Multidrug resistant *Pseudomonas aeruginosa* bloodstream infection in adult patients with hematologic malignancies

We read with interest the article by Caselli *et al.*[1] who described a 9-year retrospective series of *Pseudomonas aeruginosa* (PA) bacteremia cases from 12 Italian pediatric hematology oncology centers and reported a total of 127 patients with *Pseudomonas aeruginosa* bloodstream infections (BSIs), with a percentage of multidrug resistant *Pseudomonas aeruginosa* (MDRPA) isolates of 31.4%. The 30-day mortality rates were 19.6% for all patients and 35.8% for those with MDRPA BSI, and only the isolation of an MDRPA showed a significant association with infection-related death.

PA-BSIs are severe events associated with increased morbidity, mortality, and cost.[2] MDRPA strains, which were first reported in patients with cystic fibrosis, are increasing in frequency,[3] and have been very recently described as a growing problem also in adult onco-hematologic patients.[4] However, up till now, no previous studies have analyzed the clinical impact of infections caused by MDRPA in adult patients with hematologic malignancies.

In January 2009, we started a prospective study in 9 Italian tertiary care centers or university hospitals among adult patients diagnosed with hematologic malignancies; each patient with PA-BSI, defined as the presence of at least one positive blood culture, was included in this study.

At the present moment, a total of 38 patients have been diagnosed with BSI caused by *Pseudomonas aeruginosa* in our population. Surprisingly, we found 27 cases of MDRPA (according to the definition by Caselli *et al.*)[1] BSIs, thus resulting in a percentage of isolation of an MDRPA in adult patients with hematologic malignancies which was more than twice as high as that reported in the study by Caselli *et al.* in pediatrics (71.1% *vs.* 31.4%).[1] The characteristics of the patients with PA BSIs, divided according to the multidrug resistance pattern shown by the isolates, are presented in Table 1.

The percentages of *in vitro* resistance of 38 *Pseudomonas aeruginosa* isolated in our population to most of the antimicrobial classes also appeared much higher than in the study of Caselli *et al.*[1] In particular, we found higher overall percentages of resistance to carbapenems (imipenem and meropenem, 60% *vs.* 25%), antipseudomonal cephalosporins (ceftazidime and cefepime, 42% *vs.* 33%), amikacin (50% *vs.* 11%), and ciprofloxacin (66% *vs.* 18%), whereas the percentage of resistance to piperacillin was fairly similar in the two cohorts (24% and 27%). Figure 1 summarizes the percentages of resistance to major antimicrobial classes of our *Pseudomonas aeruginosa* isolates, according to the multidrug resistance pattern.

Similarly to that reported by Caselli *et al.*,[1] in our cohort, death within 30 days of the first positive blood culture occurred in almost one third (12/38, 31.6%) of patients and it was almost significantly higher in the MDRPA BSIs than the non-MDRPA BSIs group (40.1% *vs.* 9.1%, P=0.06).

Univariate analysis revealed some significant differences between the survivor and non-survivor subgroups. A significantly higher percentage of non-survivors had an indwelling urinary catheter (P=0.004), had BSIs caused by

Table 1. Clinical and epidemiological characteristics of patients, according to multi-drug resistance of isolates.

