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ORIGINAL ARTICLE

P. aeruginosa bloodstream infections among hematological patients: an old or new question?

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Abstract *Pseudomonas aeruginosa* is a well-known cause of severe and potentially life-threatening infections among hematological patients. A prospective epidemiological surveillance program ongoing at our Hematology Unit revealed an increase over time of *P. aeruginosa* bloodstream infections (BSI). Their impact on outcome and antibiotic susceptibility was analyzed. BSI which consecutively occurred at our institution during a 70-month period were evaluated and correlated with type of pathogen, status of underlying disease, neutropenia, previous antibiotic therapy, resistance to antibiotics, and outcome. During the observation period, 441 BSI were recorded. Frequency of Gram-negative BSI was higher than that of other pathogens (57.3%). Overall, 66 *P. aeruginosa* BSI were recorded; 22 out of 66 were multiresistant (MR *P. aeruginosa*). Thirty-day mortality for all BSI was 11.3%; it was 27.3% for *P. aeruginosa* BSI and 36.4% for MR *P. aeruginosa*. At multivariate analysis, only active hematological disease and *P. aeruginosa* BSI were associated to an increased risk of death. For MR *P. aeruginosa*, BSI mortality was 83.3% vs. 18.8% when empiric therapy included or not an antibiotic with in vitro activity against *P. aeruginosa* (p=0.011). Together with active disease, the emergence of *P. aeruginosa* BSI, particularly if multiresistant, was responsible for an increased risk of death among hematological patients at our institution. In this scenario, reconsidering the type of combination antibiotic therapy to be used as empiric treatment of neutropenic fever was worthwhile.

Keywords Hematological patients · Bloodstream infections · *P. aeruginosa* · Antibiotic resistance · Outcome

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Introduction

Many observational studies have confirmed a recent shift towards Gram-negative rod (GNR) infections among hematological patients [1, 2] during the last years. Reasons for this changing pattern are still not completely understood; however, it is accepted that the widespread use of fluoroquinolone (Fq) prophylaxis among neutropenic cancer patients at least contributed to select Fq-resistant GNR infections [3].

Another major problem is the emergence of multiresistant strains, particularly in nosocomial infections [4] Among enterobacteriaceae, extended-spectrum betalactamase and carbapenemase producers are increasing in all populations and also among hematological patients [5, 6]. Multiresistant *Pseudomonas aeruginosa* (MR *P. aeruginosa*) and *Acinetobacter* spp. recently emerged as the most worrisome phenomenon, due to the scarcity of available antimicrobial agents active against these pathogens [7].

Considering MR *P. aeruginosa*, resistance is often the result of an interplay of various mechanisms (β-lactamases, aminoglycoside-modifying enzymes, topoisomerase mutations, decreased permeability, and the activities of efflux pumps) [8]. The precise impact of MR *P. aeruginosa* on outcome is not easily evaluable and comparable due to the different definitions of multiresistant phenotype [9], but an

increase in mortality and in the duration of hospitalization was frequently observed among MR *P. aeruginosa*-infected patients [10], also in hematological patients [11–14]. While the usefulness of environmental studies is still debated, close epidemiological surveillance at a Hematology Unit allows for early detection of changing patterns in the type of isolated pathogens and in their antibiotic susceptibility, allowing to adopt more adequate strategies for a successful empiric antibiotic therapy.

Since June 2004, a program of active epidemiological surveillance is ongoing at our institute. In our previous experiences [2, 15], we described the epidemiology observed at our institution during a 16- and 36-month period, respectively. The present study extends epidemiological surveillance over a 70-month period, with a focus on bloodstream infections (BSI). As an increasing frequency of *P. aeruginosa* BSI was observed over time, we evaluated the impact of *P. aeruginosa*, including multiresistant strains, on the outcome of hematological patients in comparison with other pathogens.

