Original Article

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Temporal Trend of Carbapenem Utilizations in Community-Onset Urinary Tract Infection in Hospitalization in Taiwan (1997 – 2012): Risk Factor and Mortality Analysis

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Objective: To ascertain whether there is an increased in temporal trend of carbapenem utilization in community-onset urinary tract infection (UTI) in Taiwan which would suggest multidrug resistance and explore some possible mortality risk factors.

Methods: We used National Health Insurance Research Database in Taiwan from 1997 to 2012 to identify carbapenem user in inpatients with community onset urinary tract infection. Non-carbapenem user was selected in a matched control group in a 1:10 ratio. We performed a case-control study to compare the comorbidity and mortality.

Results: In hospitalized patients with extended spectrum beta lactamase (ESBL) *Escherichia coli* infection, carbapenem is the drug of choices as definitive therapy. And we found the carbapenem user in community onset urinary tract infection with hospitalization increased rapidly after 2003. And we found diabetes mellitus and beta-lactam or fluoroquinolone use were associated with carbapenem use during hospitalization. Carbapenem use (adjusted hazard ratio (HR): 2.09; 95% confidence interval (CI) 1.18 – 3.73) was independent associated with Day 90 mortality after adjusting other confounding factors. Other risk factor included cancer (adjusted HR: 2.03; 95% CI: 1.23 – 3.33).

Conclusions: Our nationwide study confirmed the increased temporal trend of carbapenem utilization, which is highly indicative and corresponds very well with the international trend of increased burden of multidrug resistance in community-onset UTI.

Key words: urinary tract infection, carbapenem, ESBL

Introduction

In recent years, there has been an increased trend of antibiotic resistance in community urinary tract infections (UTIs), and more incidence of community onset extended-spectrum β-lactamase (ESBL) *Escherichia coli (E. coli)* urinary tract infection (UTI) emerged. This may be explained by CTX-M 14 or CTX-M

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15 and sequence type (ST) 131 epidemic clone worldwide.[1,2] The epidemic clone is characterized by co-resistance to fluoroquinolone, aminoglycosides and trimethoprim-sulfamethoxazole.[1-5] And these pathogens have been reported in healthy patients with acute pyelonephritis.[6,7]

Resistant pathogens such as ESBL *E. coli* infection is associated with a delay in administration of active antimicrobial agents. In hospitalized patients with ESBL *E. coli* infection with or without bacteremia, carbapenem is the drug of choices as definitive therapy.[8] And increasing resistant pathogens in community onset UTI leads to more carbapenem use. Like the international guideline or consensus, we used cephalosporin, fluoroquinolone, or aminoglycoside for community onset-UTI patients requiring hospitalization in Taiwan.[9-11] Carbapenem is reserved and only used after bacterial culture result showing resistant to cephalosporin and fluoroquinolone.

In a single center study in northern Taiwan showed similar mortality rate in ESBL in comparison with non ESBL *E. coli* and *Klebsiella pneumonia* bacteremic UTI.[12] But another study in Korea showed there was a trend toward mortality being higher in the ESBL group compared with the non-ESBL *E. coli* bacteremia.[13] There are lacking of studies about long-term follow-up especially after discharge in these cohort to evaluate the mortality in resistant pathogen-related UTI needing hospitalization. Besides, we do not know if the trend of carbapenem consumption in community onset UTI need hospitalization which implies the burden of resistant pathogens infection in a nationwide level in Taiwan is similar to other area in the world. And we do not know if the case of community onset resistant pathogen-related UTI had different co-morbidity, antibiotic exposure and outcome in comparison with non-resistant pathogen-related UTI. To better understand these issues, we conduct a retrospective population-based cohort study used data from the Longitudinal Health Insurance Database in Taiwan. In this study, we assume that the use of broad-spectrum antibiotic (e.g., carbapenem) for community UTIs is highly related with ESBL pathogens, as consistent with other studies in Taiwan and other countries.[19]

