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Original article

Clinical evaluation of the need for carbapenems to treat community-acquired and healthcare-associated pneumonia

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ABSTRACT

Carbapenems have an overall broad antibacterial spectrum and should be protected against from the acquisition of drug resistance. The clinical advantages of carbapenem in cases of pneumonia have not been certified and the need for antipseudomonal antimicrobial agents to treat healthcare-associated pneumonia (HCAP) remains controversial. We introduced an antimicrobial stewardship program for carbapenem and tazobactam/piperacillin use and investigated the effects of this program on the clinical outcomes of 591 pneumonia cases that did not require intensive care unit management, mechanical ventilation or treatment with vasopressor agents [221 patients with community-acquired pneumonia (CAP) and 370 patients with HCAP]. Compared with the pre-intervention period, age, comorbidities and the severity and etiology of pneumonia did not differ during the intervention period. Carbapenems were rarely used during the intervention period in cases of pneumonia (CAP: 12% vs. 1%, HCAP: 13% vs. 1%), while antipseudomonal beta-lactam use was reduced from 33% to 8% among cases with HCAP. This reduction in the rate of carbapenem administration did not have an impact on the prognosis in the cases of CAP, and the in-hospital mortality was lower among the patients with HCAP during the intervention period (15% vs. 5%, $p = 0.013$). The causes of death in the cases of HCAP were not directly related to pneumonia during the intervention period. The current study shows that carbapenem use can be avoided in cases of CAP or HCAP that are not in a critical condition. The frequent use of antipseudomonal beta-lactams does not improve the clinical outcomes of HCAP.

1. Introduction

Carbapenems have the broadest spectrum of activity against Gram-positive and -negative bacteria among beta-lactam antimicrobials and are currently recognized as “last-line agents” in clinical practice. Since the discovery of thienamycin produced from *Streptomyces cattleya* [1] and the commercial implementation of treatment with imipenem/cilastatin [2], several carbapenems (meropenem, doripenem, imipenem/cilastatin, ertapenem, biapenem, panipenem/betamipron) have been released [3], and their use has increased globally by 45% in the last 10 years [4].

While carbapenems have strong potency for penicillin-binding proteins and are not hydrolyzed from many beta-lactamases, including extended-spectrum beta lactamases (ESBLs), and AmpC beta-lactamases [3], carbapenem resistance has emerged frequently during the course of clinical use of these agents [5], with the production of carbapenase and/or mutations in outer membrane porin proteins. Hence, the application of these drugs should be avoided if alternative antimicrobial agents are available.

Pneumonia is the most common infectious disease in humans, with *Streptococcus pneumoniae* being the leading causative pathogen, followed by *Haemophilus influenzae*, *Klebsiella pneumoniae*,

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Mycoplasma pneumoniae, *Staphylococcus aureus* [6–9] and others. In order to identify high-risk patients with pneumonia caused by *Pseudomonas aeruginosa* or other multidrug-resistant organisms (MDROs), the concept of health-care associated pneumonia (HCAP) was developed, and antipseudomonal antimicrobial agents are currently recommended for patients with HCAP [10], especially those with high risks [8]. However, the prognostic advantages for initial Pseudomonas coverage are unclear with respect to over-treatment, and the necessity of carbapenem administration has not been investigated in either CAP or HCAP.

At our facility, the frequent use of carbapenems was significant problem until June 2011, during which time antipseudomonal beta-lactams were commonly prescribed for pneumonia, especially in patients with HCAP. We therefore implemented new regulations regarding our carbapenem policy [11], and since July 2011, carbapenems have been rarely used for the treatment of CAP or HCAP. In this study, we investigated the need for carbapenems to treat CAP and/or HCAP among newly hospitalized adult patients.

2. Patients and methods

This study was performed at Tsukuba Medical Center Hospital (TMCH, 413 beds), which is located next to the University of Tsukuba Hospital and plays a role as a tertiary emergency medical center in the Tsukuba district of Japan. The intervention was performed as a part of infection control, and carbapenem use was restricted to the treatment of bacterial meningitis, febrile neutropenia, rapidly progressive sepsis, nosocomial onset intra-abdominal infection and infections with highly drug-resistant Gram-negative bacteria. The use of carbapenems in patients without these conditions was not recommended, and the prescribing physicians were individually instructed with daily monitoring by an Infectious Disease (ID) physician. An alternative increase in the rate of tazobactam/piperacillin (TAZ/PIPC) administration was anticipated; thus, all individual prescriptions of TAZ/PIPC were also monitored daily, and the use of these drugs in patients without life-threatening conditions, hospital-acquired infections or highly drug-resistant Gram-negative infections was not recommended during the intervention period.

