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Clinical characteristics of patients with community-acquired complicated intra-abdominal infections: A prospective, multicentre, observational study

Shio-Shin Jean[a], Wen-Chien Ko[b], Yang Xie[c], Vaishali Pawar[d], Dongmu Zhang[c], Girish Prajapati[e], Myrna Mendoza[f], Pattarachai Kiratisin[g], Elmano Ramalheira[h], Ana Paula Castro[i], Fernando Rosso[j], Po-Ren Hsueh[k,*]

[a] *Department of Emergency Medicine, Wan Fang Hospital, Taipei Medical University, Taipei, Taiwan*
[b] *Department of Medicine at National Cheng Kung University Medical College and Hospital, Tainan, Taiwan*
[c] *Merck & Co, Inc., Global Health Outcomes, Whitehouse Station, NJ, USA*
[d] *Rutgers University, Ernest Mario School of Pharmacy, Piscataway, NJ, USA*
[e] *All Source PPS, Huntington Beach, CA, USA*
[f] *Section of Infectious Diseases, Department of Medicine, University of the Philippines, Philippine General Hospital, Taft, Manila, Philippines*
[g] *Department of Microbiology, Faculty of Medicine Siriraj Hospital, Bangkok, Thailand*
[h] *Clinical Pathology Department, Hospital Infante Dom Pedro – Aveiro, Aveiro, Portugal*
[i] *Clinical Pathology Department/Microbiology Service, Hospital Geral de Santo António, Porto, Portugal*
[j] *Infectious Diseases, Fundacion Clinica Valle del Lili, Cali, Colombia*
[k] *Departments of Laboratory Medicine and Internal Medicine, National Taiwan University Hospital, National Taiwan University College of Medicine, No. 7 Chung-Shan South Road, Taipei 100, Taiwan*

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ABSTRACT

In this prospective, observational, multicentre study using data from five countries (Columbia, The Philippines, Portugal, Taiwan and Thailand), the clinical impact of extended-spectrum β-lactamase (ESBL)-producing organisms on hospitalised patients with community-acquired complicated intra-abdominal infections (CA-cIAIs) was compared with that of non-ESBL-producing organisms during the period April 2010 to December 2011. Adult patients (aged ≥18 years) requiring surgery or percutaneous drainage were enrolled and were followed during the first hospitalisation course. An unadjusted statistical comparison of risk factors for ESBL-positive and ESBL-negative patients was performed. Multivariate regression analyses were performed to assess whether length of stay (LOS) in hospital, clinical cure rate and some important clinical characteristics were associated with ESBL positivity. During the study period, a total of 105 adult patients from five countries were enrolled, of whom 17 (16.2%) had CA-cIAI due to ESBL-positive organisms and 88 (83.8%) had CA-cIAI due to ESBL-negative organisms. *Escherichia coli* was isolated in 73.3% of all samples. Infections were cured in 8 (47.1%) of the patients with CA-cIAI due to ESBL-positive organisms and in 59 (67.0%) of the patients with CA-cIAI due to ESBL-negative organisms ($P = 0.285$). The median LOS was 11.6 days for patients with infections due to ESBL-negative organisms and 17.6 days for patients with infections due to ESBL-positive organisms ($P = 0.011$). Multivariate logistic regression analysis revealed that pre-existing co-morbidities, but not ESBL positivity, were adversely associated with clinical cure of CA-cIAIs. In contrast, duration of hospitalisation was longer for patients with CA-cIAI due to ESBL-positive organisms.

1. Introduction

Intra-abdominal infections (IAIs) encompass a broad group of infections and are primarily classified as uncomplicated or complicated according to severity. In uncomplicated IAIs, only a single organ is involved and the infection does not spread to the peritoneum. These patients are treated either conservatively with antibiotics or with surgery. Complicated IAIs (cIAIs), however, extend beyond a single affected organ and result in either localised peritonitis (intra-abdominal abscess) or diffuse peritonitis. cIAIs often cause significant morbidity and are frequently associated with poor prognosis, especially in patients with certain risk factors.

* Corresponding author. Tel.: +886 2 2312 3456x5355; fax: +886 2 2322 4263.
E-mail address: hsporen@ntu.edu.tw (P.-R. Hsueh).

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IAIs can be either community-acquired (CA) or hospital-acquired [1]. The major pathogens involved in CA-IAIs are Enterobacteriaceae spp. and anaerobic microbes (especially *Bacteroides fragilis*). However, the emergence of multidrug-resistant organisms such as vancomycin-resistant enterococci, meticillin-resistant *Staphylococcus aureus* (MRSA) and, more recently, extended-spectrum β-lactamase (ESBL)-producing Enterobacteriaceae has raised considerable concern regarding the appropriate treatment of IAIs.

