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Original Article

Antimicrobial-Resistant Bacteremia in the Elderly: Risk of Previous Hospitalization☆

Yung-Cheng Su [1,2], Lu-Chih Kung [3†], Chao-Hsiung Lee [4], Wen-Han Chang [3,6], Chung-Lieh Hung [5,6], Chih-Chen Tsao [7‡], Ming-Yuan Huang [3,6*]

[1] *Emergency Department, Buddhist Tzu Chi Dalin General Hospital, Chiayi County,* [2] *School of Medicine, Tzu Zhi University, Hualien,* [3] *Emergency Department, Mackay Memorial Hospital, Taipei,* [4] *Emergency Department, Mackay Memorial Hospital, Taitung,* [5] *Division of Cardiology, Department of Internal Medicine, Mackay Memorial Hospital, Taipei,* [6] *Department of Medicine, Mackay Medical College, New Taipei City,* [7] *Department of Emergency, Tungs' Taichung Metro Harbor Hospital, Taichung, Taiwan*

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SUMMARY

Background: Studies have shown a positive correlation between hospital admission and antimicrobial-resistant bacteria (ARB)-related community-acquired bacteremia (CAB), however, the definition regarding the duration from prior hospitalization as having risks for such infections varies between literatures. Therefore, we conducted a retrospective analysis to determine the time-effect of recent hospitalization on the risk of CAB due to extended-spectrum beta-lactamases (ESBLs)-producing *Enterobacteriaceae* in elderly patients.

Methods: From 2006 to 2008, all consecutive episodes of documented bacteremia developed within first 48 h of hospital admission due to *E. coli* and *K. pneumoniae* in patient age of 65 or greater were retrospectively enrolled.

Results: Out of 494 non-duplicated CAB episodes, 9.5% were due to ESBLs-producing *E. coli/K. pneumoniae*. Age, history of previous hospital admission, and nursing home residents were independently associated with the risk for CAB due to ESBLs-producing *E. coli/K. pneumoniae*. History of previous hospitalization was the most significant one among these risks and the effect was time-dependent: within 2~30 days (OR 8.8; 95% CI 1.9 to 41.2), 31~90 days (OR 9.0; 95% CI 1.9 to 41.2), 91~180 days (OR 5.6; 95% CI 1.1 to 29.1), 181~360 days (OR 5.5; 95% CI 1.0 to 29.1) and over 360 days (OR 3.5; 95% CI 0.5 to 22.7).

Conclusion: Our study showed that the risk of CAB in elderly due to ESBLs-producing *E. coli/K. pneumoniae* was highly associated with history of recent hospital admissions, and the effect can be prolonged up to 360 days after discharge.

1. Introductions

Infections due to ESBLs (Extensive-spectrum β-lactamases) producing gram-negative bacteria is a great challenge to clinician. Because the ESBLs enzyme is capable of hydrolyzing almost all β-lactam antibiotics, including penicillins, wide spectrum of cephalosporins and monobactams, and more importantly, plasmids that encode ESBLs genes are frequently co-harboring additional resistance elements for different antibiotic classes, such as aminoglycosides, fluoroquinolone and Trimethoprim-sulfamethoxazole[1]. It is very clear that such multiple drug resistance features limit treatment options for infections due to ESBLs producers, and initial empirical antibiotics treatments are usually inappropriate and ineffective and therefore associated with worse clinical outcomes[2,3]. While Carbapenem and Tigecycline are the drugs of choice for infections due to such pathogens, these agents are considered as the last resort of antibiotics and the empirical use of these drugs in the community or emergency settings is not encouraged[4]. Hence, early identification of potential infections

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* Correspondence to: Ming-Yuan Huang, MD, MSc, Emergency Department, Mackay Memorial Hospital, 92, Section 2, Chung-Shan North Road, Taipei 104, Taiwan. Fax: +886 2 25433642.
E-mail address: m.c.yuan928@gmail.com (M.-Y. Huang).
† Co-first author.
‡ Co-corresponding author.

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due to ESBLs producers is important in both treatment guidance and infection control measures.

Since *Enterobacteriaceae* are common community pathogens[5–7], such organisms that express ESBLs activity influence the public health greater than many other multiple drug resistance pathogens that predominantly acquired at hospital. This concern has became a serious issue as ESBLs-producing *E. coli* and *K. pneumoniae* are increasing reported worldwide and are now emerging as a major multiple drug resistance pathogen associated with community-acquired infections[8,9]. Prompt diagnosis is difficult because detection of ESBLs phenotype is time-consuming. As a result, stratification of patients with infections into risk groups to guide initial therapy is the mainstay in many clinical settings, particularly in the emergency settings. Old age (greater than 65 year-old) and health-care exposure (recent hospitalization, resident in nursing home or long-term care facilities) are known risk indicators for community-acquired infections caused by ESBLs producers[10,11]. However, the definition of recent hospital exposure is heterogenic among literatures, ranging from 30 to 180 days from previous hospitalization[12–15]. It is very important to know that the dichotomy classification to define health-care associated risk by using different time period from previous hospitalization may over- or under-estimated the impact of the risk. To better define this particular health-care associated indicator, we aimed to investigate the significance of previous hospital admission in the risk of community-acquired bacteremia (CAB) caused by ESBLs-producing *E. coli* and *K. pneumoniae*, particularly among the aged population.

