An 18-case outbreak of drug-resistant *Pseudomonas aeruginosa* bacteriemia in hematology patients

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We retrospectively identified an outbreak of 18 episodes of *P. aeruginosa* bacteriemia in 17 patients with hematologic malignancies in 2004. All strains were ticarcillin I/R, 77% ciprofloxacin I/R, 72% ceftazidime I/R, 72% amikacin I/R and 50% imipenem I/R. The outbreak was multiclonal. Colistin was employed for documented therapy in ten cases including seven in which it was the only active drug. Outcomes were resolution of infection in 12 out of 18 episodes (67%), and death in six cases, five (25%) of which were attributable to the infection. Colistin was useful even in highly resistant strains and the efficacy of antibacterial therapy was similar (57%)in bacteriemia due to strains only susceptible to colistin.

Key words: *Pseudomonas aeruginosa*, bacteriemia, colistin, hematologic malignancy.

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Pseudomonas aeruginosa is a frequent pathogen associated with hospital acquired infections. Multidrug-resistant *P. aeruginosa* infections,[1] bacteriemia,[2] and severe neutropenia,[3,4] are often associated with increased mortality. In our hematology department, *P. aeruginosa* bacteriemia represented less than 5% of positive blood cultures before 2003. In 2004 we observed an increase of *P. aeruginosa* bacteriemia with antibiotic resistant phenotypes resulting in an increased use of colistin. Colistin, an old antimicrobial drug, was recently reported to be effective against multidrug-resistant *P. aeruginosa* in intensive care units,[2,5] although earlier reports had described failure with this drug.[4] Here we report the successful use of this antibiotic in our unit.

Design and Methods

Setting

We conducted a retrospective study of *P. aeruginosa* bacteriemias occurring in 2004 in the 63-bed Lille University adult hematology department. This department includes a 15-bed day care center, a 28-bed ward and a 20-bed isolation unit. All rooms are single, with their own toilet and washroom. All the isolation rooms use high-efficiency particulate air (HEPA) filtering and are at positive pressure. During neutropenia, patients are cared for using strict contact and respiratory isolation procedures.

Bacteriological investigations

P. aeruginosa strains isolated from clinical samples were identified by the microbiology laboratory. Strains were tested for antibiotic susceptibility using the automated Vitek 2 system (Biomérieux, Marcy l'Etoile, France), according to the French Society of Microbiology Antibiogram Committee (CA-SFM) criteria. Antibiotics tested included ticarcillin, piperacillin-tazobactam, ceftazidime, imipenem, aztreonam, amikacin, ciprofloxacin and colistin. Pulsed-field gel electrophoresis (PFGE) was performed using an in-house protocol for 14 clinical strains and two environnemental strains. Oropharyngeal and rectal swab samples were collected systematically upon admission and weekly for patients hospitalized in the isolation unit. During the investigation of the outbreak, environmental samples were collected from tap and toilet water in both hospitalization sectors.

Antimicrobial management

Systemic antimicrobial prophylaxis is not part of patient management in our institution. Allogenic bone marrow transplant recipients receive gentamicin and colistin orally, from admission to engraftment. The management of febrile neutropenia is based on local written algorithms. Empirical combinations of broad-spectrum antibiotics are administered following fever, defined as a single oral temperature of ≥38.5°C or a temperature of ≥38.0°C for ≥1 h. Two algorithms are available depending on the duration of previous hospitalization and/or antibiotic exposure. For patients who have been in hospital for less than 2 weeks, first line therapy includes ceftriaxone or cefotaxime and gentamicin or ofloxacin. Second line treat-

ment was piperacillin-tazobactam or cefepime and amikacin or ciprofloxacin. Imipenem and ceftazidime are generally used only in second or third line regimens. Aminoglycosides are administered for 3 days excepted in cases of *P. aeruginosa* infection, when they are given for 5 days. Beta lactams are administered at the usual recommended dosages, amikacin as a once daily 20 mg/kg infusion and gentamycin as a once daily 5 mg/kg infusion. Colistin is not included in standard guidelines. This antibiotic is administered on a case to case basis as thrice daily infusions at a dose of 50000-10000 units/kg/day adjusted to renal function.

