American Journal of Infection Control 45 (2017) 735-9

Contents lists available at ScienceDirect

American Journal of Infection Control

journal homepage: www.ajicjournal.org

Major Article

Is surveillance for colonization of carbapenem-resistant gram-negative bacteria important in adult bone marrow transplantation units?

Hayati Demiraslan MD [a,*], Fatma Cevahir MS [b], Elife Berk MD [c], Gokhan Metan MD [d], Mustafa Cetin MD [e], Emine Alp MD, PhD [a,b]

[a] Department of Infectious Diseases and Clinical Microbiology, Erciyes University, Melikgazi, Kayseri, Turkey
[b] Infection Control Committee, Erciyes University, Kayseri, Turkey
[c] Department of Medical Microbiology, Erciyes University, Kayseri, Turkey
[d] Department of Infectious Diseases and Clinical Microbiology, Hacettepe University, Ankara, Turkey
[e] Department of Hematology, Erciyes University, Kayseri, Turkey

Key Words:
Carbapenem resistance
Gram-negative bacterial colonization
Hematopoietic stem cell transplantation
HSCT
Risk factors
Surveillance

Background: The aim of this study was to investigate the rate of carbapenem-resistant gram-negative bacilli (CRGNB) colonization and to analyze the risk factors associated with CRGNB colonization.
Methods: This prospective study was conducted in adult patients hospitalized in hematopoietic stem cell transplantation (HSCT) units over a period of 8 months. Rectal swab samples were obtained from each participant every Monday, and patients CRGNB positive on admission were excluded.
Results: Of 185 participants, the median age was 47 years, and 59.5% were men. CRGNB colonization was detected in 21 (11.4%) patients. The most commonly isolated CRGNB were *Escherichia coli*, *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa*. Multivariate analysis revealed that busulfan use (11.9 times), fludarabine use (6.4 times), transfer from another hospital (7.8 times), transfer between units (9.3 times), and central venous catheterization (5.1 times) were risk factors for CRGNB colonization. During the study period, febrile neutropenia (FN) developed in 9 (56.2%) of the 21 colonized patients, and 1 patient died.
Conclusions: Screening of patients for CRGNB colonization may have a role in preventing the spread of CRGNB. However, the empirical antimicrobial treatment for FN in patients with CRGNB colonization did not change, and their mortality rates were similar.

The antimicrobial treatment of neutropenic patients is difficult, and it almost always includes an empirical approach.[1] An appropriate antimicrobial therapy is crucial for patients, and it generally depends on the patient's microflora and the antimicrobial susceptibility pattern of bacteria.[2] Surveillance is the best way to determine the agents of colonization with resistant microorganisms in targeted units. With respect to the source of infections in neutropenic patients, the main source is the patient's own skin bacterial flora followed by gut microbial flora.[3,4] Colonization with gram-negative bacteria of the gastrointestinal tract may cause bloodstream infection through small mucosal injuries as a result of cancer chemotherapy regimens.[5] In recent years, mucosal barrier injury–related bloodstream infection was defined as mucosal translocation of enteric bacteria in neutropenic patients.[6] Carbapenems was first-line therapy because of the high rate of extended-spectrum β-lactamase (ESBL)–producing *Enterobacteriaceae* bacteremia in hematologic malignancy patients with febrile neutropenia (FN).[1] The bacteremia caused by carbapenem-resistant gram-negative bacteria (CRGNB) was rare and limited to *Acinetobacter baumannii* and *Pseudomonas aeruginosa* in the febrile neutropenic patients in our center.[7] However, a carbapenem-resistant *A baumannii* outbreak was experienced recently in the hematology wards, and sporadic cases of carbapenem-resistant *Klebsiella pneumoniae* (CRKP) bacteremia were detected.[8,9] In hospitals where CRGNB infections are frequent, active surveillance for detecting CRGNB colonization may be useful in order to administer an effective empirical antimicrobial and prevent transmission to noncolonized patients in the ward.

* Address correspondence to Hayati Demiraslan, MD, Department of Infectious Diseases, Faculty of Medicine, Erciyes University, Melikgazi, Kayseri 38039, Turkey.
E-mail address: tigin68@hotmail.com (H. Demiraslan).
Previous presentation: A part of this study was presented as a poster at the 6th Eurasia Congress of Infectious Diseases, September 24-27, 2014, Belgrade, Serbia.
Funding/support: Supported by the Scientific Research Foundation of Erciyes University (project no. TYL-2014-5026).
Conflicts of interest: None to report.

0196-6553/
http://dx.doi.org/10.1016/j.ajic.2017.01.006

Active surveillance in patients who are exposed to carbapenem-resistant *Enterobacteriaceae*-infected or -colonized patients is recommended as part of infection control.[10] Patients infected or colonized with CRGNB in a unit may be a source of resistant microorganisms.[4] Although many studies have been reported about colonization with ESBL-producing pathogens or CRKP, few studies on colonization with CRGNB have been conducted, especially in hematology patients.[11-14]

The aim of this prospective observational study was to determine the frequency of CRGNB colonization, risk factors, and rate of bacteremia with CRGNB in colonized hematology patients.