2. Methods

2.1. Subjects

Mackay Memorial hospital, a 1100-bed medical center, and along with its 800-bed branch hospital provide healthcare service to around 6 million residents in northern Taiwan. They provide primary and tertiary care to the community and have approximately 200,000 ED visits and 100,000 discharges yearly.

All patients of age 65 or greater with a positive blood culture reports of *E. coli* and *K. pneumoniae* between 2006 June to 2008 May were enrolled in this study. All clinical courses of the study population were reviewed independently by two physicians to avoid any possible registry error. As the main purpose of the study, we particularly focused on the correctness of the data on whether these individuals had been admitted to the hospital for at two days prior to current admission, and the time period to the preceding hospital admission, if any, was recorded. Demographic features for each patient and information about underlying medical disorders that may predispose to infections were obtained through the chart review. Only the antibiotic susceptibility profiles of all ESBLs-producing isolates among all bacteremic episodes caused by *E. coli* and *K. pneumoniae* were noted. This study was approved by the institutional review board and a waiver of the requirement to obtain a signed informed consent was also approved.

2.2. Definition

A case episode is defined as at least one set of positive blood culture that yielded *E. coli* and *K. pneumoniae* regardless of mono- or poly-microbial infection in patients with clinically systemic inflammatory response syndrome. Only one episode of positive blood culture per patient was included in the study. Episodes that are hospital-acquired were excluded as defined by the development of infection 48 h after hospital admission. Patients who were transferred from another hospital were also considered as hospital-acquired and were therefore excluded from the analysis. Data that were missing or unable to obtain information about the history of previous hospitalization were also excluded. According to the time period from prior hospitalization, all episodes of community-onset bacteremia were classified into six different risk groups, namely 1~30, 31~90, 91~180, 181~365, over 365 days and no prior hospital admission.

2.3. Microbiological detections

E. coli and *K. pneumoniae* were isolated from blood culture following standard techniques, and the identification of microorganisms and the subsequent antibiotic susceptibility profile were determined by VITEKR2 systems (BioMerieux), interpreted according to Clinical and Laboratory Standards Institute (CLSI) criteria.

The ESBL screening was performed by VITEK 2 system with their commercial ESBL test panel using incubation wells containing cefepime, cefotaxime, and ceftazidime alone and in combination with different concentrations of clavulanic acid.

2.4. Statistical analysis

All analyses were performed using SAS software version 9.1 (SAS institute Inc, Cary, NC). All covariates were taken as categorical variables, except for age, white blood cell (WBC) count, neutrophil, hemoglobin (Hb), Hematocrit (Hct) and C-reactive protein (CRP), which were treated as continuous variables. Categorical variables were compared by use of Pearson's chi-square test (and continuous variables by use of the two sample t-test) to determine baseline heterogeneity in the two groups.

Univariate logistic regressions were applied to evaluate the odds ratios of CAB due to ESBLs-producing *E. coli* and *K. pneumoniae* for covariates which are distributed differently in the baseline characteristics. Significant factors with p value less than 0.05 in the univariate analyses were included in a multiple logistic regression analysis to evaluate the independent predisposing factors for bacteremia due to ESBLs-producing *E. coli* and *K. pneumoniae*. Difference among groups of various time periods from previous hospitalization were evaluated by using no prior hospital admission group as reference. For all statistical comparisons, significance was preset as p-value <0.05.

3. Results

During the two years of retrospective review, a total of 494 episodes of community-onset bacteremia due to *E. coli* and *K. pneumoniae* in patients with age of or greater than 65 year-old were identified, of which 47 (9.5%) episodes were caused by ESBLs-producing isolates (32 isolates of ESBLs-producing *E. coli* and 15 of ESBLs-producing *K. pneumoniae*). Patients who had bacteremia due to ESBLs-producing *E. coli* and *K. pneumoniae* were older (age of 82.8 $\pm$ 7.8, mean $\pm$ SD) than those due to non-ESBLs producers (79.1 $\pm$ 7.5) (Table 1). Medical disorders, such as diabetes mellitus (DM), uremia on hemodialysis, liver cirrhosis, malignancies and receipts of active intravenous chemotherapy, that were considered as predisposing factors to infections showed no difference between patients infected with non-ESBLs- and ESBLs-producing isolates. Classification of patients on the basis of previous hospital exposure revealed that about two-thirds (64.9%) of cases with non-ESBLs-producing organism had a history of prior hospital admission, however, near all (95.7%) of the patients that were infected by ESBLs-producing isolates had been hospitalized previously.

On univariable and multivariable analysis (Table 2), risk of CAB by ESBLs-producing *E. coli* and *K. pneumoniae* were significantly