Prevalence of infectious multi-drug resistant bacteria isolated from immunocompromised patients in Tunisia

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Abstract

Objectives: A retrospective study was conducted in the Bone Marrow Transplant Center of Tunisia during a period of 10 years (from 2002 to 2011) in order to report the prevalence of infectious multi-drug resistant bacteria.

Methods: Bacterial identification was carried on the basis of biochemical characteristics and API identification systems. Antibiotic susceptibility was tested by disc diffusion method on Muller-Hinton agar.

Results: During the study period, 34.5% of 142 *Klebsiella pneumoniae* strains and 11.46% of 218 *Escherichia coli* strains were extended-spectrum beta-lactamase (ESBL) producers. Also, 32.8% of 210 strains of *Pseudomonas aeruginosa* were imipenem and/or ceftazidime resistant and 20.75% of 106 strains of *Staphylococcus aureus* were methicillin resistant. A rising trend was observed for the prevalence of the selected multidrug resistant bacteria.

Conclusion: These findings may have important clinical implications in prophylaxis and selection of antibiotic treatment. Continuous surveillance is needed, especially for onco-hematological patients.

Keywords: Infectious multi-drug resistant bacteria, immunocompromised patients, Tunisia.

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Introduction

Increasing antibiotic resistance in bacteria is a cause of concern in the treatment of infections, particularly in hematopoietic stem cell transplant patients who have a greater propensity toward acquiring infections because of the underlying immunosuppression. Multidrug-resistant infections pose a major quandary for clinicians by complicating therapy choice, compromising patient recovery, and creating a serious threat to public health[1].

Multidrug resistant (MDR) organisms are defined as microorganisms that are resistant to one or more classes of antimicrobial agents[2]. In Northern Africa, there is a paucity of data concerning MDR profiles in hematology centers .

Organisms such as methicillin-resistant *Staphylococcus aureus*, imipenem and/or ceftazidime resistant *Pseudomonas aeruginosa*, and ESBL producing *Enterobacteriaceae* have become problematic at variable frequencies in different transplantation centers. These organisms can be acquired through the gastrointestinal tract early after hematopoietic stem cell transplantation and later through multiple different routes, especially in people in whom endogenous flora have been altered due to prolonged or recurrent antibiotic exposure. In addition, bacteria have the ability of easily transfer genes, which contributes to perpetuation of the resistant species[3].

Facing the growing problem of bacterial resistance, the aim of this study was to evaluate the MDR prevalence among hematological cell transplant patients, to provide information to fight against these organisms spread.

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Materials and methods

Bacterial collection

From 2002 to 2011, infectious bacteria isolated from pa-

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tients monitored in the Bone Marrow Transplant Center of Tunisia, were screened for multidrug resistance. Only one representative isolate from each specimen per patient, regardless of clinical significant isolates, was included in the analysis. Bacterial isolates included in the present study were ESBL producing *Escherichia coli* and *Klebsiella pneumoniae*, imipenem and/or ceftazidime resistant *P. aeruginosa* and methicillin resistant *S. aureus*.

Patients

Allogeneic stem cells recipients were hospitalized in laminar air-flow rooms, whereas autologous stem cells recipients were treated in single conventional rooms. All patients received non absorbable oral antibiotic (colimycin and gentamycin). Oral amphotericin B was administered as antifungal prophylaxis. Antibacterial prophylaxis with fluoroquinolones was not given. No systemic antibiotic was used as routine prophylaxis. The initial empirical treatment of neutropenic fever consisted of piperacilline-tazobactam associated with amikacin or ciprofloxacin. Glycopeptides or intravenous amphotericin B deoxycholate are used in second or third line therapy.

Bacterial identification

Bacterial identification was carried on the basis of standard cultural, morphological and biochemical characteristics (Gram staining, catalase and oxydase tests) and by the API identification systems (bioMérieux, Marcy-l'Étoile, France).

Antimicrobial susceptibility testing

Antibiotic susceptibility of the isolates was tested by disc diffusion method according to the recommendations of the Antibiogram Committee of the French Society for Microbiology (http://www.sfm-microbiologie.org/). *E. coli* CIP 7624 (ATCC 25922) was used as reference strain for antibiotic susceptibility testing quality control. Also, external quality controls were conducted regularly by the Tunisian health ministry.