Variables	Non-MDR group (n=11)	MDR group (n=27)	*P* values
Demographic information			
Male sex	7 (63.6)	18 (66.7)	0.57
Age (year [mean SD])	58±12	48±17	0.05
History and clinical presentation			
Previous hospitalization[a]	8 (72.7)	20 (74.1)	0.61
Previous bacterial infections[b]	0	7 (25.9)	0.07
Invasive procedures[c]	4 (36.4)	9 (33.3)	0.57
Indwelling central venous catheter	8 (72.7)	24 (88.9)	0.22
Indwelling urinary catheter	2 (18.2)	8 (29.6)	0.38
Indwelling naso-gastric tube	0	2 (7.4)	0.49
Total parenteral nutrition	6 (54.5)	10 (37)	0.26
Corticosteroid therapy[c]	6 (54.5)	12 (44.4)	0.41
Immunosuppressive therapy[c]	1 (9.1)	4 (14.8)	0.54
Radiotherapy[b]	1 (9.1)	1 (3.7)	0.50
Chemotherapy[b]	6 (54.5)	15 (55.5)	0.61
Neutrophil count <500/mm^3	11 (100)	26 (96.3)	0.71
Neutrophil count <500/mm^3 >10 days	4 (36.4)	20 (74.1)	0.04
Epidemiological classification of bloodstream infection			
Nosocomial	9 (81.8)	25 (92.6)	0.32
Health-care associated	2 (18.2)	2 (7.4)	0.32
Source of bacteremia			
Central venous catheter	1 (9.1)	6 (22.2)	0.32
Urinary tract	1 (9.1)	0	0.28
Respiratory tract	1 (9.1)	5 (18.5)	0.42
Skin and soft tissues	2 (18.2)	1 (3.7)	0.19
Unknown	7 (63.6)	10 (37)	0.13
Others	1 (9.1)	6 (22.2)	0.32
Hematologic malignancy			
Acute myeloid leukemia	14 (51.8)	4 (36.4)	0.30
Acute lymphatic leukemia	0	6 (22.2)	0.11
Non Hodgkin's lymphoma	4 (36.4)	6 (22.2)	0.30
Multiple myeloma	3 (27.3)	1 (3.7)	0.06
Hematopoietic stem cell transplantation (HSCT)	3 (27.3)	9 (33.3)	0.51
Autologous	2 (18.2)	3 (11.1)	0.45
Allogeneic-matched	1 (9.1)	3 (11.1)	0.67
Allogeneic-mismatched	0	3 (11.1)	0.34
Comorbidities			
Diabetes mellitus	1 (9.1)	3 (11.1)	0.67
Chronic renal failure	0	1 (3.7)	0.71
Liver disease	1 (9.1)	2 (7.4)	0.65
Heart failure	0	1 (3.7)	0.71
Solid tumor	1 (9.1)	1 (3.7)	0.50
G-CSF	10 (90.9)	23 (85.2)	0.54
Human immunodeficiency virus (HIV) infection	1 (9.1)	1 (3.7)	0.50
Charlson Comorbidity Index (score [mean SD])	3.1±2.2	2.8±2.1	0.67
Antimicrobial prophylaxis			
Fluoroquinolones	4 (36.4)	16 (59.3)	0.18
Fluconazole	5 (45.4)	9 (33.3)	0.36
Itraconazole	2 (18.2)	10 (37)	0.23
Previous antibiotic therapy[c]			
β-Lactam-β-lactamase inhibitors	1 (9.1)	3 (11.1)	0.67
Cephalosporins	1 (9.1)	5 (18.5)	0.42
Fluoroquinolone	2 (18.2)	3 (11.1)	0.45
Aminoglycosides	0	1 (3.7)	0.71
Carbapenems	0	1 (3.7)	0.71
Glycopeptides	1 (9.1)	2 (7.4)	0.65
Outcome			
Septic shock	1 (9.1)	6 (22.2)	0.32
Acute renal failure	0	4 (14.8)	0.23
21-day mortality	1 (9.1)	11 (40.7)	0.06

Values are n (%) unless otherwise noted. MDR, multi-drug resistant. [a]Within the 12 months preceding infection onset. [b]Within the three months preceding infection onset. [c]Within the 30 days preceding infection onset.