Patients and methods

Epidemiological surveillance program

All patients admitted to our institute were recorded for fever or infections, after they had given their written informed consent. Fever was defined as a single oral temperature measurement of ≥38.3°C or a temperature of ≥38°C sustained over a 1-h period, as reported by the IDSA clinical practice guideline for the use of antimicrobial agents in neutropenic cancer patients [16]; an infection was considered microbiologically documented when microorganisms responsible for symptoms and clinical/radiological signs were isolated. All patients showing fever or signs/symptoms of infection underwent thorax X-ray and culture of any other fluid/drainage obtained from a suspected infection site.

Prophylaxis with levofloxacin was administered in case of expected neutropenia lasting ≥7 days. Beta-lactam±aminoglycoside±vancomycin was the regimen adopted for empiric antibiotic therapy in neutropenic patients with fever. A database containing information of each patient with fever or infections on the type and status of underlying hematological disease, presence or absence of neutropenia (<0.5× 10^9/L), previous exposure to any antibiotic therapy, including prophylaxis with fluoroquinolones or treatment of prior infectious episodes, invasive disposables (central venous catheter, CVC), type of infection, microbiological isolate, and outcome was performed. A BSI was defined nosocomial if detected after ≥48 h from admittance to a hospital. Collected data were periodically analyzed in order to evaluate the occurrence of emerging pathogens or antibiotic resistances. For the purpose of the study, we extracted data concerning all BSI which consecutively occurred at our institution during a 70-month period (June 2004–January 2010).

Definitions

P. aeruginosa showing resistance to at least one agent in three or more antimicrobial categories was defined "multiresistant" (MR) [17]. Empiric antibiotic therapy was appropriate if the initial antibiotics, which were administered within 24 h after acquisition of blood culture samples, included at least one antibiotic that was active in vitro against the causative microorganisms and when the dosage and route of administration conformed with current medical standards [18], and it was considered "inadequate" if MR *P. aeruginosa* was not susceptible to any of the antibiotics (ATB) delivered or if antibiotic resistance emerged during initial appropriate therapy. Bacteremia was defined as CVC related when the blood culture specimen obtained from the catheter became positive at least 2 h before the specimen obtained from the peripheral vein [19].

Susceptibility tests

Antimicrobial susceptibility was determined using the Vitek II system (bioMérieux) according to the manufacturer's recommendations. The microorganisms from colonies grown on McConkey Agar after 18-h incubation were suspended in sterilized physiological saline to 0.5 McFarland standards. The bacterial suspension was used to fill the identification card and the antimicrobial susceptibility card which were then inserted into the incubator reader of the Vitek II system. The breakpoints for susceptibility or resistance were defined according to the CLSI criteria [20].

Statistical analysis

Statistical analysis was performed by logistic regression to define the covariates related to risk of death (univariate and multivariate analysis). The Fisher exact test was also performed to define the factors related to the outcome of MR *P. aeruginosa*. In all the analyses, we used a significance limit of $p=0.05$.

Results

Epidemiology

During the observation period, 441 BSI were recorded from 305 patients during different phases of their underlying hematological disease. Patients with CVC were 387; in 62

(16.7%) cases, BSI was considered CVC related. Additional sites of infections were observed in 60 (13.6%) cases, caused by the same or different pathogens.

BSI were nosocomial in 341/441 (77.3%) cases. GNR bacteria were responsible for BSI in 253 (57.3%) cases and Gram-positive cocci (GPC) bacteria in 148 (33.6%). Fungi (F) were responsible for BSI in six cases (1.4%, all *Candida* spp.); in 34 (7.7%) cases, a polymicrobial (PM) BSI was observed.

Overall, 66 *P. aeruginosa* BSI were recorded (15%). Twenty-two out of 66 (33.3%) were MR *P. aeruginosa*; all but two were nosocomial (90.9%), in comparison with 33/44 susceptible strains (75%) (p=0.13).

Previous antibiotic exposure was not associated to a higher frequency of MR *P. aeruginosa* in comparison with susceptible strains (19/22, 96% vs. 34/44, 77% respectively, p=0.38). Figure 1 shows the distribution of *P. aeruginosa* BSI over time and their increasing frequency during the observation period. Moreover, *P. aeruginosa* was detectable in 11 cases of PM BSI; 3 of 11 (27.3%) were MR *P. aeruginosa*.