PATIENTS AND METHODS

Setting

This study was conducted at the HSCT unit of the Erciyes University Hospital, a 1,300-bed, tertiary care center in the Central Anatolia region of Turkey, between November 2013 and June 2014. The HSCT units have 28-bed capacity, and all rooms have positive pressure air circulation filtered by a high-efficiency particulate air filter. Also, there is a 7-bed unit that has a portable air filter and purifier. Each patient has a single bedroom. Antimicrobial prophylaxis in allogeneic or autologous HSCT was given to patients, according to the guidelines.[4] Antibacterial prophylaxis with levofloxacin was administered on the same day as stem cell infusion and continued until recovery of neutropenia with engraftment. Acyclovir was administered, including in the posttransplant first 4-week period. Moreover, a preemptive approach was preferred for prevention of cytomegalovirus (CMV) disease, and CMV viremia was surveilled by using polymerase chain reaction weekly. An antifungal (fluconazole or posaconazole if the patient suffered from advanced graft versus host disease) was used in the first 75 days depending on risk status for mold infection, and trimethoprim-sulfamethoxazole (SXT) for *Pneumocystis jirovecii* was given from after engraftment up to day 180.

Colonization was defined as the existence of at least 1 positive rectal swab sample for CRGNB.[15] Clearance of colonization was defined as ≥3 consecutive cultures from rectal swab samples in which CRGNB was not recovered.[16] No decolonization procedure was administered during this study period. Antimicrobial therapy used in the last 90 days and cancer drugs used in the last 30 days were recorded.

Patients and study design

All adult patients (≥18 years) who had undergone or were undergoing HSCT were included and were evaluated for each hospitalization in the study. Demographic characteristics and risk factors of the patients were recorded at the time of rectal swabbing. Rectal swab samples were obtained from each participant in the first 48 hours of admission and every Monday. The patients who had a CRGNB, recovered from rectal sample or blood on admission and who were admitted to the outpatient clinic were excluded from the study. Thereafter, obtained samples were swabbed on selective media CHROMagar KPC (CHROMagar, Paris, France). In case of isolation of the bacterial colony from the selective media, it was gram stained, and carbapenem resistance was confirmed by modified Hodge test. Also, identification of the bacteria was performed by API20E/20NE (bioMérieux, Craponne, France).

Statistical analysis

Patients with and without colonization with CRGNB were compared for risk factors. Univariate analysis and multivariate logistic regression analysis were performed (95% confidence interval). A *P* value <.05 was accepted as statistically significant. The SPSS 15.0 package program (SPSS, Chicago, IL) was used for statistical analysis. This study was approved by the local ethics committee (approval no. 2013/644). Informed consent was obtained from all individual participants included in the study.

RESULTS

A total of 352 hospitalizations of 200 patients were detected during the study period; 15 patients were excluded because of CRGNB colonization or infection at the start of the study (n = 6) or because they did not give acceptance for rectal swab sample (n = 9). A total of 1,225 rectal swab samples were obtained from 185 participants. The median age was 47 (range, 18-75) years, and 59.5% were men. Underlying diseases were acute leukemia (36.8%), multiple myeloma (35.1%), lymphoma (14.6%), aplastic anemia, myelodysplastic syndrome (8.1%), and testis tumor (1.6%). The number of HSCT recipients was 107 (57.8%): 53 patients were autologous HSCT recipients, and 54 were allogeneic HSCT recipients (including 18 haploidentical recipients [33.3%]). The median length of hospital stay before colonization was 22 days (25th-75th quartile range, 14-30 days) (Table 1).

Colonization with CRGNB

Of the 185 patients, 21 (11.4%) were colonized with CRGNB. The median duration for CRGNB colonization was 24 days (range, 8-165 days). The earliest detected colonization time was day 8 in 1 patient. The average follow-up period was from 1 week to 8 months for colonized patients. The median sample number was 4 (range, 1-40) for each patient. Patients were colonized with *Escherichia coli* (n = 10), *K pneumoniae* (n = 4), *P aeruginosa* (n = 5), *A baumannii* (n = 2), *Enterobacter cloacae* (n = 1), and *Stenotrophomonas maltophilia* (n = 1). In 2 patients, multiple bacteria were isolated as *E coli–K pneumoniae* and *P aeruginosa–A baumannii*. The mean colonization days after admission to hospital were 26.2 (range, 18-165) for *E coli*, 52.0 (range, 8-54) for *P aeruginosa*, and 22.7 (range, 14-34) for *K pneumoniae*; there was no difference among isolated bacterial types in terms of mean colonization days (*P* = .778).

Risk factors for colonization

There were no statistically significant differences between patients with and without colonization of CRGNB in terms of diabetes mellitus, obesity, diarrhea, serum CMV DNA positivity, number of red blood cell transfusion, port and peripheral venous catheterization, cancer chemotherapeutics (melphalan, cyclophosphamide, etoposide, cytarabine), and previous antimicrobial use in 90 days (β-lactam, carbapenem, quinolone, colistin, metronidazole, fluconazole, voriconazole, posaconazole, and amphotericin B). Table 1 shows overall characteristics of patients with or without colonization of carbapenem-resistant gram-negative bacteria in univariate analysis.

In univariate analysis, significant variables were found to be steroid use, presence of concurrent invasive fungal infection, total parenteral nutrition, central venous and urinary catheterization, use of cancer drugs (thymoglobulin, busulfan, fludarabine, and thiotepa), use of antibiotics (SXT, glycopeptides, and caspofungin), a transfer from another hospital or unit, and previous intensive care unit (ICU) stay. Multivariate analysis showed that busulfan use (risk ratio [RR], 9.0), fludarabine use (RR, 6.4), transfer from another hospital (RR, 7.8), transfer from another unit (RR, 9.3), and central venous catheterization (RR, 5.1) were risk factors for CRGNB colonization (Table 1). The rate of urinary catheterization in patients who stayed