In a review of the literature, Paterson and Bonomo found that 5–8% of Enterobacteriaceae spp. isolated from patients in South Korea, Japan, Malaysia and Singapore were ESBL producers, whereas in Thailand, Taiwan and The Philippines the isolation rate of ESBL-producing Enterobacteriaceae spp. ranged from 12% to 24% [2]. The Study for Monitoring Antimicrobial Resistance Trends (SMART) revealed a gradually increasing trend in the worldwide prevalence of ESBL-producing organisms amongst Enterobacteriaceae spp. [3–5]. In addition, Chen et al. found that the rates of antimicrobial resistance as well as the prevalence of ESBL-producing intra-abdominal Gram-negative bacilli (GNB) were alarmingly high in the Asia-Pacific region, with the highest rates being found in India (57–67%), China (32–65%) and Thailand (48–56%) [6]. Although ESBL-producing members of the Enterobacteriaceae family are mainly isolated from the hospital setting, ESBL-producing organisms have been isolated with increasing frequency from community settings [7]. According to the preliminary report from the Complicated Intra-Abdominal Infections Observational European study (CIAO Study), ESBL-producing *Escherichia coli* accounted for 8.1% of all *E. coli* isolates, and 19.3% of all *Klebsiella pneumoniae* isolates were ESBL producers [8]. In the CIAO study, Enterobacteriaceae spp. still accounted for the majority of causative organisms (86%), of which most were *E. coli* (48%), followed by *Klebsiella* spp. (16%) [8].

Krobot et al. demonstrated that use of appropriate antibiotics for the treatment of CA-cIAIs was significantly associated with clinical success, which was defined as fewer days of using parenteral therapy and shorter length of hospital stay [9]. In contrast, inappropriate selection of antimicrobial agents frequently led to treatment failure, which was defined as re-operation, the necessity of switching to second-line antibiotics, longer hospitalisation and greater hospital-associated costs [10]. Although many previous studies have evaluated the acquisition risk factors, bacteriologic profiles and clinical outcomes of patients infected with hospital-acquired ESBL-producing organisms [11–13], very few studies have explored the risk factors, antimicrobial resistance profiles and outcomes of patients with ESBL-producing organisms isolated from IAIs of community origin [14].

In this prospective, observational, multicentre study using data from five countries, the clinical impact of ESBL-producing organisms on hospitalised patients with CA-cIAIs was compared with that of non-ESBL-producing organisms during the period April 2010 to December 2011.

2. Patients and methods

2.1. Study subjects and design

This prospective, observational study of patients with CA-cIAIs was conducted at multiple sites in five countries, including Thailand, Taiwan, The Philippines, Portugal and Columbia. Patients were recruited from sites that contributed isolates to the 2010 SMART surveillance programme. A total of 127 patients with cIAIs were enrolled from April 2010 through December 2011. Adult patients (aged ≥18 years) who required surgery or percutaneous drainage were included. All patients received initial empirical antibiotic therapy, and their clinical responses were recorded in detail until discharge from hospital or until death. Patients with traumatic intestinal perforations (i.e. stomach or duodenum) requiring surgery within 12 h of hospital arrival, those with primary peritonitis or cholecystitis with inflammation confined to the gallbladder, non-perforated appendicitis without peri-appendicular abscess, and acute infected pancreatitis were excluded from the study. Patients with cIAIs underwent timely percutaneous drainage or surgery after evaluation by a general surgeon. Isolates collected during surgery or drainage were sent to SMART central laboratories to determine the antimicrobial susceptibility profiles and their ESBL status. Only patients with CA-cIAIs caused by *E. coli* or *Klebsiella* spp. were enrolled into the study. All patients were followed through their first hospitalisation course to assess their baseline characteristics, clinical responses and appropriateness of empirical antibiotic regimens.

The Charlson Comorbidity Index (CCI) was used to determine the underlying co-morbid conditions in the patients. The CCI assigns weights for a number of major conditions present amongst secondary diagnoses. The index score is the sum of assigned weights and represents a measure of the burden of co-morbid disease. A baseline score of 0 indicates no co-morbidity, and scores of 1, 2 and ≥3 were assigned to stratify patients based upon their co-morbid conditions.

2.2. Data collection

Data were collected prospectively by the investigators at each site and were reported using an electronic case report form. All investigators were blinded to the patients' respective clinical and laboratory data. In this study, the following data were collected: demographic profile; co-morbid conditions; infectious origin; causative micro-organism; prior use of antibiotic therapy; urinary or venous catheterisation within 3 months prior to this hospitalisation course; and response to clinical management. Clinical response was recorded as (i) cure, which represented complete resolution of the symptoms/signs after surgery and antimicrobial therapy, (ii) improvement but not cure, which was defined as partial resolution of the infection with therapy, and (iii) failure, which was defined as no improvement in symptoms or signs, the need for surgical re-intervention, or death attributable to cIAI. The cause of death was recorded as death attributable to cIAI, or death not related to cIAI. The hospital length of stay (LOS) was calculated from the date of admission to the date of death or discharge. The appropriateness of empirical antimicrobial regimens to specific causative organisms was also evaluated. Adjustment of antibiotic therapy was done immediately after the antibiotic susceptibility testing results were available regardless of the degree of clinical severity.

2.3. Species identification

Isolates collected within 48 h after admission were presumptively categorised as CA-IAIs, whereas those collected >48 h after admission were classified as hospital-acquired infections. Bacterial species were identified at each hospital of admission; however, resistance data and ESBL status were determined at the central SMART laboratory. Traditional ESBL confirmation methods employing a disc containing 30 μg of ceftazidime (or cefotaxime) alone or in combination with a 10 μg of clavulanic acid disc are known to have low sensitivity at detecting bacteria that potentially produce AmpC β-lactamase (*E. coli* and *K. pneumoniae*) [15]. Thus, in this survey, in addition to the standard method using cefotaxime/ceftazidime with or without clavulanic acid by potentiation of discs, the modified double-disc synergy test (DDST) was also applied, which involves a disc containing 30 μg of cefepime with or without a disc containing 10 μg of clavulanic acid (at a centre-to-centre distance of 30 mm) to further confirm ESBL production.