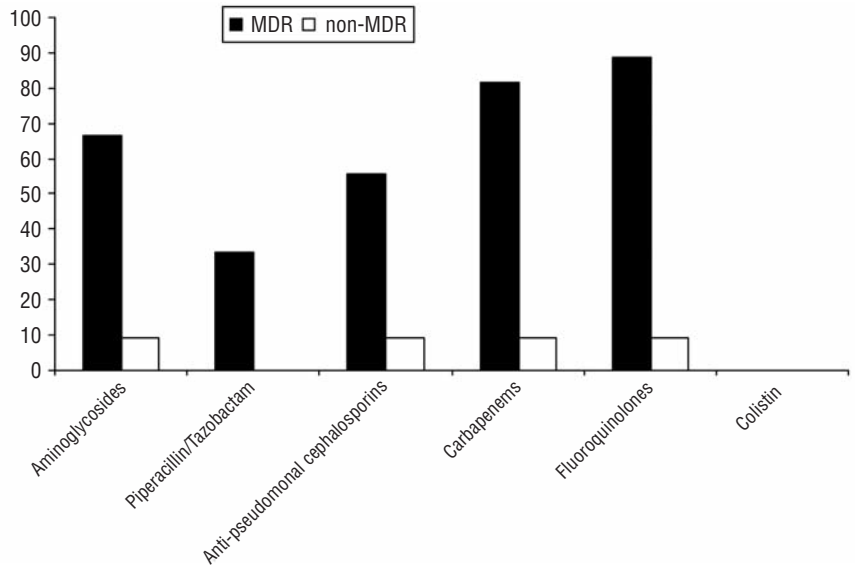

Figure 1. Percentages of *in vitro* resistance of *P. aeruginosa* strains to major antibiotic classes, according to multidrug resistance of isolates. (Aminoglycosides: amikacin and gentamicin; anti-pseudomonal cephalosporins: cefepime and ceftazidime; carbapenems: meropenem and imipenem; fluoroquinolones: ciprofloxacin and levofloxacin).

MDRPA (P=0.05), and had received an inadequate initial antimicrobial regimen (IIAT, i.e. administration of antimicrobial treatment based on a drug or a combination of drugs which showed no *in vitro* activity against the strain responsible for the BSI) (P<0.001).

In the multivariate analysis (including the variables found to be significant in univariate testing), only the IIAT resulted independently associated with mortality (P=0.006). Despite the small size of the population sample, using the Hosmer and Lemeshow goodness-of-fit statistic, the logistic model showed a good fit (P=0.26). In difference to the data from Caselli *et al.*,[1] infection due to MDRPA has not been shown to be independently associated to mortality in our adult population. However, in line with their results, in our previous studies on BSIs in patients with hematologic malignancies we found that isolation of an antibiotic resistant Gram-negative bacteria were independent risk factors for mortality,[5,6] and the lack of this association in the present study could be related to the small number of patients in our cohort. On the other hand, unfortunately, in the study of Caselli *et al.* the impact of IIAT on outcome was not evaluated. The inadequacy of empirical antimicrobial treatment has been shown to predict mortality in patients with bloodstream infection and severe sepsis, and it is more likely to occur in BSIs caused by antibiotic resistant bacteria.[2,3,7] In addition, we have previously demonstrated that IIAT was the strongest independent predictor of 30-day mortality in patients suffering from hematologic malignancies with BSIs caused by *E. coli*,[4] despite prompt administration of empirical broad-spectrum antibacterial therapy as recommended by the current clinical practice guidelines for the management of high-risk febrile neutropenic patients with cancer.[8]

Our preliminary data highlight the dramatic increasing spread of MDRPA causing BSI in adult patients with hematologic malignancies in several Italian hematology-oncology centers, probably related to the common use of fluoroquinolones for prophylaxis, as reported by Rangaraj *et al.*[4] The higher percentage of MDRPA in our cohort of adult patients than that in pediatrics reported by Caselli *et al.* could be related to the different age of the two populations, or, more probably, to the different time period of the studies: the study of Caselli *et al.* included data of infections collected from 2000 to 2008,[1] while our data consisted only in recent episodes of PA-BSIs (2009-September 2010). In addition, the latter explanation could be true also for the low percentage of MDRPA-BSIs reported by Rangaraj *et al.* (2.5%), whose study was conducted from July 2005 to December 2006 in Texas (USA).[4]

In conclusion, since the risk of inadequate treatment is higher if the BSI is caused by MDR bacterial strains, physicians should base empirical treatment protocols on a sound, updated knowledge of local prevalence of MDRPA isolates in order to consider also the empirical use of antimicrobial agents which is usually less preferred because of the risk of toxicity.

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