Materials and Methods

Source of data

The Taiwan Department of Health had placed all public insurance systems under the National Health Insurance (NHI) program in 1995 to cover the health care of all residents. The National Health Research Institute (NHRI) of Taiwan manages the medical benefit claims of all 22.9 million residents of Taiwan, covering more than 99% of the population. The NHRI established several claims data files for public use. We requested the National Health Insurance Research Database (NHIRD) from the institute, which covers claims data from 1997 to 2012 (Fig. 1). The completeness and accuracy of the NHIRD were guaranteed by the Department of Health and the NHI Bureau of Taiwan. The insurance authority released the insured medical records as de-identified secondary data to the public for the purpose of research. This study was thus exempted from an ethics review. This retrospective population-based cohort study used data from the Longitudinal Health Insurance Database 2000 (LHID2000), which is a subset of the NHIRD. The LHID2000 contains the complete original claims data of one million insured individuals who were randomly sampled from the NHIRD registry in 2000. Until the end of 2011, all sampled individuals were followed up for outcome identification using the International Classification of Disease, 9th Revision, Clinical Modification (ICD-9-CM). Hospitalized patients with a principal diagnosis of UTI (ICD-9-CM code 599.0) were identified. Other diagnosis, chronic pyelonephritis without

lesion of renal medullary necrosis (ICD-9-CM code 590.00), chronic pyelonephritis with lesion of renal medullary necrosis (ICD-9-CM code 590.01), renal and perinephric abscess (ICD-9-CM code 590.2), pyelonephritis, unspecified (ICD-9-CM code 590.80), infection of kidney, unspecified (ICD-9-CM code 590.9), acute cystitis (ICD-9-CM code 595), septicemia (ICD-9-CM code 038.XX), unspecified bacterial infection of unspecified site (ICD-9-CM code 041.9), and bacteremia (ICD-9-CM code 790.7). The study was exempted from a full review by the local ethics review committee.

Subjects

Subjects were selected from the LHID2000 and LHID2005 and included inpatients aged 18 or above with newly diagnosed urinary tract infection (and/or septicemia) (defined as the index hospitalization) between January 1, 1997 and June 30, 2012. Inpatients with more than 3 weeks or less than 7 days at the hospitalization, or with other hospitalization between the half year before the index hospitalization and the index hospitalization were excluded the study. During the hospitalization, patients taking carbapenem (i.e., imipenem, meropenem, ertapenem and doripenem) more than 7 days were defined as carbapenem users. The index date were defined as the 45 days (confirm the hospitalization treatment successful) after the discharged from hospital. Further, a retrospective cohort study from the selected subjects was conducted with two cohorts: a carbapenem cohort and a matched comparison cohort. Urinary tract infection subjects without carbapenem claims, matched (10:1) for gender, age, and index date, were randomly selected as the comparison cohort. Inpatients with medication of beta lactam or quinolone claims between the index hospitalization and

