Available online at www.sciencedirect.com
ScienceDirect
Diagnostic Microbiology and Infectious Disease 56 (2006) 351–357
DIAGNOSTIC MICROBIOLOGY AND INFECTIOUS DISEASE
www.elsevier.com/locate/diagmicrobio

Outcome of cephalosporin treatment of bacteremia due to CTX-M–type extended-spectrum β-lactamase–producing *Escherichia coli*

Cao Bin[a], Wang Hui[b], Zhu Renyuan[b], Ning Yongzhong[c], Xie Xiuli[b], Xu Yingchun[b], Zhu Yuanjue[a], Chen Minjun[b,*]

[a]*Department of Pulmonary Medicine, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences, Dongdan, Beijing 100730, People's Republic of China*
[b]*Department of Microbiology, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences, Dongdan, Beijing 100730, People's Republic of China*
[c]*Department of Microbiology, Peking University No. 3 hospital, Beijing 100730, People's Republic of China*

Received 20 January 2006; accepted 16 June 2006

Abstract

The aim of the study was to analyze the outcome of different antibiotic treatments for bacteremia due to CTX-M–type extended-spectrum β-lactamase (ESBL)–producing *Escherichia coli*. In a prospective controlled clinical study from October 2002 to April 2005, 22 consecutive cases of bacteremia due to ESBL-producing *E. coli* with a ceftazidime-inhibition zone diameter of ≥18 mm were studied. The Etest method was used to determine the MIC values of cefotaxime, ceftazidime, imipenem, gentamicin, and ciprofloxacin against 22 isolates of *E. coli*. The polymerase chain reaction and sequencing analyses were used to determine the genotypes of the ESBLs. Of these 22 episodes, 7 were treated with ceftazidime, 8 were treated with imipenem/cilastatin, and 7 were treated with cefoperazone/sulbactam after detection of bacteremia. The demographic characteristics were comparable between the 3 groups. The treatment success ratio was similar (ceftazidime 85.7%, imipenem/cilastatin 87.5%, cefoperazone/sulbactam 71.4%, $P = 0.637$). Difficulties arose during treatment of peritonitis caused by CTX-M–producing *E. coli* bacteremia. Patients with bacteremia associated with urinary tract infection or biliary tract infection had a better chance of survival. All the 22 strains of *E. coli* produced CTX-M ESBLs (CTX-M-3, CTX-M-14, or CTX-M-27). The MICs of ceftazidime for 22 strains of *E. coli* were ≤8 μg/mL. All 7 patients who received ceftazidime survived, 6 of them were cured. Treatment in one patient with a ceftazidime MIC of 2 μg/mL failed because of abdominal abscess. Treatment with ceftazidime in vivo was effective against cases of CTX-M ESBL-producing *E. coli* bacteremia due to urinary tract infections and biliary tract infection when the MICs of ceftazidime were ≤8 μg/mL.

Keywords: Ceftazidime; *E. coli*; ESBLs; CTX-M; Bacteremia

1. Introduction

In the past 2 decades, antibiotic-resistant strains that produced extended-spectrum β-lactamases (ESBLs) have emerged among the Enterobacteriaceae, predominantly *Escherichia coli* and *Klebsiella pneumoniae* (Jacoby and Munoz-Price, 2005). Based on their substrate preferences, the ESBL enzymes are broadly classified as ceftazidimases (preferential hydrolysis of ceftazidime) and cefotaximases (preferential hydrolysis of cefotaxime). Recently, a family of ESBLs that preferentially hydrolyze cefotaxime (CTX), the CTX-M β-lactamase, has been recognized and reported with increasing frequency (Pitout et al., 2004).

Initial challenges to the notion that ESBL-producing organisms for which the MICs of extended-spectrum cephalosporins (ESCs) are in the susceptible range may not be truly susceptible came from in vitro studies of the "inoculum effect" and from animal studies (Fantin et al., 1990; Rice et al., 1991; Thauvin-Eliopoulos et al., 1997). Later there were clinical reports of therapeutic failures due to ESBL-producing strains treated with ESCs, which had been tested as susceptible (Emery and Weymouth, 1997; Ho et al., 2002). In the 1990s, the National Committee on Clinical Laboratory Standards (NCCLS/Clinical and Laboratory Standards Institute [CLSI]) recommended ESBL screening and confirmatory tests in *E. coli* and

* Corresponding author. Fax: +86-10-65295406.
E-mail address: chmj1933@263.net (C. Minjun).

0732-8893/$ – see front matter © 2006 Elsevier Inc. All rights reserved.
doi:10.1016/j.diagmicrobio.2006.06.015

Klebsiella spp. and suggested that none of the penicillins or cephalosporins nor aztreonam should be used in infections caused by ESBL-producing strains, regardless of whether the in vitro susceptibility results were low or high (NCCLS, 1999).

