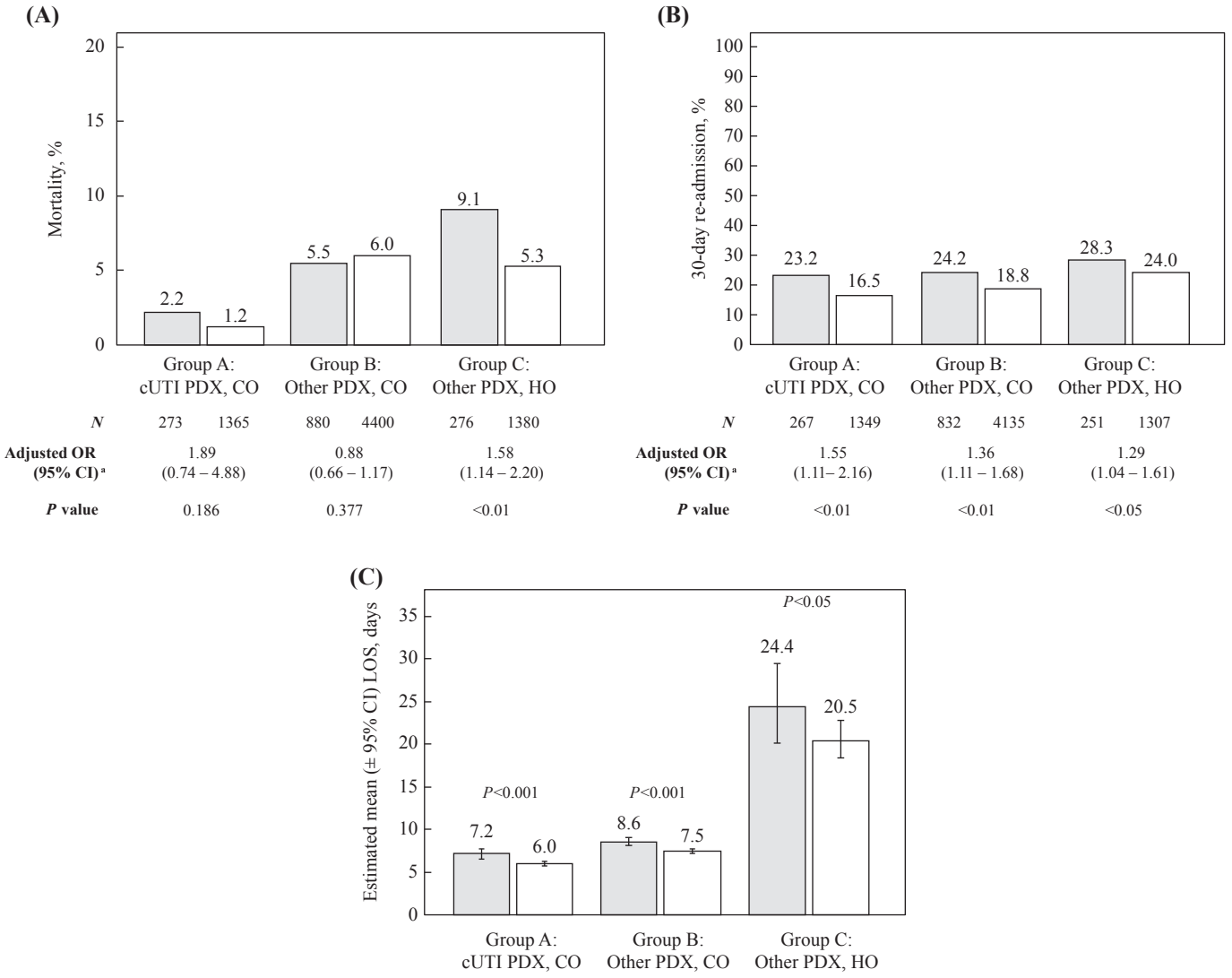

Figure 2. Outcomes by propensity-score-matched patient cohorts [carbapenem-non-susceptible (C-NS; shaded bars) cases vs carbapenem-susceptible (C-S; open bars) cases]. (A) Mortality. (B) 30-day re-admission. 30-day re-admission was only measured in patients who were alive at discharge. (C) Length of stay (LOS). [a]Odds ratios (ORs) were not calculated for LOS. CI, confidence interval; CO, community onset; cUTI, complicated urinary tract infection; HO, hospital onset; PDX, principal diagnosis.

for more aggressive prevention of hospital-onset infections in acute care settings. Direct comparisons of costs in the present study with costs in other retrospective studies are difficult due to limited data in this specific population. One retrospective study reported a total cost of US$33,400 for patients hospitalized with community-onset UTIs due to CRE [14]. A second retrospective study which included any cUTI, whether resistant to carbapenems or not, observed a mean cost of US$38,422 per index hospitalization or emergency department outpatient treatment [27]. These findings from the literature fall within the range observed in the current analysis.