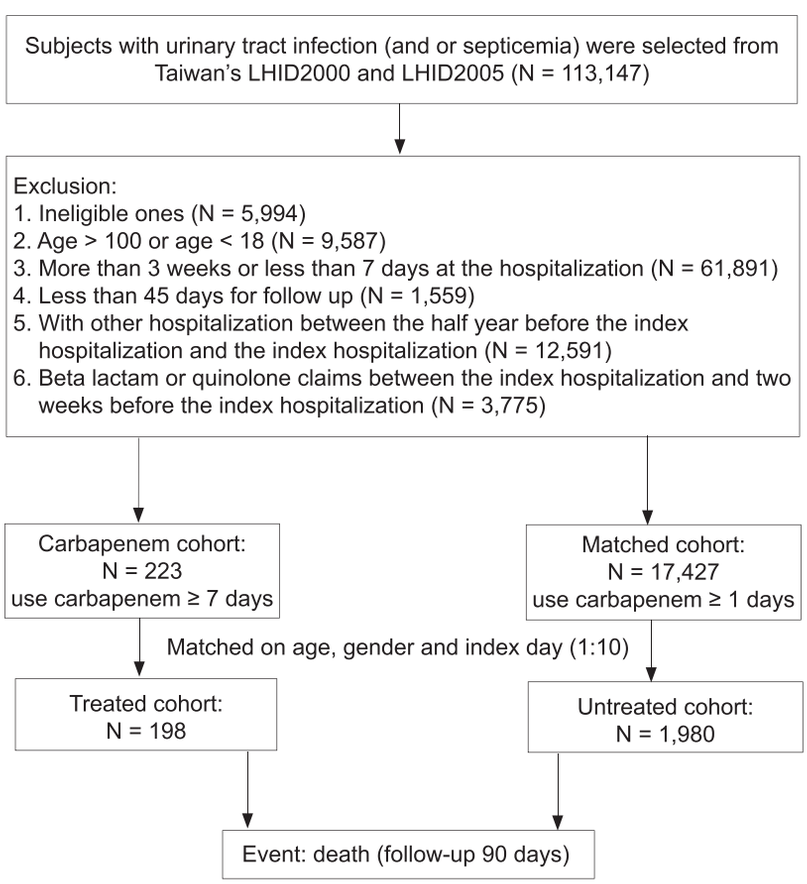

Fig. 1 Study flow.

two weeks before the index hospitalization were excluded the study. Comorbidities presented before the index date was defined are as follows: hypertension, cardiovascular disease, cerebrovascular disease, peripheral vascular, disease, diabetes, retinopathy, nephropathy, neuropathy, chronic renal failure, chronic liver disease, chronic lung disease, cancer, and GU tract abnormality. Both cohorts were followed up to death, or 90 days. The identification numbers of all individuals in the NHIRD were encrypted to protect their privacy.

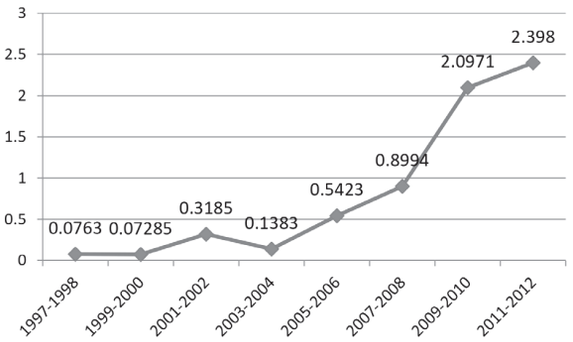

Fig. 2 Temporal trend of carbapenem use in community onset UTI with hospitalization in Taiwan (1997 – 2012).

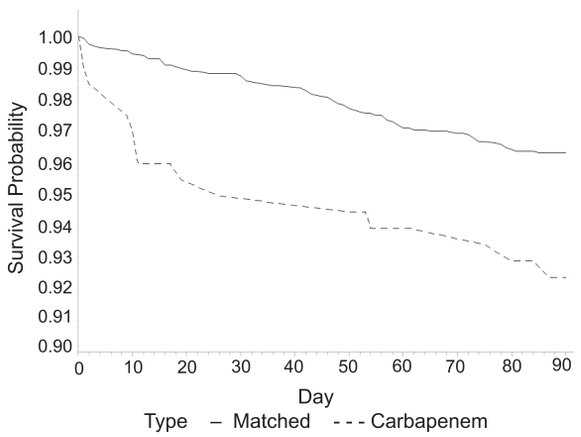

Fig. 3 Survival probability for carbapenem cohort and matched cohort. Log-rank test: $p < 0.0001$.

Statistical analysis

Continuous variables were summarized in terms of mean and standard deviation, and categorical variables were summarized in terms of number and proportion. The cumulative mortality were calculated from a 90 days of follow up. The study used the Cox proportional hazards regression model to determine the hazard ratios (HRs) of death for carbapenem patients compared with the matched cohort. The variables in the model included age, gender, and comorbidities. All data management and HR calculations were performed using the Statistical Package for the Social Sciences (version 10.0; SPSS Inc, Chicago, IL). The calculated results were expressed with the ratio and their 95% confidence intervals (CIs). All statistical tests were defined as significant with a p value of less than 0.05.

Results

In the temporal trend (Fig. 2), there was a rapidly increasing carbapenem use in community onset UTI needing hospitalization since 2003. In comparison in 2011 – 2012 with 2001 – 2002, the rate increase 7 folds (from 0.3185 to 2.3980 per 100,000 populations).

In comparison with matched cohort (Table 1), carbapenem use cohort had similar sex and age distribution. And in underlying comorbidities, carbapenem cohort was more likely to have cerebrovascular disease, peripheral vascular disease and diabetes mellitus ($p < 0.05$). And the percentage of beta-lactam use and quinolone use before admission was higher in carbapenem use cohort ($p < 0.05$).

