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Risk factors for nosocomial imipenem-resistant *Acinetobacter baumannii* infections

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Summary
Objectives: To identify the risk factors for nosocomial imipenem-resistant *Acinetobacter baumannii* (IRAB) infections.
Methods: A prospective case—control study, set in an 1100-bed referral and tertiary-care hospital, of all patients who had nosocomial *A. baumannii* infections between January 1 and December 31, 2004. Only the first isolation of *A. baumannii* was considered.
Results: IRAB was isolated from 66 (53.7%) patients and imipenem-sensitive *Acinetobacter baumannii* (ISAB) was isolated from 57 (46.3%) patients during the study period. The mean duration of hospital stay until *A. baumannii* isolation was 20.8 ± 13.6 days in IRAB infections, whereas it was 15.4 ± 9.4 days in ISAB infections. Of the patients, 65.2% with IRAB infections and 40.4% with ISAB infections were followed at the intensive care unit (ICU). Previous carbapenem use was present in 43.9% of the patients with IRAB and 12.3% of the patients with ISAB infection. In univariate analysis female sex, longer duration of hospital stay until infection, ICU stay, emergent surgical operation, total parenteral nutrition, having a central venous catheter, endotracheal tube, urinary catheter or nasogastric tube, previous antibiotic use, and previous administration of carbapenems were significant risk factors for IRAB infections ($p < 0.05$). In multivariate analysis, longer duration of hospital stay until *A. baumannii* isolation (odds ratio (OR) 1.043; 95% confidence interval (CI) 1.003—1.084; $p = 0.032$), previous antibiotic use (OR 5.051; 95% CI 1.004—25.396; $p = 0.049$), and ICU stay (OR 3.100; 95% CI 1.398—6.873; $p = 0.005$) were independently associated with imipenem resistance.
Conclusions: Our results suggest that the nosocomial occurrence of IRAB is strongly related to an ICU stay and duration of hospital stay, and that IRAB occurrence may be favored by the selection pressure of previously used antibiotics.

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Introduction

Acinetobacter baumannii is an important cause of nosocomial infections in many hospitals, which is difficult to both control and treat because of its prolonged environmental survival and its ability to develop resistance to multiple antimicrobial agents.[1,2] *Acinetobacter baumannii* appears to have a propensity for developing antimicrobial resistance extremely rapidly. Moreover this resistance is multiple, causing serious therapeutic problems.[1] Carbapenems are usually the antibiotics of choice for treating serious infections caused by *A. baumannii*. However, reports of imipenem-resistant *A. baumannii* (IRAB) strains have been rising steadily during the past few years, and these isolates are often multidrug-resistant.[3–6] This emergence of IRAB has become a worldwide problem and a troublesome development that threatens the continued successful treatment of *Acinetobacter* infections.[1,7]

More data regarding the risk factors for IRAB infection are needed in order to prevent infection and to optimize therapy. Previous studies of risk factors for IRAB have focused on an outbreak or colonized/infected patients evaluated together. *Acinetobacter baumannii* is frequently encountered in Turkish hospitals, and many isolates exhibit resistance to the antimicrobials commonly used against such bacterial infections. The present study investigated the risk factors for nosocomial IRAB infections.

Methods

The hospital setting and study population

A prospective case—control study was performed at Ankara Numune Education and Research Hospital (ANERH) in Turkey. ANERH is an 1100-bed referral and tertiary-care hospital. The hospital provides all major services except a pediatric department, including medical and surgical sub-specialties, and medical and surgical intensive care units (ICUs). The annual number of discharges was 55 422 in 2004.

Antibiotic policy

An antibiotic restriction policy has been in effect at ANERH since January 1999. The restriction is for orders of certain antibiotics; a prior consultation with an infectious diseases (ID) specialist is required for ceftazidime, cefepime, imipenem, meropenem, ticarcillin—clavulanate, piperacillin—tazobactam, cefoperazone—sulbactam, intravenous quinolones, intravenous aminoglycosides, vancomycin, and teicoplanin.

Case definition and collection of data

Prospective surveillance was conducted. Patients who had *A. baumannii* infections from January to December 2004 were included in the study. Patients from whom *A. baumannii* isolates had been recovered within 48 h of admission and those younger than 16 years of age were excluded.

Only one isolate from each patient was included (only the first *A. baumannii*-positive specimen). The clinical significance (colonization or infection) of each *A. baumannii* isolate and the type of infection were assessed according to CDC criteria[8,9] by infectious diseases specialists. A urinary tract infection in a patient with an indwelling bladder catheter was diagnosed with detection of pyuria ($\geq$10 leukocytes/mm^3), growth of $\geq 10^5$ CFU/ml bacteria (no more than two species) in urine culture, and clinical signs of infection (fever $\geq$38 °C, leukocytosis, abnormal macroscopic appearance of urine, presence of urinary nitrites). In patients assisted by mechanical ventilation, pneumonia was diagnosed when a new or progressive infiltrate or consolidation in chest X-ray in the presence of purulent tracheal secretions, supported by a growth of $\geq 10^5$ CFU/ml bacteria in a quantitative culture of deep endotracheal aspirate was found. For non-ventilated patients, the diagnosis of nosocomial pneumonia was considered when they had a compatible chest X-ray and purulent sputum, with Gram stain and sputum culture documenting the presence of a pathogen microorganism. Surgical site infection was defined as the presence of purulent drainage and positive clinical findings (incision site pain, tenderness, localized swelling, redness or heat, spontaneous opening of the incision) supported by microbiologic analysis of specimens. Sepsis was diagnosed by the presence of the sepsis criteria and positive blood cultures. Patients colonized with *A. baumannii* were excluded.

Data were recorded on individual forms for each patient. The form included age, sex, diagnosis, date of admission to hospital and ICU, hospitalization period before ICU, length of hospital and 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, ventilator support, physical examination findings, hematological and biochemical test results, antibiotics given to the patient, culture and antimicrobial susceptibility test results, and time between admission and isolation of the first positive *A. baumannii* culture.

Prior exposures to antimicrobial drugs were also explored. Prior antibiotic exposures were defined as at least 24 h of therapy during the 14 days prior to isolation of the *A. baumannii*.

The patients were assigned as IRAB cases (case patients) if they had imipenem-resistant *A. baumannii* infections and as ISAB cases (control patients) if they had imipenem-sensitive *A. baumannii* infections.

Microbiological examination

Identification and antimicrobial susceptibility of the Gram-negative bacteria isolated from ICU-acquired infections were performed by VITEK automated system (BioMerieux). The GNI+ panel was used for identification and GN528 panel for the detection of antimicrobial susceptibility. The isolates with a minimum inhibitory concentration (MIC) value ≥ 8 μg/ml were recorded as imipenem-resistant and those with a MIC value <8 μg/ml as imipenem-sensitive. All of the strains were tested against the following antibiotics: amikacin, gentamicin, aztreonam, ceftazidime, cefepime, imipenem, netilmicin, ciprofloxacin, pefloxacin, piperacillin, piperacillin—tazobactam, ticarcillin, ticarcillin—clavulanate, and trimethoprim—sulfamethoxazole. Intermediately susceptible strains were accepted as resistant.