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Clostridium Difficile Infection in Patients with Acute Myelogenous Leukemia and in Patients Undergoing Allogeneic Stem Cell Transplantation: Epidemiology and Risk Factor Analysis

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A B S T R A C T

Patients receiving treatment for acute myelogenous leukemia (AML) and recipients of allogeneic stem cell transplantation (aSCT) are at high risk of contracting *Clostridium difficile* infection (CDI), the most frequently observed nosocomial diarrhea and enterocolitis. Data were retrieved from the prospective Cologne Cohort of Neutropenic Patients. Patients hospitalized for aSCT as well as patients receiving treatment for AML were included in the analysis. Risk factor analysis for the occurrence of CDI was performed by backward-stepwise logistic regression ($P < .1$). During the period from January 2007 to August 2010, 310 hospitalizations of 152 patients with AML and 229 hospitalizations of 223 patients undergoing aSCT were eligible for analysis. Incidence rates for CDI per 10,000 patient days were 17.9 for AML patients and 27.4 for aSCT recipients. Among AML and aSCT patients, median time from initiation of chemotherapy to CDI was 10 days (range, −8 to 101 days) and 17 days (range, 6 to 79), respectively. Logistic regression identified carbapenem exposure to be associated with development of CDI in AML patients (odds ratio [OR], 2.2) and aSCT recipients (OR, 1.4). In both groups, previous exposure to carbapenems was significantly associated with development of CDI. A follow-up study, assessing the effect of an antibiotic stewardship intervention to decrease the administration of carbapenems in hematological high-risk patients, is warranted.

INTRODUCTION

Clostridium difficile infection (CDI), the most frequently observed type of nosocomial diarrhea, is defined as the presence of gastrointestinal symptoms and microbiological findings indicating the presence of toxin-producing *C. difficile* or colonoscopic findings showing typical signs of pseudomembranous colitis [1,2]. Clinical manifestation is variable, ranging from mild or moderate diarrhea to fulminant, life-threatening pseudomembranous colitis [2].

Earlier studies have identified a variety of risk factors associated with development of CDI. Disruption of enteric flora by antibiotic exposure, especially with cephalosporins and clindamycin, seems to play a key role in manifestation of CDI [3]. Concordantly, patient groups with severe immunosuppression and high antibiotic exposure, eg, patients receiving chemotherapy for acute myelogenous leukemia (AML) or undergoing allogeneic stem cell transplantation (aSCT), were identified as high-risk populations displaying incidence rates per hospitalization of 4.8% to 9.3% [4,5] and 12.5% to 30% [6-8], respectively.

In view of these considerably elevated rates, it seems reasonable to identify and explore potentially preventive measures. In addition, it has been hypothesized that gastrointestinal graft-versus-host disease (GVHD), a severe complication in aSCT recipients, may be triggered by CDI [7,9-11]. Preventing CDI may, therefore, reduce the incidence of gastrointestinal GVHD, with the potential of reducing severe morbidity and even mortality.

Previous publications have shown that antibiotic stewardship may effectively decrease the rate of CDI [12,13]; however, identification of antimicrobials driving development of CDI in these high-risk populations would have to precede such an intervention. Only a few authors have assessed risk factors for CDI in patients undergoing treatment for AML [4] and recipients of an aSCT [7,8]. These

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studies have covered the period of 2003 to 2008, when myeloablative conditioning regimens with high doses of total body irradiation (TBI) were still the predominant treatment strategy. Furthermore, only 1 of these studies evaluated different classes of antibiotics as independent risk factors [7]. However, some standard-of-care agents for patients with febrile neutropenia, eg, the carbapenems [14], were not included into this analysis.

Further studies are needed to identify potential targets for an antibiotic stewardship intervention that might decrease the incidence of CDI in hematological high-risk patients. To this end, we performed a prospective cohort study that assessed the epidemiology of and risk factors for CDI at the Department I of Internal Medicine, University Hospital of Cologne, Germany.

DESIGN AND METHODS

Trial Design

For this study, data were retrieved from the prospective Cologne Cohort of Neutropenic Patients, analyzed, and reported in agreement with Strengthening the Reporting of Observational Studies in Epidemiology statement [15]. The Cologne Cohort of Neutropenic Patients is a non-interventional cohort in which data on risk factors, interventions, and outcome of immunocompromised patients at risk of opportunistic infections are collected (NCT01821456). Data from all patients undergoing chemotherapy at the Department I of Internal Medicine at the University Hospital of Cologne, Cologne, Germany, are incorporated into the database.

Data capture included demographic data; gender; weight; height; underlying disease; dates of admission and discharge; type of conditioning treatment; type of transplantation; duration of neutropenia; information on donor mismatch status; cytomegalovirus status of transplant donor and recipient; occurrence and severity of acute GVHD; onset and duration of diarrhea; *C. difficile* toxin test results; administration of antimicrobials, proton pump inhibitors (PPI), and immunosuppressants; use of hematopoietic growth factors; admission to intensive care unit; follow-up duration; and survival.

For documentation, a custom platform based on Microsoft SQL Server 2005 and Microsoft Access 2007 (both by Microsoft Corporation, Redmond, WA) was developed in cooperation with System AG für IT-Lösungen, Lohmar, Germany.

Additional data were obtained from the gastroenterology unit, including macroscopic and histological findings of all colonoscopies and sigmoidoscopies carried out in the documented period to identify all patients in whom an acute GVHD or pseudomembraneous colitis was diagnosed.

