Journal of Hospital Infection (2005) **59**, 317–323

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Risk factors for ICU-acquired imipenem-resistant Gram-negative bacterial infections

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Received 29 February 2004; accepted 19 September 2004
Available online 27 January 2005

KEYWORDS
Antibiotic resistance;
Imipenem;
Acinetobacter;
Pseudomonas aeruginosa

Summary Intensive care units (ICUs) are high-risk areas for infections caused by antibiotic-resistant bacteria. This study investigated the risk factors for ICU-acquired imipenem-resistant Gram-negative infections. It was conducted prospectively in three surgical ICUs and one medical ICU from April to December 2002. ICU-acquired Gram-negative infections were found in 128 patients. Of these, 42 had imipenem-resistant and 86 had imipenem-sensitive Gram-negative bacteria as the cause of infection. According to the univariate analysis results, hospital stay before ICU admission, hospitalization period before ICU admission, length of ICU stay, surgical ICU stay, surgical operation and previous antibiotic use were significant risk factors for the acquisition of imipenem-resistant infections. In the multivariate analysis, length of ICU stay, surgical operation and previous carbapenem use were independently associated with imipenem resistance.

Introduction

The incidence of imipenem resistance is increasing among Gram-negative bacilli, particularly *Pseudomonas aeruginosa* and *Acinetobacter* spp.[1–4] Nosocomial infections due to multidrug-resistant *Acinetobacter* and *Pseudomonas* strains are a growing problem in intensive care units (ICUs) of tertiary care hospitals.[4–6]

Several reports have shown an increase in the frequency of imipenem-resistant (IR) *Acinetobacter* and *Pseudomonas* spp. Ruiz *et al*. reported the percentages of IR *Acinetobacter* strains in 1991 and 1996 as 1.3% and 80%, respectively.[2] Gaynes and Culver found that between 1986–1988 and 1989–1990, the percentage of *P. aeruginosa* isolates resistant to imipenem rose by 25% among teaching hospitals.[4]

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doi:10.1016/j.jhin.2004.09.030

Resistance to imipenem in *P. aeruginosa* is mostly at low level [minimum inhibitory concentration (MIC) 8–32 mg/L]. It is related to diminished penetration due to loss of the outer membrane protein (OmpD2) and continued expression of the chromosomal β-lactamase.[7,8] It has been suggested that imipenem resistance reflects an interplay of the enzyme and impermeability, rather than either factor alone.[9] High-level resistance to imipenem (MIC > 32 mg/L) is still uncommon in *P. aeruginosa* but it can be caused by the presence of transferable plasmid-mediated metallo-β-lactamases.[10] Although this mechanism of resistance is rare, it has the potential for rapid spread.[11] The first metallo-β-lactamase was described in *P. aeruginosa* in Japan.[12] Related to the extensive use of carbapenems, this resistance determinant was disseminated in Japanese hospitals and European countries including the UK, Italy, Greece and Portugal.[11,13–17]

Imipenem resistance in *Acinetobacter* spp. has been associated with a loss of the outer membrane protein or an alteration in penicillin-binding proteins.[18,19] Recently, carbapenem-hydrolysing enzymes have been detected in some acinetobacter isolates and several of these enzymes showed characteristics of metallo-enzymes.[20–22]

ICU-acquired infections due to IR Gram-negative bacteria are not uncommon in our hospital, causing serious therapeutic problems when choosing antibiotic treatment. Thus, we implemented this study to investigate the risk factors for ICU-acquired IR Gram-negative bacterial infections.

Methods

Hospital setting and study population

A prospective case-control study was performed at Ankara Numune Education and Research Hospital (ANERH) in Turkey. ANERH is a 1100-bed referral and tertiary care hospital. The hospital contains all major services, medical and surgical subspecialities, medical and surgical ICUs, except a paediatric department. In total, the ICUs at ANERH have 70 beds and approximately 3700 patients are treated in the ICUs each year. This study was conducted in three surgical ICUs (20 beds) and one medical (eight beds) ICU.

Antibiotic policy

An antibiotic restriction policy has been in operation since January 1999. The approval of an infectious diseases specialist is required for prescribing ceftazidime, cefepime, imipenem, meropenem, ticarcillin-clavulanate, piperacillin-tazobactam, intravenous quinolones, aminoglycosides, vancomycin and teicoplanin, except in the haematology, oncology and bone marrow transplant units.

Collection of data

This study was conducted in three surgical ICUs and one medical ICU from April to December 2002. Patients younger than 16 years of age were excluded. All patients were visited by two infectious diseases specialists daily. Patients who had ICU-acquired Gram-negative bacterial infections were included in the study. Data were recorded on individual forms for each patient until discharge or death. The form included age, sex, diagnosis, date of admission to hospital and ICU, hospitalization period before ICU, length of ICU stay, transfer from another hospital, comorbidity (renal failure, hepatic failure, malignancy, immunosuppression, diabetes mellitus, chronic lung disease, malnutrition, transplantation), elective or emergent surgical operations, APACHE II (Acute Physiological and Chronic Health Evaluation) score,[23] ventilator support, daily physical examination findings, haematological and biochemical test results, nosocomial infections during ICU stay, antibiotics given to the patient in the ICU, culture and antimicrobial susceptibility test results, time between ICU admission and isolation of the first positive culture, and outcome of the patient. The patients were designated as IR cases (case patients) if they had IR bacterial infections and as imipenem-sensitive (IS) cases (control patients) if they had IS bacterial infections. Emergence of resistance during imipenem therapy was also recorded.

Definitions

The diagnosis of ICU-acquired infections was based on the criteria of the Centers for Disease Control and Prevention.[24] An infection that occurred more than 48 h after admission to the ICU was defined as an ICU-acquired infection. Definitions of ICU-acquired infections are shown in Table I.

Microbiological investigations

Identification and antimicrobial susceptibility of Gram-negative bacteria isolated from ICU-acquired infections were performed using a VITEK automated system (biomerieux, France). GNI + panel was used for identification and GNS-111 panel for the detection of antimicrobial susceptibility. Imipenem