Definitions

Bacteriemia was defined as one or more *P. aeruginosa* - positive blood cultures associated with fever, chills or hypotension. Other sites of infection were considered related to the bacteriemia if *P. aeruginosa* was isolated from these sites, or in the absence of any other pathogen or alternative cause. Colonization was defined as the presence of *P. aeruginosa* without clinical signs of infection. Septic shock was defined as sepsis with hypotension (systolic blood pressure < 100 mm/Hg), despite adequate fluid replacement, requiring vasoactive drugs. Clinical resolution was defined as the resolution of all signs and symptoms of *P. aeruginosa* infection and the absence of recurrence for at least 7 days after the discontinuation of antibiotic therapy. Mortality was considered due to *P. aeruginosa* bacteriemia if the patient was still febrile, with increased inflammatory parameters and in the absence of another cause at the time of death.

Patients whose death was not related to *P. aeruginosa* were considered to have had treatment failure. Autopsies were not performed. The analyses were performed per episode.

Results and Discussion

Clinical results

We identified 18 episodes of *P. aeruginosa* bacteriemia in 17 patients. These cases accounted for 13.2% of all positive blood cultures and a 120% rise compared to the previous year, 2003. One patient had two bacteriemia episodes with two different strains (strains 2 and 5) over 94 days. The patients' initial characteristics are summarized in Table 1. In four cases, anal colonization with a strain of the same serotype had been identified before the diagnosis of bacteriemia and in four additional patients *P. aeruginosa* of the same serotype was isolated from the stool after the diagnosis of bacteriemia. In 16 cases, the patients had had intensive exposure to antibiotics prior to infection. The median duration between onset of fever and first positive blood culture was 0 days (range, 0-20). Clinical presentation and biological characteristics on the day of the first positive blood culture are summarized in Table 2.

Table 1. Main characteristics of 17 patients with 18 *episodes of P. aeruginosa* bacteriemia.

Characteristic	*Value*
Age, median, years (range)	48 (20-80)
Sex, no. of patients	
Male	10
Female	7
Underlying disease, no of patients	
Acute leukemia	12
Chronic myeloid leukemia	2
Non-Hodgkin's lymphoma	2
Multiple myeloma	1
Reason for hospitalization, no. of patients	
Induction treatment	7
Consolidation treatment	6
Stem cell transplantation	4
Autografting	1
Hospitalization setting, no. of patients	
Conventional rooms	10
HEPA filtered rooms	8
Duration of hospital stay before episode, median, days (range)	16 (1-64)
Days from onset of neutropenia to infection,* median, (range)	7 (2-42)

**Three patients were not in aplastic but after stem cell transplantation; HEPA: high-efficiency particulate air.*

The strain serotypes, antibiotic resistance patterns, and previous antibiotic exposure are presented Table 3. The most frequent serotypes were in O11 (n=6, 33%) and O12 (n=5, 28%). Three (17%) strains, considered as wild type, were not susceptible to ticarcillin. Resistant strains were highly prevalent with only 50% (n=9) susceptible to imipenem, 28% (n=5) to ceftazidime and amikacin, 23% (n=4) to ciprofloxacin, and none to ticarcillin. All strains were susceptible *in vitro* to colistin.

Treatment and outcome

Among 16 empirical treatment regimens, only eight (50%) included at least one antibiotic active against the strain subsequently found. The median time between taking samples for blood cultures and the first administration of an active antibiotic was 2 days. Colistin was used in 10 cases (median treatment duration: 15 days, range, 1-27) at a median (and mean) dosage of a 80 000 units/kg/day. The most commonly used antipseudomonal agent was imipenem (n=12). The most frequent combination therapy was imipenem and colistin (n=7). All but one patient received combination therapy. In nine cases colistin was the only agent to which the strain was susceptible; seven of those cases effectively received colistin. One patient (with strain 9) had a second line of therapy following failure of the first line regimen. The breakthrough strain exhibited a more resistant phenotype. The median duration of treatment for surviving patients was 15 days (range, 6-27). In two cases local surgical treatment (bedside debridement) was associated. Central venous catheters were removed from nine

Table 3. Outcome and characteristics of 18 bacteriemic strains of *P. aeruginosa* in 17 hematology patients.