Setting

All patients were diagnosed and treated in accordance with local hospital care standards, which are defined during regular meetings by specialists in oncology, hematology, transplantation medicine, and infectious diseases. Patients receiving treatment for acute leukemia received antibiotic prophylaxis with trimethoprim and sulfomethoxazole. Fluoroquinolone prophylaxis was provided to transplant recipients with the start of the conditioning regimen. AML patients were treated in a regular ward in single or double rooms. All aSCT recipients were treated in single rooms with high-efficiency particulate absorption filtration on an isolation ward.

Study Patients and Patient Groups

All consecutive patients hospitalized at the Department I of Internal Medicine for an aSCT and patients receiving treatment for AML during the period from January 2007 to August 2010 were included into the analysis. Earlier patients were excluded because of major changes in treatment practice in 2006 (introduction of posaconazole for AML patients and abolishment of sterile care for aSCT recipients). There were no formal exclusion criteria. Because of substantial differences in potential risk factors, patient groups (AML patients and aSCT recipients) were analyzed separately.

Definitions and Endpoints

Diarrhea was defined as 3 or more unformed stools within 24 hours or $>$ 600 mL unformed stool in patients with a rectal stool collector.

A case of CDI was defined according to the European Society of Clinical Microbiology and Infectious Diseases [1]. The diagnosis of CDI was confirmed when a patient presented with diarrhea and a stool test was positive for toxin-producing *C. difficile*. We required a positive stool toxin assay at most 4 days before or after diarrhea for diagnosis of CDI. The toxin assay used by the hospitals laboratory at the time of the study was an EIA for toxin A and B (RIDASCREEN, R-Biopharm, Darmstadt, Germany). Only unformed stool samples are tested for *C. difficile* toxin in our microbiology department. Relapse of CDI was defined as new onset of CDI as defined above after at least 7 days without clinical symptoms of CDI.

Neutropenia was defined as an absolute neutrophil count of less than 500 neutrophils/μL or, if not available, a white blood cell count of less than 1000 leukocytes/μL.

The observational period started with admission and ended upon discharge from hospital or death, whichever occurred first.

Acute GVHD of the gastrointestinal tract was diagnosed by histology obtained during endoscopy (sigmoidoscopy or colonoscopy). If there was no pathologic report available, diagnosis was exclusively based on macroscopic endoscopic evaluation.

Response to CDI treatment was defined as resolution of diarrhea within 10 days of specific antibiotic therapy (metronidazole i.v./per oral [p.o.] and/or and vancomycin p.o.). When a combination of both antibiotics was used, beginning of antibiotic treatment was the first day of administration of the first substance used.

Data Analysis and Endpoints

Statistical analyses were carried out using IBM SPSS Statistics software (version 21, IBM Corporation, Armonk, NY). Analysis of frequencies was performed in a descriptive fashion. Risk factor analyses for the occurrence of CDI (AML patients and aSCT recipients) and of acute gastrointestinal GVHD (aSCT recipients only) were performed by backward-stepwise logistic regression analysis. Potential risk factors were eliminated on $P \geq .1$.

Variables were preselected based on a literature search on potential risk factors and confounders. For AML patients, the following variables were included into the analysis: age $>$ 60 years; chemotherapy type; duration of neutropenia; duration of hospitalization; administration of cephalosporins, fluorquinolones, acylaminopenicillin+ß-lactamase inhibitors, carbapenems, glycopeptides, and aminoglycosides; overall number of antibiotics; and PPI administration [3,4,16]. For the detection of potential risk factors for CDI in aSCT recipients, the following variables were included into the analysis: age $>$ 60 years; underlying condition; conditioning regimen; chemotherapy before aSCT; duration of neutropenia; duration of hospitalization; TBI $\geq$ 12 Gy; acute gastrointestinal GVHD; administration of fluorquinolones, acylaminopenicillin+ß-lactamase inhibitors, carbapenems, and glycopeptides; overall number of antibiotics; and PPI administration [3,7,8,11,16]. As opposed to the analysis for the group of patients with AML, this analysis did not include cephalosporins, as they are not part of our standard of care in aSCT patients.

For the detection of potential risk factors for acute gastrointestinal GVHD in aSCT recipients, the following variables were included into the analysis: age $>$ 60, cytomegalovirus donor status, mismatches, TBI $\geq$ 12 Gy, CDI, and glycopeptide administration [7,9-11,17]. For all logistic regression analyses, only the first hospitalization of each patient was used.

Ethical Statement

This study is a strictly observational epidemiological cohort study. Only data that were collected as part of standard care have been analyzed. All authors were directly involved in patient care at the University Hospital of Cologne. Data were collected and stored on site in accordance with current techniques of privacy assurance. Under these circumstances, according to § 15 subparagraph 1 "Berufsordnung für die nordrheinischen Ärztinnen und Ärzte" (code of medical ethics for physicians in the state of Northrhine-Westfalia) [18] and § 6 subparagraph 2 "Gesundheitsdatenschutzgesetz - GDSG NRW" (health privacy law for the state of Northrhine-Westfalia) [19], no formal vote by an ethics committee or informed consent was necessary for this study.

RESULTS

A total of 310 hospitalizations of 153 patients receiving treatment for AML and 235 hospitalizations of 229 patients receiving aSCT were identified. After exclusion of hospitalizations with incomplete files, 310 hospitalizations of 153 patients with AML and 229 hospitalizations of 223 patients undergoing aSCT were eligible for further analysis (Supplementary Figure 1).

C. Difficile Infection in AML Patients

Detailed characteristics during first documented episodes of patients with AML and patients receiving aSCT are shown in Tables 1 and 2, respectively. The majority of