Outcome of BSI

Crude 30-day mortality for all BSI was 50/441, 11.3%. It was 3/6 (50%) for F, 9/149 (6%) for GPC, 30/253 (11.8%) for GNR, and 8/34 (23.5%) for PM BSI. Death due to *P. aeruginosa* BSI was observed in 18/66 cases (27.3%), with no differences between MR (8/22, 36.4%) and non-MR *P. aeruginosa* (10/44, 22.7%), p=0.26.

As shown in Table 1, active disease, *Enterococcus* spp., *P. aeruginosa*, fungal, and PM BSI, together with additional documentation of infection at other sites, were associated with an increased risk of death. A diagnosis of acute leukemia, presence of neutropenia, and CVC, *Escherichia coli* BSI resulted protective against fatal outcome (univariate analysis). At multivariate analysis, only active disease and *P. aeruginosa* BSI were associated with an increased risk of death.

Outcome of MR *P. aeruginosa* according to empiric antibiotic therapy

Data concerning antibiotic susceptibility of MR *P. aeruginosa* were analyzed. Empiric antibiotic therapy started was considered inadequate in 3/22 MR *P. aeruginosa* BSI (n. 16, 23, and 27; see Table 2). In three further cases (n. 20, 25, and 26), *P. aeruginosa* showed a shift toward resistance to ongoing antibiotic therapy within 96 h. In two cases (20 and 26), *P. aeruginosa* developed resistance to piperacillin/tazobactam; case 25 showed an acquired resistance to amikacin and a reduced susceptibility to piperacillin/tazobactam (8S→64S); case 26 also showed a reduced susceptibility to amikacin (8S→16S).

Thirty-day mortality was 5/6 (83.3%) among cases initially treated with inadequate empiric antibiotic therapy or acquiring new antibiotic resistance during treatment vs. 3/16 (18.8%) in the remaining cases (p=0.011). Table 2 shows ATB susceptibility of MR *P. aeruginosa* and outcome in relation to type of ATB therapy delivered and eventual ATB susceptibility shift.

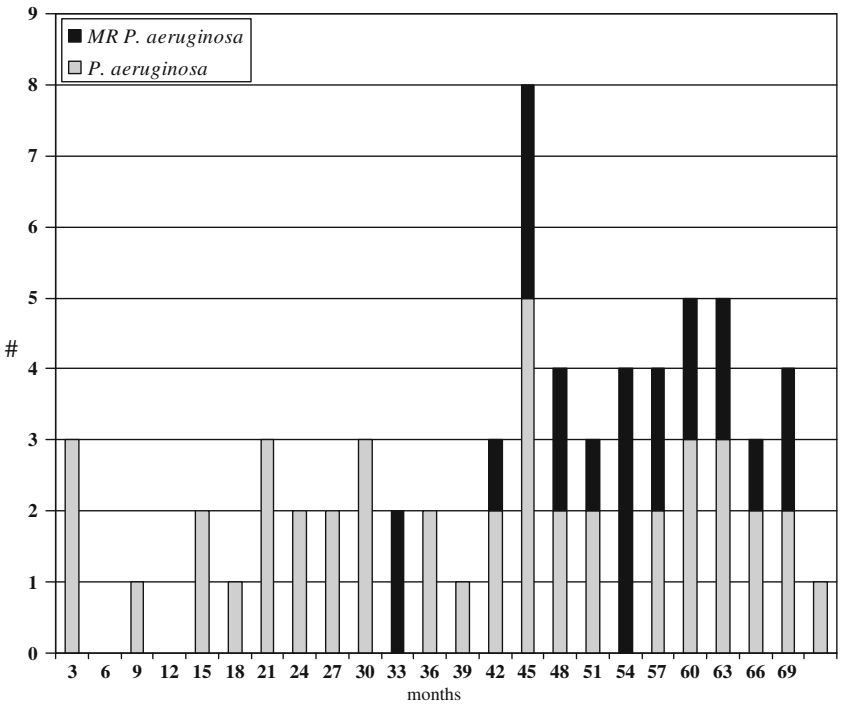

Fig. 1 Distribution of *P. aeruginosa* BSI over time (months)