The mortality rates observed in this study were at the lower end of what has been reported in recent literature for UTIs or cUTIs due to CRE or carbapenem-resistant *K. pneumoniae* (7–17.3%) [5,14,28,29]. For this critical endpoint, C-NS-attributable burden was only significant in patients with hospital-onset infections (Group C: other principal diagnosis, hospital onset). In this subgroup, patients did not have a principal diagnosis of cUTI, and therefore it is possible that their mortality risk might be influenced by their primary underlying diseases of other vital organs or systems (insufficient numbers prevented assessment of the planned cUTI principal diagnosis, hospital-onset subgroup).

The primary limitation of this study is its retrospective observational nature, which is inherently prone to bias and confounding; however, propensity score matching was used to ensure that potential confounding factors were sufficiently balanced at baseline to minimize the risk of bias. Propensity score matching is not without its own limitations, which include the inability to balance for unmeasured confounders that could potentially impact outcomes. A further limitation is the use of ICD-9-CM diagnostic coding to identify cUTI cases. ICD-9-CM principal diagnosis codes that are assigned for billing and business purposes may not accurately reflect the true clinical picture, and it is not possible to identify the secondary diagnoses assigned to patients using this data set; thus, some

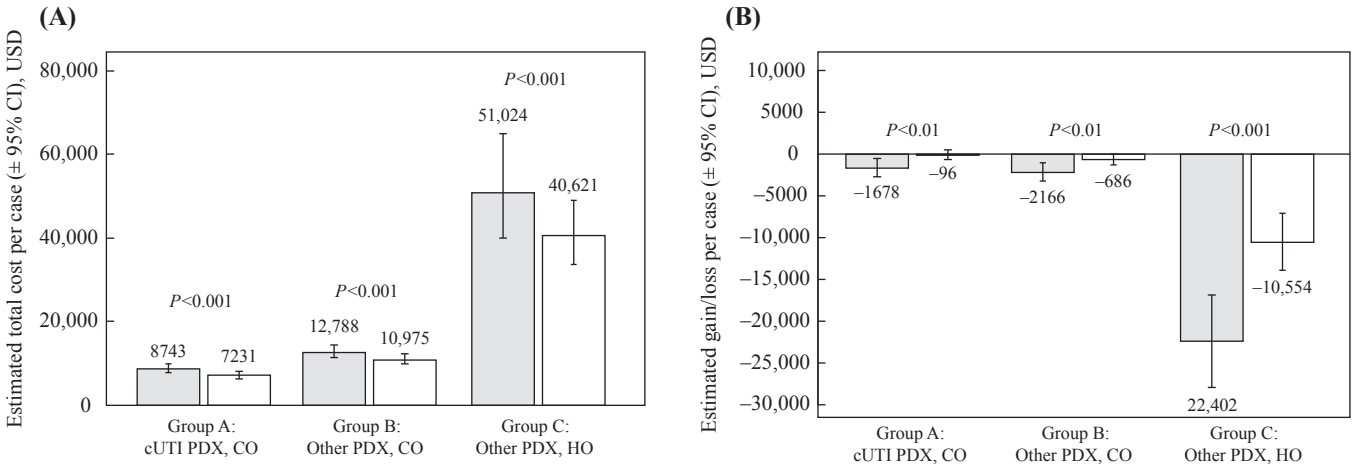

Figure 3. (A) Total cost and (B) net gain/loss by propensity-score-matched patient cohorts [carbapenem-non-susceptible (C-NS; shaded bars) cases vs carbapenem-susceptible (C-S; open bars) cases]. CI, confidence interval; CO, community onset; cUTI, complicated urinary tract infection; HO, hospital onset; PDX, principal diagnosis; USD, United States dollars.

relevant cUTI cases may have been excluded from the analysis, particularly if these infections occurred in the context of multiple diagnoses. This may have contributed to the low number of hospital-onset cUTI cases ($N = 92$), which prevented analysis of this important subgroup. However, given that all patients had culture-confirmed urinary tract isolates that were tested for carbapenem susceptibility, and the patients' conditions were sufficiently severe to warrant hospitalization, the all-cause probability of true infections (as opposed to colonization) could still be considered high.

Future studies that use secondary ICD-9-CM codes could improve the likelihood that clinically relevant cases of cUTI are included in the analysis. It would also be of interest to evaluate antibiotic usage before and during the index hospitalization to provide further evidence that the patient has a clinically relevant infection, and to determine whether any relationships exist between antibiotic prescribing and the observed clinical and economic outcomes.