Until now, few have presented sufficient clinical data establishing the relationship between MICs, the ESBL type, and cephalosporin treatment outcomes. Good clinical outcomes were observed when ESCs were used to treat urinary tract infections due to ESBL-producing organisms (Brun-Buisson et al., 1987). However, much more controversy has occurred as to whether ESC therapy is appropriate for more severe infections, such as bacteremia caused by ESBL-producing organisms for which cephalosporin MICs are in the susceptible range.

In this study, we evaluated 22 cases of bloodstream infection due to CTX-M–type ESBL-producing *E. coli* that were susceptible to ceftazidime in vitro. All the cases occurred during a 30-month period and were not associated with an outbreak of such infections. The objective of the study was to evaluate the clinical outcome of different antibiotic treatments for bacteremia due to CTX-M–type ESBL-producing *E. coli*, and to examine the MICs, the molecular basis related to treatment outcomes, with a focus on ESCs.

2. Materials and methods

2.1. Patients

A prospective observational study of consecutive patients with ESBL-producing *E. coli* bloodstream infections was performed in 10 wards (including emergency room, respiratory medicine, rheumatology, kidney disease, abdominal surgery, liver surgery, vascular surgery, general medicine, and traditional medicine) at the Peking Union Medical College Hospital (PUMCH). PUMCH is a teaching hospital with 1200 beds located in the central area of Beijing City. The study period was from October 2002 to April 31, 2005. Patients older than 18 years with blood cultures positive for ESBL-producing *E. coli* and with ceftazidime inhibition zone diameters of $\geq$18 mm were consecutively enrolled. Patients were monitored for 1 month after the onset of infections to assess clinical outcomes as well as mortality. The study was observational in that administration of antimicrobial agents and other therapeutic management was controlled by the patient's physicians, not by the investigators.

Information extracted from medical charts included the following: demographic data, presence of comorbid illnesses (including malignancy, end-stage kidney or liver disease, and neutropenia), the APACHE II (acute physiology and chronic health evaluation II), and modified multisystem organ failure score (MSOF). For definitions of organ dysfunction, we used those proposed by Herbert et al. (1993) with modifications. Organ failures were defined as follows: renal serum creatinine level of >2 mg/dL or a 2-fold rise in the creatinine level from baseline value (Jacoby and Munoz-Price, 2005); hepatic bilirubin level of >2.0 mg/dL or an alkaline phosphatase level of >350 U/L (Pitout et al., 2004); pulmonary requirement for mechanical ventilation or a PaO_2 <60 mm Hg while breathing a fraction of inspired oxygen of >0.5 or the use of >10 cm H_2O positive end-expiratory pressure (Fantin et al., 1990); cardiovascular systolic blood pressure $\leq$90 mm Hg or need for treatment with any vasopressor (Rice et al., 1991); hematologic failure, white blood cell count of <2000/μL, or a platelet count <75 000/μL, and/or an international normalized ratio of >2.0 (Thauvin-Eliopoulos et al., 1997); neurologic failure, Glasgow Coma Scale of <10 or a decrease in the Glasgow Coma Scale score by 3 if a primary CNS injury is present (Emery and Weymouth, 1997); and gastrointestinal fresh blood from a nasogastric or orogastric tube, and/or melena or fresh blood from the rectum accompanied by a fall in hemoglobin of >20 g/L, requiring at least 2 U of packed red blood cells in 24 h (Ho et al., 2002). Each organ failure was determined to be either present or absent in all patients on day 1 of the bacteremia diagnosis. The worst value within 24 h before was used to determine the MSOF score of the patient.

The infections leading to bacteremia were identified as urinary tract infection, biliary tract infection, pneumonia, peritonitis, or a primary bloodstream infection according to definitions by the US Centers for Disease Control and Prevention (Garner et al., 1988).

2.2. Inclusion criteria and definition of failure of therapy

Patients with bacteremia due to ESBL-producing *E .coli* who had antimicrobial susceptibility test results of susceptible or intermediate to ceftazidime using CLSI definitions were included in this analysis. Infections caused by AmpC–producing organisms were excluded.

Failure of antibiotic therapy was defined as persistence of fever after 48 h of antibiotic treatment or a positive culture for bacteremia despite 72 h of antibiotic usage, or septic shock after 72 h of treatment, or death of the patient within 14 days.

2.3. Antimicrobial susceptibility testing

The antibiotic susceptibility level of each isolate was determined by disk diffusion methods. ESBL production was phenotypically determined using CLSI performance standards (NCCLS, 1999): the inhibition zone diameter of cefotaxime and ceftazidime alone and in combination with 10 μg of clavulanic acid disk was determined. A zone diameter of $\geq$18 mm for ceftazidime indicates susceptibility. A $\geq$5-mm increase in the zone diameter for either antimicrobial agent tested in combination with clavulanic acid versus the zone when tested alone indicates that the bacterium is ESBL-positive. *E. coli* ATCC 25922 and *K. pneumoniae* ATCC 700603 were used as ESBL-negative and ESBL-positive controls, respectively. Isolate from each