Ethics statement

This study was performed with approval from the Local Medical Ethical Committee of Charles Nicolle Hospital, Tunis, Tunisia. As the strains were deidentified and analyzed anonymously, and the strains, not a human, were studied, this is exempt from human research committee approval according to the regulations of the Local Medical Ethical Committee of Charles Nicolle Hospital, Tunis, Tunisia and informed consent is not required according to the Ethical Committee.

Results

In the study period, we isolated 218 *E. coli*, 210 *P. aeruginosa*, 142 *K. pneumoniae* and 106 *S. aureus* (Table1).

The rate of ESBL producing strains was of 34.5% (49/142) for *K. pneumoniae* and 11.46% for *E. coli* (25/218). Imipenem and/or ceftazidime resistance rate accounted for 32.8% (69/210) in *P. aeruginosa*. Methicillin resistant *S. aureus* was of 20.75% (22/106) (Table 1).

Table 1. Distribution of MDR bacteria rates by species

	P. aeruginosa	*K. pneumoniae*	*E. coli*	*S. aureus*	Total
Total isolates	210	142	218	106	676
MDR %	69(32.8%)	49 (34.5%)	25 (11.46%)	22 (20.75%)	165 (24.4%)
MDR rates /1000 patients-days	1.32	0.94	0.48	0.42	3.03

The prevalence of MRSA increased from 0 to 0.22 per 1,000 patient days. The frequency of ESBL producing organisms trended up from 0 to 1.32 per 1,000 patient days for *K. pneumoniae* and from 0.25 to 1.55 per 1,000 patient days for *E. coli*. The rate of imipenem and/or ceftazidime resistance increased from 2.07 to 2.21 per 1,000 patient days for *P. aeruginosa* (Figure 1).

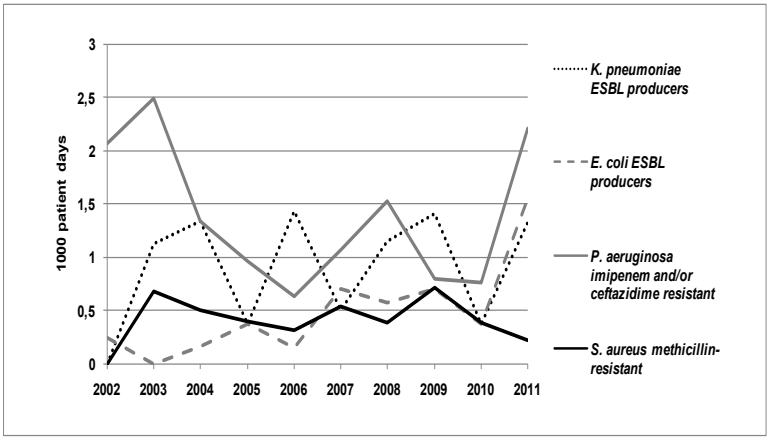

Figure 1. Percentage of MDR bacteria rates expressed by 1,000 patient days

Discussion

Infections caused by MDR organisms are associated with increased mortality, hospital length of stay, and health care costs[4]. Patients with cancer are exposed to a wide range of infections. Many of the challenges surrounding infection control are the same for patients with cancer as for other hospital in-patients[5].

In our study, the most common MDR organisms were *K. pneumoniae* (34.5%) and *P. aeruginosa* (32.8%) followed by *S. aureus* (20.75%) and *E. coli* (11.46%). These differences in MDR organisms incidence may be the evidence that measures taken for the global MDR organisms reduction may have distinct effect for each micro-organism.

Methicillin-resistant *S. aureus* is the most important cause of antibiotic-resistant healthcare-associated infections worldwide. Also, MRSA bloodstream infections can cause significant morbidity and mortality in patients with cancer[6]. In the study period, an increasing trend was observed among our MRSA isolates from 0 to 0.22 per 1,000 patient days. Similarly, the rate of MRSA trended up from 0.3 to 1.0 isolates/1000 patient in an American hematological malignancy and transplantation unit, from 1999 to 2004[7]. In contrast, the rate of MRSA health care-associated infection declined 3.4 fold in an American liver transplant intensive care unit from 4.1 per 1,000 patient days during 2001–2003 to 1.2 per 1,000 patient days during 2004–2006[8].

In our study, 20.75% of our *S. aureus* strains were methicillin resistant. Similarly, 23% of Pennsylvanian patients who received liver transplants develop MRSA infections, from 1990 through 1998[9]. The same percentage of MRSA (23%) is found in an American study conducted from 1999 to 2006, among *S. aureus* causing bacteremia after allogeneic hematopoietic stem cell transplantation[10]. MRSA account for 36% in German patients with a bone marrow or peripheral blood, from 2000 to 2003[11]. MRSA rate among American patients with febrile neutropenia, from 1999 to 2004, is approximately four times higher than that reported in our study (80% vs 20.75%) .