In conclusion, a greater clinical and economic burden was observed in propensity-score-matched hospitalized patients with C-NS urinary tract isolates compared with C-S urinary tract isolates, regardless of whether cUTI or another condition was recorded as the principal diagnosis. For 30-day re-admissions, LOS, cost and net loss, there was significant C-NS-attributable burden for both community-onset and hospital-onset infections, although the burden was most acute in hospital-onset infections. In these hospital-onset infections, C-NS-attributable mortality was also significantly higher. The observation that, in comparison with C-S cases, C-NS cases were associated with an increased LOS ranging from 1.1 days to 3.9 days, increased costs of up to approximately US$10,000, and an operating loss in excess of US$11,000 highlights the considerable clinical and economic burden related to C-NS infections, and the need for improved prevention, management and treatment strategies for patients with these difficult-to-treat infections.

Acknowledgements

The authors wish to thank Dr Richard S. Johannes for his clinical insight and contribution at the early stage of this study, and Stephen Kurtz and John Murray for their dedicated contribution to database management and programming assistance. Editorial assistance was provided by Robert Schupp, PharmD, CMPP, of The Lockwood Group in accordance with Good Publication Practice (GPP3) guidelines, funded by Merck Sharp & Dohme Corp, a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA (MSD).

Conflict of interest statement

YPT, GY, LV and VG are employees of Becton, Dickinson and Company, Franklin Lakes, NJ, USA. EM is an employee of MSD, who may own stock and/or hold stock options in the Company. AHS was an employee of MSD at the time of manuscript preparation.

Funding source

This study and editorial assistance for the development of the manuscript were funded by MSD.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhin.2018.11.018.

References

[1] Lo E, Nicolle LE, Coffin SE, Gould C, Maragakis LL, Meddings J, et al. Strategies to prevent catheter-associated urinary tract infections in acute care hospitals: 2014 update. Infect Control Hosp Epidemiol 2014;35(Suppl. 2):S32–47.

[2] Weber DJ, Sickbert-Bennett EE, Gould CV, Brown VM, Huslage K, Rutala WA. Incidence of catheter-associated and non-catheter-associated urinary tract infections in a healthcare system. Infect Control Hosp Epidemiol 2011;32:822–3.

[3] Hooton TM, Bradley SF, Cardenas DD, Colgan R, Geerlings SE, Rice JC, et al. Diagnosis, prevention, and treatment of catheter-associated urinary tract infection in adults: 2009 International Clinical Practice Guidelines from the Infectious Diseases Society of America. Clin Infect Dis 2010;50:625–63.

[4] Pallett A, Hand K. Complicated urinary tract infections: practical solutions for the treatment of multiresistant Gram-

