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Incidence and clinical impact of extended-spectrum-β-lactamase (ESBL) production and fluoroquinolone resistance in bloodstream infections caused by *Escherichia coli* in patients with hematological malignancies

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Summary *Objectives:* To identify risk factors for mortality in patients suffering from hematological malignancies with concurrent bacteremia caused by *Escherichia coli*. Particular attention was focused on defining the impact of extended-spectrum-β-lactamase (ESBL) production and fluoroquinolone resistance by the bacterial isolates on mortality.
Materials and methods: A retrospective eight-year cohort study design was employed. The outcome measured was death within 30 days of the first positive blood culture. Survivor and non-survivor subgroups were compared to identify predictors of mortality.
Results: A total of 62 episodes of bacteremia caused by *E. coli* were analyzed. The overall incidences of ESBL production and fluoroquinolone resistance were 41.9% and 62.9%, respectively. The overall 30-day mortality rate was 20.9% (13/62). In a multivariate analysis, significant predictors of mortality were inadequate initial antimicrobial therapy (OR = 14.96, 95% CI 1.95–114.51; $P = 0.009$), infection caused by ESBL-producing isolates (OR = 8.84, 95% CI 1.48–52.91; $P = 0.01$), and prolonged neutropenia (OR = 8.10, 95% CI 1.29–50.57; $P = 0.02$).

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Conclusions: Sound knowledge of the local distribution of pathogens and their susceptibility patterns and prompt initiation of effective antimicrobial treatment are essential in patients suffering from hematological malignancies with BSIs caused by *E. coli*.

Introduction

Bloodstream infections (BSIs) are among the most common complications observed in patients with lymphomas, leukemias, multiple myeloma, and febrile neutropenia, with a prevalence that ranges from 11% to 38%.[1–4] In 2001, Collin et al. reported BSI occurrence within 5 days of bone marrow infusion in approximately 35% of patients who underwent bone marrow transplantation.[5] *Enterobacteriaceae*, in particular *Escherichia coli*, have been reported, at different frequencies, as the most prevalent gram-negative organisms that cause bacteremia in cancer patients.[5–11]

Increasing rates of drug resistance among gram-negative bacteria are reported in several hospitals, including cancer centers.[5,10,11] In particular, antibiotic-resistant mutant strains that produce extended-spectrum-β-lactamases (ESBLs) have emerged among the *Enterobacteriaceae*, predominantly *Klebsiella pneumoniae* and *E. coli*.[12–15] ESBLs are plasmid-mediated β-lactamases that confer resistance to oxyimino cephalosporins and monobactams.[16] These enzymes are globally widespread, but the prevalence and phenotypic characteristics among clinical isolates may vary among geographical areas.[17,18]

The routine introduction of antibiotic prophylaxis in high-risk neutropenic patients, especially with fluoroquinolones, significantly reduced infection-related mortality.[19] Several studies have reported increasing rates of fluoroquinolone resistance, particularly in *Enterobacteriaceae*, worldwide throughout the last two decades, and many have identified previous fluoroquinolone exposure as the most significant risk factor.[20–25] Although a recent meta-analysis demonstrated that there is no significant relationship between fluoroquinolone-based prophylaxis and colonization and/or infections by quinolone-resistant bacteria in neutropenic patients,[26] the role of fluoroquinolone prophylaxis in the increase in infections caused by fluoroquinolone-resistant gram-negative bacteria and their clinical impact remain unclear.

The aims of the present study, conducted in an Italian university hospital over an eight-year period, were: to evaluate the percentage of ESBL production and resistance to fluoroquinolone among *E. coli* strains causing BSI in patients with hematological malignancies; to identify the primary characteristics of patients according to ESBL production and/or fluoroquinolone resistance of bacterial isolates; and to evaluate the impact of ESBL production and fluoroquinolone resistance on 30-day mortality.

Materials and methods

Setting

The Catholic University Hospital is a 1700-bed university hospital located in Rome, Italy, and admits approximately 60,000 patients per year. The hospital has medical, surgical, and neonatal wards, as well as intensive care and post-surgical units. The hematology ward has a total of 30 beds, 8 of which are reserved for patients undergoing hematopoietic stem cell transplantation (HSCT).

Study design and patients

The computerized database maintained by the hospital microbiology laboratory was used to identify episodes of bacteremia caused by *E. coli* in patients aged ≥ 15 years who had been admitted to the hematology ward with a diagnosis of hematological malignancy between 1 January 2000 and 31 December 2007. The patients were divided into groups according to fluoroquinolone resistance and production of ESBL by the bacterial isolates. Recurrent infections were excluded, and only the first episode per patient was included in our analysis.

A retrospective cohort study design was used. The outcome measure was death within 30 days of the first positive blood culture. Survivor and non-survivor subgroups were compared in order to identify predictors of 30-day mortality.

Definition of study terms

Data collected from the hospital charts and the laboratory database included patient demographics, disease and disease stage at time of bacteremia, type of HSCT (autologous or allogeneic), medical history, clinical and laboratory findings, treatment, and outcome of infection. The following terms were defined prior to data analysis:

E. coli-BSI — a bloodstream infection (BSI) documented by blood culture positivity (at least one specimen) for a strain of *E. coli* in patients with systemic inflammatory response syndrome (e.g., fever, tachycardia, tachypnea, and leukocytosis).[27]

Stages of hematological malignancies — (a) induction of complete remission (CR): in this category were included those patients who developed bacteremia during the aplasia that followed chemotherapy performed in order to induce a first CR, or during reinduction therapy after the first relapse of hematological malignancy; (b) patients in CR: this group comprised patients who developed bacteremia when they had already achieved CR; and (c) refractory/relapsed: this group included patients who were unresponsive to chemotherapy and those who had relapsed after two or more complete remissions.

BSI onset — the date of collection of the first blood culture yielding the study isolate (index culture).

BSI source — infection at a distant site caused by a microbial strain identical to the bloodstream isolate, as documented by microbiological and physicians' findings.