The clinical evaluation was performed by comparing the outcomes in the pre-intervention period (July 2010 to June 2011) with those obtained during the two-year intervention period (July 2011 to June 2013). The two-year intervention period was divided into two categories, (i) phase I (July 2011 to June 2012) and (ii) phase II (July 2012 to June 2013), as most of the physicians at TMCH agreed to comply with our carbapenem policy in the phase II intervention period after being informed of the results of the phase I intervention period [11]. This study was approved by the ethics committee of TMCH (approved number: 2014–002).

2.1. Patients with pneumonia and definitions of CAP and HCAP

At TMCH, almost all adult pneumonia patients (18 years of age or older) who required inpatient care are admitted to the Department of Respiratory Medicine (RM) or Department of General Medicine and Primary Care (GM). Therefore, we reviewed the records of all patients discharged from RM or GM between July 2010 and June 2013. The initial chart review was performed by an ID physician (H.S.), and cases suspicious for a diagnosis of pneumonia were further reviewed by a pulmonologist (K.K) and radiologist (S.S) individually; only patients diagnosed with pneumonia by both physicians were included in this study. Patients with lung abscesses [12] or empyema [13,14] and/or those diagnosed with an active infection of tuberculosis, non-tuberculous mycobacteria or fungi were excluded from this study.

Following the identification of adult patients clinically diagnosed with pneumonia, we reviewed their clinical information and excluded patients who did not fulfill the study criteria for pneumonia, determined based on previous research [6]. Carbapenem use was not avoided in life-threatening cases and we thus excluded patients with pneumonia who required initial intensive care unit (ICU) management or treatment with vasopressor agents or mechanical ventilation in this study. The requirement of ICU management was determined by each physician.

HCAP was considered in cases of pneumonia in which the patient met the pneumonia-specific criteria for HCAP [10], including: hospitalization for $\geq$2 days during the previous 90 days, antibiotic use during the previous 90 days, a non-ambulatory status, tube feeding, an immunocompromised status or the use of gastric acid suppressive agents.

2.2. Clinical assessment and outcome measurements

We compared the baseline characteristics, comorbidities, severity of pneumonia, laboratory findings on admission, causative pathogens, concurrent infections, treatment and prognosis. The severity of pneumonia was assessed according to the Pneumonia Severity Index (PSI) and A-DROP scale (age, dehydration, respiratory failure, orientation disturbance and low blood pressure) [15,16]. Causative pathogens were considered if (i) the bacteria were isolated from good quality sputum (Geckler class 4 or more) and the Gram stain findings were compatible with the isolated bacteria, (ii) blood cultures were positive and the same bacteria were isolated from a sputum culture or (iii) urine antigen and/or antibody testing was positive for the target pathogens. Treatment was evaluated based on the use of carbapenems, antipseudomonal agents and the frequency of combination therapy. Dose adequacy was assessed according to the defined daily dose [17] adjusted for the renal function in each case.

The primary outcome was in-hospital mortality, and the secondary outcomes were 30-day mortality, deterioration of activities of daily living (new onset of a bed-ridden status), new requirements for tube feeding or parental nutrition (PN) and/or the new introduction of home oxygen therapy (HOT).

2.3. Statistical analysis

We compared the patients with pneumonia among three periods (pre-intervention period, intervention period phase I, intervention period phase II). The comparisons were made separately between the cases of CAP and those of HCAP. Categorical variables were analyzed using the χ^2 test, and continuous variables were assessed using a one-way analysis of variance (ANOVA). Variables found to be significantly different ($p < 0.05$) were further evaluated using Bonferroni-corrected P values. In all patients with pneumonia in each of the three periods, independent factors associated with in-hospital mortality were assessed using a multivariable adjusted logistic regression analysis to evaluate the clinical significance of HCAP. Variables with a significant association ($p < 0.05$) in the univariate analysis were included in the multivariate analysis after adjusting for confounding factors. The SPSS version 20 software package (IBM, Armonk, NY, USA) was used for all analyses.

3. Results

The hospital environment did not differ during the study period (July 2010 to June 2013) (Table 1). A total of 4313 admissions were recorded at RM or GM and assessed for eligibility (Fig. 1). Consequently, we identified 591 patients with pneumonia who

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