ESBL-producing *K. pneumoniae* may cause serious infections such as bacteremia, pneumonia, and urinary tract infection especially in critically ill patients[12]. In our study, the frequency of *K. pneumoniae* ESBL producers organisms trended up from 0 to 1.32 per 1,000 patient days. In an American neonatal intensive care unit, the incidence of *K. pneumoniae* ESBL infection peaked from 0 in June 2000 to 4.1 cases per 1,000 patient-days in April 2001[13]. During this study period, the level of *K. pneumoniae* ESBL producers reached 34.5%. This rate was two times lower than that reported in a Korean blood and marrow transplantation center, from 2009 to 2010, among *K. pneumoniae* ESBL producers causing blood stream infections (34.5%. vs 71.0%). A comparable rate (37.8%) was found among *K. pneumoniae* ESBL-producers strains causing

bloodstream infection in a Brazilian cancer center, from 2000 to 2002[15]. A higher rate of 51.6% is found in ESBL *K. pneumoniae* bloodstream infection among Malaysian febrile neutropenic patients, between 1996 and 1997[16].

E. coli is the most common Gram-negative bacterium causing bacteremia among neutropenic hosts[17]. The frequency of our *E. coli* ESBL producers strains increased from 0.25 to 1.55 per 1,000 patient days, in the study period. In contrast, ESBL-producing *E. coli* had non-significant decrease from 0.38 to 0.11 per 100 patient-days in a Brazilian non-teaching hospital[18]. In our center, *E. coli* ESBL producing was of 11.46%. A comparable rate of 12.6% is found in *E. coli* ESBL strains causing bacteraemia among Spanish patients with cancer[19]. According to a Brazilian study conducted in a cancer center from 2000 to 2002, *E. coli* ESBL producing strains isolated from bloodstream infection were of 8.9%[15]. In contrast, ESBL producers accounted for 31.9% of *E. coli* strains of bloodstream infections in a Korean blood and marrow transplantation center, during the period from 2009 to 2010[14]. A much higher rate of *E. coli* ESBL producers (55%) is found among Texan patients with hematologic malignancies, during the period from 2003 to 2007[20]. The rate of acute prostatitis caused by *E. coli* ESBL after transrectal prostate biopsy was of 43% in a Turkish study conducted from 2003 to 2008[21].

MDR *P. aeruginosa* strains are increasing in frequency[22] and have been very recently described as a growing problem also in adult onco-hematologic patients[23]. In our study, the imipenem and/or ceftazidime resistance rate among *P. aeruginosa* strains increased from 2.07 to 2.21 per 1,000 patient days. In a Brazilian non-teaching hospital, the rate of imipenem resistant- *P. aeruginosa* decreased from 1.37 per 100 patient-days (June-December 2002) to 0.78 per 100 patient-days (December 2002-May 2003)[18]. 32.8% of our *P. aeruginosa* strains were imipenem and/or ceftazidime resistant. In a Chinese hematology and oncology department, resistance rates are found to be 0% for imipenem and 100% for ceftazidime among *P. aeruginosa* strains isolated from patients with bloodstream infections, between January and December 2010[24]. In an Italian study, imipenem and ceftazidime resistance rates are respectively determined to 24% and 30% among *P. aeruginosa* isolated from infection in children undergoing chemotherapy and hematopoietic stem cell transplantation, from 2000 to 2008[25]. According to a Brazilian study, imipenem and ceftazidime resistance rates are respectively found as 80% and 100% among *P. aeruginosa* isolated from bacteremia among hematopoietic stem cell transplant recipients, in 2004[26]. An Italian hematology ward report an imipenem and ceftazidime resistance rates of 74% and 31% respectively, among *P. aeruginosa* strains during a study conducted from 1998 to 1999[27].

Conclusion

During this study period, we reported a significant increase in the incidence of the selected MDR bacteria. Thus, systematic screening of multi-drug resistant bacteria carriage is needed to be continued in our center especially because of the high frequency of ESBL producing *K. pneumoniae* and *E. coli* in our country. A multidisciplinary approach is needed, involving oncologists, microbiologists, and infection-control personnel.

Conflict of interest

We declare that there is no conflict of interest regarding the publication of this article.

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