The mortality before index day was similar between carbapenem and control cohort (data not shown). Day 90 mortality in carbapenem group were about 2 folds higher than control group (7.58% vs. 3.64%, $p < 0.05$). In mortality analysis, in univariate and multivariate analysis, carbapenem treated cohort was independent related to mortality (adjusted HR: 2.09; 95% CI: 1.18 – 3.73) and other risk factor included cancer (adjusted HR: 2.03; 95% CI: 1.23 – 3.33) (Table 2). Similarly, survival analysis (Fig. 3) of the post discharge Day 90 mortality risk among patients with carbapenem

Table 1. Characteristics of the study subjects.

	Carbapenem cohort (N = 198)	Matched cohort (N = 1,980)	*p*-value
Age	70.77 12.79	70.76 12.72	0.9873
18 – 39	4 (2.02)	40 (2.02)	0.9883
40 – 59	40 (20.20)	391 (19.75)	
60 – 79	94 (47.47)	966 (48.79)	
80	60 (30.30)	583 (29.44)	
Male gender	61 (30.81)	610 (30.81)	> 0.9999
Comorbidities			
Hypertension	147 (74.24)	1,441 (72.78)	0.6584
Cardiovascular disease	162 (81.82)	1,575 (79.55)	0.4480
Cerebrovascular disease	97 (48.99)	776 (39.19)	0.0073
Peripheral vascular disease	27 (13.64)	169 (8.54)	0.0168
Diabetes mellitus	107 (54.04)	894 (45.15)	0.0167
Retinopathy	19 (9.60)	210 (10.61)	0.6586
Nephropathy	197 (99.49)	1,971 (99.55)	> 0.9999
Neuropathy	55 (27.78)	586 (29.60)	0.5925
Chronic renal failure	24 (12.12)	205 (10.35)	0.4394
Chronic liver disease	58 (29.29)	488 (24.65)	0.1503
Chronic lung disease	101 (51.01)	883 (44.60)	0.0838
Cancer	37 (18.69)	292 (14.75)	0.1400
GU tract abnormality	71 (35.86)	664 (33.54)	0.5098
Antibiotic (> 3 days)			
Beta-lactam	22 (11.11)	143 (7.22)	0.0486
Quinolone	6 (3.03)	19 (0.96)	0.0213
Event			
Death	15 (7.58)	72 (3.64)	0.0070

treatment and control showed a significantly higher mortality risk among carbapenem cohort compared with control cohort ($p < 0.0001$, log-rank test).

Discussion

Using a nationwide data and excluding cases with prolonged hospitalization or having hospitalization history in half years, we try to identify case of carbapenem user in community onset UTI. Although carbapenem is not a recommend suggested empirical antibiotic in community onset UTI, this study showed the increase trend of carbapenem consumption in community onset UTI needing hospitalization in 2000s. Because we only select carbapenem use more than 7 days, i.e., definitive treatment but no empirical treatment patients were included, this implies the emerging of ESBL producing pathogens in community onset UTI. The trend is similar to the global increased ESBL producing pathogens in community onset UTI. The carbapenem treated cohort was associated with higher 90-day mortality after hospital discharge after adjusting underlying disease.

The trend of increasing carbapenem use in our cohort response to the increased EBSL *E. coli* burden in other countries. Surveillance UTI data in US showed increased ESBL pathogen to 300% from 2000 – 2009.[14] Retrospective review from multicenter in Canada showed increasing incidence of ESBL-producing pathogens from 0.12 per 1,000 inpatient days during 2005 to 0.47 per 1,000 inpatient days during 2009.[15] In Spain, there was an also increase resistance to both fluoroquinolones and third-generation cephalosporins for *E. coli* infections (from 1.6% in 1999 to 11.3% in

2010).[16] In Taiwan, our data in a local center showed the rapid increasing of ESBL *E. coli* bacteremia since 2009, and both ST131 and non-131 clone exist.[17]

Similar to the cohort in Korea, ESBL group were more like to have diabetes mellitus and hemiplegia.[13,18] Our cohort showed carbapenem treated cohort was more likely to have diabetes mellitus, cerebrovascular disease and peripheral vascular disease. And in previous study,[19] more antibiotics usage such as fluoroquinolone and beta-lactam during the previous year was found in ESBL group. Our cohort only included antibiotic use in 3 months and found carbapenem group were more like to have beta-lactam and fluoroquinolone use.