Table 1 Correlation between clinical or microbiological parameters and death

	Univariate analysis OR (CI 95%), *p* value	Multivariate analysis OR (CI 95%), *p* value
Acute leukemia	0.53 (0.29–0.96), 0.036	–
Active disease	13.23 (4.68–37.41), <0.001	9.61 (3.27–28.23), <0.001
Neutropenia	0.44 (0.24–0.8), 0.007	0.46 (0.34–0.91), 0.026
Previous antibiotic therapy[a]	0.57 (0.29–1.13), 0.1	–
CVC	0.24 (0.12–0.48), <0.001	0.48 (0.22–1.01), 0.054
G+	0.89 (0.49–1.64), 0.7	–
S. aureus	1.19 (0.34–4.18), 0.78	–
Enterococci	2.81 (1.24–6.36), 0.013	2.27 (0.91–5.66), 0.08
CoNS	0.57 (0.22–1.49), 0.25	–
S. viridans	1.1 (0.36–3.2), 0.89	–
G−	1.1 (0.59–1.99), 0.79	–
E. coli	0.49 (0.25–0.97), 0.04	–
Enterobact other than *E. coli*	0.51 (0.12–2.23), 0.38	–
P. aeruginosa	3.7 (1.98–6.95), <0.001	5.04 (2.45–10.38), <0.001
Fungi	5.32 (1.45–19.52), 0.012	4.13 (0.94–4.13), 0.06
Polymicrobic infection	3.18 (1.39–7.29), 0.006	–
Other site of infection	2.13 (1.04–4.35), 0.037	–
CVC-related BSI	0.48 (0.16–1.37), 0.17	–
Nosocomial infection	1.28 (0.62–2.66), 0.5	–

[a]Including levofloxacin prophylaxis

Table 2 Antibiotic susceptibility of MR *Pseudomonas* and empiric antibiotic therapy

Case	AMI	CAZ	CIP	IMP	TZP	Empiric therapy	R shift	Outcome
1	S	R	R	R	R	TZP+AMI	N	A
3	S	R	R	R	S	TZP+AMI	N	A
4	S	R	R	R	S	TZP+AMI	N	A
5	S	R	R	R	S	TZP+AMI	N	A
8	R	S	R	R	S	TZP+AMI	N	A
9	R	S	R	R	S	CAZ	N	A
11	S	R	R	R	S	TZP+AMI	N	A
12	S	R	R	R	S	TZP+AMI	N	A
13	S	R	R	R	S	TZP	N	A
14	S	R	R	R	R	TZP+AMI	N	A
16	S	R	R	R	R	Ceftriaxone	N	A
17	S	R	R	R	R	CAZ+AMI	N	A
18	S	R	R	R	R	Ceftriaxone+AMI	N	A
19	S	R	R	R	R	TZP+AMI	N	D
20	S	R	R	R	S	TZP	Y	D
22	R	S	R	R	S	TZP+AMI	N	A
23	R	R	R	R	R	TZP	N	D
24	S	R	R	R	S	TZP+AMI	N	D
25	S	S	R	R	S	TZP+AMI	Y	D
26	S	R	R	R	S	TZP+AMI	Y	D
27	S	R	R	R	R	Ertapenem	N	D
28	S	R	R	R	R	TZP+AMI	N	D

AMI amikacin, *CAZ* ceftazidime, *CIP* ciprofloxacin, *IMP* Imipenem, *TZP* piperacillin/tazobactam, *R shift* acquiring antibiotic resistance during therapy, *A* alive, *D* dead

Discussion

Many recent epidemiological studies among hematological patients showed invasive fungal infections as the most dangerous infectious complication in this setting [21]. However, during the last years, a reduced fungal-, and particularly mold-, related mortality has been demonstrated, probably as a result of new available antifungal agents and of accurate diagnostic workup [22]. Epidemiological scenario of infections in hematology is changing again, as an increasing incidence of GNR infections among hematological cancer patients has been already described, together with a worrisome emerging epidemiology characterized by multidrug-resistant strains [23, 24]. This phenomenon is frequently related to a significantly increased risk of death, also among hematological patients [13], mainly because of the lack of appropriate antibiotic therapy.

