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A Nosocomial Outbreak Due to Novel CTX-M-2-Producing Strains of *Citrobacter koseri* in a Hematological Ward

Tsuyoshi Muta*, Nobuko Tsuruta¹, Yumiko Seki², Rika Ota², Satowa Suzuki¹, Naohiro Shibata¹, Koji Kato, Tetsuya Eto, Hisashi Gondo and Yoshichika Arakawa¹

Department of Hematology, ¹Department of Respiratory Disease and ²Department of Clinical Microbiology, Hamanomachi Hospital, Fukuoka 810-8539, and ³Department of Bacterial Pathogenesis and Infection Control, National Institute of Infectious Diseases, Tokyo 208-0011, Japan

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_Citrobacter koseri* is a member of the family *Enterobacteriaceae*. Urinary tract infections caused by *C. koseri* have been observed in as many as 12% of all isolates in adults (1). In compromised hosts, *Citrobacter* spp. could cause pneumonitis, empyema (2), biliary infection (3), and bacteremia (4). *Citrobacter* spp. were formerly susceptible to oximinocephalosporins including cefotaxime (3), but recently, *C. koseri* has been reported to have developed resistance to some cephalosporins and cephaplycin through the production of an inducible chromosomally-encoded cephalosporinase that can inactivate these agents (5). Most clinically isolated *C. koseri* are susceptible to oximinocephalosporins and carbapenems. Recently, oximinocephalosporin resistance among Gram-negative bacteria has been developed due to the hydrolysis of beta-lactams by beta-lactamasas including extended-spectrum beta-lactamas (ESBLs). ESBLs show variable levels of resistance to cefotaxime, ceftazidime, and other broad-spectrum cephalosporins and monobactams. Nosocomial outbreaks due to SHV-4-type ESBL-producing strains and TEM-type ESBL-producing strains of *C. koseri* have already been reported (6,7). We have identified a novel CTX-M-2-type of ESBL among nosocomially isolated *C. koseri* strains, causing a probable outbreak in the hematological ward.

Sixty-eight strains of *C. koseri* were isolated from the blood, urine, feces, sputum, ascites, and pharynx of 31 patients with a hematological malignancy that had lasted over 18 months (Figure 1). *C. koseri* not only colonized but also caused bacteremia, urinary tract infection, enteritis, and peritonitis. These strains showed similar antibiotic susceptibility profiles (Table 1). We collected 5 strains of *C. koseri* from 4 patients (Table 2) and used the double-disk synergy test and plasmid profiling to screen for ESBL-producing strains as reported previously (8,9). All of the 5 strains harbored a plasmid mediating the CTX-M-2 type beta-lactamase gene. Epidemiological study using pulsed-field gel electrophoresis (PFGE) of total DNA prepared from the 5 strains revealed patterns that were indistinguishable from each other (Figure 2). The results suggested that the 5 strains characterized belong to a single epidemic strain.

In general, multiple factors may help to decrease the immunity of patients with hematological malignancies, including impairment of phagocytosis, impaired cellular immunity, and defective production of antibodies. Moreover, intensive chemotherapies usually induce severe granulocytopenia. Thus, bacterial infections are a major cause of complications and death in patients with hematological malignancies. Recently, two studies (10,11) revealed the efficacy of the prophylactic use of quinolone by neutropenic patients. As for febrile neutropenia, empirical antibiotic therapy using ceferpine or cefotaxime has been emphasized (12,13). All 31 patients in this study had hematological malignancy and underwent intensive chemoradiotherapy. After that, most of the patients in our ward were administered prophylactic and therapeutic systemic antibiotics such as quinolone, cefepime, and cefotaxime, which might well be associated with the selection of antibiotic-resistant microorganisms. Unlike other members of the family *Enterobacteriaceae*, CTX-M-2-producing *C. koseri* might survive in a patient’s bowel flora, because of its resistance to oximinocephalosporins and cephalosporins including cefotaxime (3), but recently, *C. koseri* was isolated. The network-breaking characters indicate the samples, from which genetically identical strains were isolated in our study. An infection control team (ICT) intervened in the ward to resolve the outbreak (see article). B, blood; U, urine; St, stool; Ph, pharynx.

*Corresponding author: Mailing address: Department of Hematology, Hamanomachi Hospital, 3-5-27 Maizuru, Chuo-ku, Fukuoka 810-8539, Japan. Tel: +81-92-721-0831, Fax: +81-92-714-3262, E-mail: muta-t@hamanomachi.jp
ance to quinolone, cefepime, and cefotaxime. In addition, urinary tract infections tended to be easily associated with urinary catheterization in our cases. We speculated that the situation was as follows. Once C. koseri colonizes in the bladder or intestine, it will then disseminate into the bloodstream causing severe bacteremia during intensive chemotherapy. The symptoms of sepsis caused by C. koseri were often very serious, and could only be cured by appropriate and immediate administration of carbapenem. However, the use of carbapenem in high amounts and at high frequency in our ward could create a grave epidemiological problem.

The number of C. koseri infections increased significantly, and standard infection control measures were not effective to stop this outbreak. Therefore, we began to enforce the following precautions. We introduced barrier precautions against not only infected patients but also colonized patients, using disposable gloves and drapes. Mandatory hand washing was done immediately before and after any manipulation involved in the nursing care. Hand hygiene using commercial alcoholic disinfectant (Welpas; Maruishi Pharmaceutical Co., Ltd., Osaka, Japan) was promoted not only for medical workers but also for patients. As for the environment, the water taps were converted to hands-free types, and all doorknobs and bars for drip injection were sterilized using 70% alcohol twice daily. We also tried to restrict the prophylactic use of quinolone for high-risk patients with neutropenia decreasing under 100/µL which was keeping for more than 1 week.

After these procedures, the incidence of C. koseri isolation decreased, but this type of infection has not yet been eradicated, as shown in Figure 1. We continue to make an effort to prevent nosocomial transmission of C. koseri.

In this report, we emphasize the appearance of C. koseri and its new type of drug resistance. We also warn that it is quite difficult to control the outbreak of such antimicrobial-resistant microorganisms in a hematological ward. In the future, we must pay close attention to the nosocomial spread of this type of C. koseri, which has demonstrated resistance to a broad spectrum of cephalosporins, cephamycins, and carbapenems.

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