We analyzed mortality rate after patients were successfully discharged. And our cohort showed higher Day 90 mortality in carbapenem group. The higher mortality risk among patients with carbapenem treated cohort could be attributed to several factors: more co-morbidity, higher virulence of ESBL pathogen and possible new carbapenem resistant pathogen developed later. In previous ESBL UTI study in Connecticut,[20] infection-related mortality and 30-day UTI readmission were higher in ESBL group. Our study showed similar mortality within 30 days which may be explained by excluding patients with early mortality. But Day 90 mortality after discharge is higher in carbapenem user in our study. We do not know if this is related to carbapenem resistant pathogen developed. Brief exposure to imipenem is a major risk factor for imipenem resistant-gram negative bacilli carriage and the risk increase after longer exposure.[21]

There were some limitations in this study. First, this cohort was from a nationwide insurance data, uncertainty in detail diagnosis and a lack of laboratory data such as pathogen identity and antibiotics susceptibility result were unavoidable. Second, although we try to analysis Day 90 mortality in carbapenem user and control group by multivariate method, some confounding factors may still exist. For example, the severity of infection may lead to the prescription of carbapenem, although there is a general policy about prescription of carbapenem in multidrug resistant pathogen infection. Third, we did not analysis the mortality of piperacillin/tazobactam, or cefepime which may be active against ESBL. Prospective data and a meta-analysis suggest that piperacillin/tazobactam are non-inferior to carbapenem in the treatment of bloodstream infections caused by ESBL producers.[22,23] We do not know if the piperacillin/tazobactam user had similar or

Table 2. Prediction for occurrence of event (all comorbidities).

	Crude HR		Adjusted HR	
	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
Treated vs. Untreated	2.22 (1.26 – 3.88)	0.0054	2.09 (1.18 – 3.73)	0.0130
Age	1.08 (0.90 – 1.29)	0.3973	1.12 (0.93 – 1.36)	0.2337
Comorbidities				
Hypertension	0.91 (0.51 – 1.63)	0.7525	1.85 (0.54 – 6.40)	0.3301
Cardiovascular disease	0.69 (0.37 – 1.30)	0.2490	0.37 (0.10 – 1.38)	0.1382
Cerebrovascular disease	1.14 (0.73 – 1.78)	0.5658	1.24 (0.77 – 1.99)	0.3733
Peripheral vascular disease	1.29 (0.64 – 2.61)	0.4835	1.11 (0.52 – 2.39)	0.7847
Diabetes	1.33 (0.85 – 2.09)	0.2139	1.37 (0.83 – 2.27)	0.2214
Retinopathy	0.71 (0.32 – 1.62)	0.4185	0.48 (0.20 – 1.16)	0.1018
Neuropathy	1.12 (0.69 – 1.82)	0.6480	1.05 (0.62 – 1.78)	0.8588
Chronic renal failure	1.44 (0.81 – 2.57)	0.2196	1.68 (0.90 – 3.13)	0.1053
Chronic liver disease	1.56 (0.96 – 2.55)	0.0747	1.42 (0.85 – 2.38)	0.1825
Chronic lung disease	1.09 (0.69 – 1.72)	0.7174	1.04 (0.65 – 1.67)	0.8727
Cancer	2.06 (1.28 – 3.34)	0.0031	2.03 (1.23 – 3.33)	0.0043
GU tract abnormality	0.67 (0.41 – 1.11)	0.1206	0.66 (0.39 – 1.10)	0.1127

better mortality data 90 days after discharges.

In conclusion, our nationwide study confirmed the increased burden and severity of multidrug resistant (MDR) pathogen in community-onset UTI as evidenced by the increased temporal trend of carbapenem use (which also corresponds very well with international trends). Higher mortality in carbapenem treated cohort after discharge will continue to present a challenge to clinicians. In facing the emergence of multi-drug resistant pathogens in community onset UTI, finding optimal preventive and treatment strategies are necessary.

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