GNR BSI were more frequent in our series, and their frequency was stable during the entire period of observation, confirming previously described epidemiological trends [2, 15]. Frequency of *P. aeruginosa* BSI was higher in the second part of the observation period, as well as presence of MR *P. aeruginosa*, which were absent in the first 30 months. Antibiotic pressure, particularly the widespread use of fluoroquinolones in prophylaxis, is increasing over time and may contribute to explain the emerging phenomenon of resistance. All *P. aeruginosa* (both MR and non-MR) BSI, in fact, were mainly recorded in patients with nosocomial infections or with previous exposure to antibiotic therapy, including levofloxacin prophylaxis.

In our series, overall GNR-related mortality was higher than GPC, as already reported [25]. When considering the type of pathogen, only *P. aeruginosa* BSI were associated to an increased risk of death at multivariate analysis. *E. coli* mortality was low. Actually, *E. coli* BSI were frequently recorded in patients with controlled underlying hematological disease during consolidation chemotherapy; this observation could explain their better outcome. As expected, mortality due to fungal BSI was particularly high (50%), but it was not associated overall to an increased risk of death ($p=0.06$), probably for the low number of cases.

MR *P. aeruginosa* BSI mortality was particularly high (36.4%). It was higher compared to non-MR *P. aeruginosa* BSI (22.7%), but the difference did not reach statistical significance. Inappropriate empiric antibiotic therapy was a major contributing factor to the high mortality rate of MR *P. aeruginosa* BSI, confirming data already reported by Cheong et al. [26]. However, in comparison with other pathogens, mortality of *P. aeruginosa* BSI was relevant also when a susceptible strain was implicated, confirming the virulence of this microorganism. The usefulness of combination antibiotic therapy (β-lactam+aminoglycosides) was not supported by a recent meta-analysis [27], although Kumar et al. [28] demonstrated that early combination therapy (any type) improved survival in septic shock. A meta-analysis concerning the outcome of GNR bacteremia conducted by Safdar et al. [29] showed a significant benefit on mortality for *P. aeruginosa* BSI using combination therapy, and ECIL-1 (European Conference on Infections in Leukemia) guidelines [30] report a CIII recommendation level for use of β-lactam+aminoglycosides in case of *P. aeruginosa* or of resistant G− infections. Our study confirms the importance of early appropriate antibiotic therapy in case of MR *P. aeruginosa*; however, the ability of *P. aeruginosa* in acquiring new antibiotic resistance during treatment could be another unpredictable cause of failure. All but one of the patients died with by *P. aeruginosa* BSI, and all those with MR *P. aeruginosa* BSI showed an uncontrolled underlying hematological disease, thus suggesting that host immunity is, once again, a major determinant for outcome.

Indeed, uncontrolled underlying hematological disease was the only hematological characteristic associated to a worse prognosis at multivariate analysis, whereas neither neutropenia nor a diagnosis of acute leukemia per se proved to be associated to a poor prognosis in patients with BSI. Indeed, neutropenia resulted to be "protective," probably as it was frequent but of brief duration in patients with controlled disease receiving consolidation chemotherapy. Among *P. aeruginosa* BSI, similar percentages of fatal events were observed among neutropenic and non-neutropenic patients (25% and 28.3%, respectively). No significant differences in terms of unfavorable outcome were also observed in neutropenic patients with MR *P. aeruginosa* BSI (7/16, 43.8%) vs. non-neutropenic patients (1/6, 16.7%; $p=0.35$), in contrast to the findings of the series reported by Tumbarello et al. [31], where neutropenia was a risk factor for death.

In conclusion, MR *P. aeruginosa* should be considered as a major problem among hematological patients, regardless of neutropenia. Infection surveillance should be considered an essential tool in order to detect epidemiological shifts and the emergence of resistant strains. It should allow to adopt a tailored early empiric antibiotic therapy, particularly in patients with active disease.

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