negative bacteria. J Antimicrob Chemother 2010;65(Suppl. 3):iii25–33.
[5] Alexander EL, Loutit J, Tumbarello M, Wunderink R, Felton T, Daikos G, et al. Carbapenem-eesistant Enterobacteriaceae infections: results from a retrospective series and implications for the design of prospective clinical trials. Open Forum Infect Dis 2017;4:ofx063.
[6] Kalal BS, Nagaraj S. Urinary tract infections: a retrospective, descriptive study of causative organisms and antimicrobial pattern of samples received for culture, from a tertiary care setting. Germs 2016;6:132–8.
[7] 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.
[8] Hirsch EB, Zucchi PC, Chen A, Raux BR, Kirby JE, McCoy C, et al. Susceptibility of multidrug-resistant Gram-negative urine isolates to oral antibiotics. Antimicrob Agents Chemother 2016;60:3138–40.
[9] Karlowsky JA, Hoban DJ, Hackel MA, Lob SH, Sahm DF. Resistance among Gram-negative ESKAPE pathogens isolated from hospitalized patients with intra-abdominal and urinary tract infections in Latin American countries: SMART 2013–2015. Braz J Infect Dis 2017;21:343–8.
[10] Morrissey I, Hackel M, Badal R, Bouchillon S, Hawser S, Biedenbach D. A review of ten years of the Study for Monitoring Antimicrobial Resistance Trends (SMART) from 2002 to 2011. Pharmaceuticals (Basel) 2013;6:1335–46.
[11] Sader HS, Flamm RK, Jones RN. Frequency of occurrence and antimicrobial susceptibility of Gram-negative bacteremia isolates in patients with urinary tract infection: results from United States and European hospitals (2009–2011). J Chemother 2014;26:133–8.
[12] Centers for Disease Control. Antibiotic resistance threats in the United States, 2013. Atlanta, GA: CDC; 2013. Available at: https://www.cdc.gov/drugresistance/pdf/ar-threats-2013-508.pdf [last accessed October 2018].
[13] World Health Organization. WHO publishes list of bacteria for which new antibiotics are urgently needed. Geneva: WHO; 2017. Available at: https://www.who.int/news-room/detail/27-02-2017-who-publishes-list-of-bacteria-for-which-new-antibiotics-are-urgently-needed [last accessed October 2018].
[14] Zilberberg MD, Nathanson BH, Sulham K, Fan W, Shorr AF. Carbapenem resistance, inappropriate empiric treatment and outcomes among patients hospitalized with Enterobacteriaceae urinary tract infection, pneumonia and sepsis. BMC Infect Dis 2017;17:279.
[15] Cai B, Echols R, Magee G, Arjona Ferreira JC, Morgan G, Ariyasu M, et al. Prevalence of carbapenem-resistant Gram-negative infections in the United States predominated by *Acinetobacter baumannii* and *Pseudomonas aeruginosa*. Open Forum Infect Dis 2017;4:ofx176.
[16] Bartsch SM, McKinnell JA, Mueller LE, Miller LG, Gohil SK, Huang SS, et al. Potential economic burden of carbapenem-resistant Enterobacteriaceae (CRE) in the United States. Clin Microbiol Infect 2017;23:48 e9–16.
[17] Gross AE, Johannes RS, Gupta V, Tabak YP, Srinivasan A, Bleasdale SC. The effect of a piperacillin/tazobactam shortage on antimicrobial prescribing and *Clostridium difficile* risk in 88 US medical centers. Clin Infect Dis 2017;65:613–8.
[18] Tabak YP, Zilberberg MD, Johannes RS, Sun X, McDonald LC. Attributable burden of hospital-onset *Clostridium difficile* infection: a propensity score matching study. Infect Control Hosp Epidemiol 2013;34:588–96.
[19] Zilberberg MD, Tabak YP, Sievert DM, Derby KG, Johannes RS, Sun X, et al. Using electronic health information to risk-stratify rates of *Clostridium difficile* infection in US hospitals. Infect Control Hosp Epidemiol 2011;32:649–55.
[20] Centers for Disease Control National Healthcare Safety Network. Multidrug-resistant organism & *Clostridium difficile* lifection (MDRO/CDI) module. Atlanta, GA: CDC NHSN; 2018. Available at: https://www.cdc.gov/nhsn/pdfs/pscmanual/12pscmdro_cdadcurrent.pdf [last accessed October 2018].
[21] Agency for Health Care Research and Quality. Clinical classifications software (CCS) for ICD-9-CM. Rockville, MD: Agency for Healthcare Research and Quality; 2015. Available at: https://www.hcup-us.ahrq.gov/toolssoftware/ccs/ccs.jsp [last accessed October 2018].
[22] Tabak YP, Sun X, Nunez CM, Johannes RS. Using electronic health record data to develop inpatient mortality predictive model: Acute Laboratory Risk of Mortality Score (ALaRMS). J Am Med Inform Assoc 2014;21:455–63.
[23] Biehle LR, Cottreau JM, Thompson DJ, Filipek RL, O'Donnell JN, Lasco TM, et al. Outcomes and risk factors for mortality among patients treated with carbapenems for *Klebsiella* spp. bacteremia. PLoS One 2015;10:e0143845.
[24] Muggeo A, Guillard T, Barbe C, Thierry A, Bajolet O, Vernet-Garnier V, et al. Factors associated with carriage of carbapenem-non-susceptible Enterobacteriaceae in North-Eastern France and outcomes of infected patients. J Antimicrob Chemother 2017;72:1496–501.
[25] Wu PF, Chuang C, Su CF, Lin YT, Chan YJ, Wang FD, et al. High minimum inhibitory concentration of imipenem as a predictor of fatal outcome in patients with carbapenem non-susceptible *Klebsiella pneumoniae*. Sci Rep 2016;6:32665.
[26] Lin YT, Chuang C, Su CF, Chan YJ, Wang LS, Huang CT, et al. Efficacy of appropriate antimicrobial therapy on the survival of patients with carbapenem nonsusceptible *Klebsiella pneumoniae* infection: a multicenter study in Taiwan. Medicine (Baltimore) 2015;94:e1405.
[27] Turner RM, Wu B, Lawrence K, Hackett J, Karve S, Tunceli O. Assessment of outpatient and inpatient antibiotic treatment patterns and health care costs of patients with complicated urinary tract infections. Clin Ther 2015;37:2037–47.
[28] Hauck C, Cober E, Richter SS, Perez F, Salata RA, Kalayjian RC, et al. Spectrum of excess mortality due to carbapenem-resistant *Klebsiella pneumoniae* infections. Clin Microbiol Infect 2016;22:513–9.
[29] van Duin D, Cober E, Richter SS, Perez F, Kalayjian RC, Salata RA, et al. Impact of therapy and strain type on outcomes in urinary tract infections caused by carbapenem-resistant *Klebsiella pneumoniae*. J Antimicrob Chemother 2015;70:1203–11.