Strain	Serotype	ATB in last 6 months	Susceptibility pattern									ATB regimens	Outcome
			TIC	TZP	ATM	CAZ	CIP	FEP	AMI	IPM	COL		
1	011	FEP (10)-IPM (9)-CIP (9) CAZ (6)-AMI (3)	R	R	R	R	R	R	R	I	S	IPM (21) - COL (21)	Survival
2	011	CIP (22)–IPM (22) – CAZ (7) FEP (3) – AMI (3)	R	R	I	R	R	I	R	I	S	IPM (13)-COL (15)	Survival
3	06	none	I	S	S	S	S	S	S	S	S	CAZ (10)-AMI (1)	Survival
4	012	CIP (20)-TZP (14)-COL (11) IPM (10)-FEP (8)-AMI (3)	R	R	R	R	R	R	R	R	S	TZP (8)-COL (6)	Death[1]
5	011	IPM (35)-CIP (24)-COL (15) CAZ (7)-FEP (3) – AMI (3)-TZP (2)	R	R	I	R	R	I	R	I	S	IPM (7)-COL (7)	Death
6	011	TZP (12)-IPM (6)-CIP (6) CAZ (3)	R	R	I	R	R	I	R	I	S	TZP (2)-GEN (2)	Death
7	NT	TZP (17)-CIP (9)-AMI(3)	R	R	I	I	R	I	R	S	S	IPM (18)-COL[2] (18)	Survival
8	012	TZP (20)-CIP (10)-AMI (9)	R	R	I	S	R	I	R	S	S	CAZ(12)[3]/COL[2](12) IPM(15)/COL (15)	Survival
9	012[4]	TZP (4)-AMI (3)	R	R	I	S	R	I	I	S	S	IPM(10)/COL(8)[5]	Death
			R	R	R	R	R	R	S	S	S	CAZ(16)/ AMI (5)	
10	011	TPZ (22)-CIP (18)-IPM (16) CIP (16)-COL (16)	R	R	R	R	R	R	R	R	S	IPM (1)-COL (1)-CIP(1)	Death
11	NT	FEP (6)-AMI (3)	I	S	S	S	S	S	S	S	S	TZP (16)-CIP (16)	Survival
12	NT	TZP (22)-IPM (15)-CIP (15) AMI (3)	I	R	I	I	R	I	R	S	S	IPM (6)-CIP (6)	Survival
13	01	CIP (8) – TZP (7)	R	I	R	I	S	I	S	S	S	IPM (10)-CIP (10)	Survival
14	01	TZP (16)-AMI (6)-CIP (6)	R	I	R	I	I	I	S	S	S	IPM (12)-CIP (12)	Survival
15	011	IPM (10)-CAZ (10)-CIP (14) AMI (6)-TZP (7)	R	R	I	R	R	R	R	I	S	IPM (21)-COL (21)-FOP (21)	Survival
16	NT	none	I	S	S	S	S	S	S	S	S	FEP (14)-CIP (14)-AMI (3)	Survival
17	012	CIP (24)-TZP (14)-IPM (14) FEP (12)-AMI (3)	R	R	I	R	R	R	R	R	S	FEP (15)-COL(15)-ATM(15)	Survival
18	012	CIP (16)-COL (15)-IPM (13) CAZ (12) – TZP (4) – AMI (3)	R	R	I	R	R	R	R	R	S	IPM (2)	Death

[1]*Death not caused directly by the pseudomonal infection;* [2]*aerosolized colistin was used in association with parenteral colistin;* [3]*change of treatment because of toxicity;* [4]*a mutation of Pseudomonas appeared in the bloodstream during the episode ,* [5]*Change for clinical failure. NT: non typeable; ATB: antibiotic; AK: amikacin; ATM: aztreonam; CAZ: ceftazidime; CIP: ciprofloxacin; COL: colistin; FEP: cefepime; FOP: cefotaxime; GEN: gentamycin; IPM: imipenem; TIC: ticarcillin; TZP: piperacillin-tazobactam.*

patients and were found to contain *P. aeruginosa* in two cases. Two-thirds (12/18, 67%) of the bacteriemias were cured. Four (57%) of the seven strains treated with colistin as the only active drug were cured. Among the six deaths, one due to cytomegalovirus disease (in a patient with strain 4 *P. aeruginosa*) was considered not attributable to the bacteriemia. Four patients died (strains 6, 10, 18, and the emerging strain 9) before the result of the blood cultures were known. All six patients who died had pneumonia associated with the bacteriemia, four of them ultimately requiring mechanical ventilation in an ICU. Only one patient among five with septic shock survived; this patient had a strain 16 infection. Overall safety was good; colistin did not result in adverse renal events (median creatinine increase from baseline: 0 mg/L, range 0 -10), and one patient (strain 8) presented with a rash ultimately attributed to ceftazidime.

Epidemiological study

Forty-four percent of bacteriemias occurred in September and October, 2004. Multiple environmental samples were cultured. *P. aeruginosa* was isolated from four tap water points (*P. aeruginosa spp.*>1000 CFU/L and two toilets of the conventional sector (*P. aeruginosa spp.*

Table 2. Clinical and biological features of 18 episodes of *P. aeruginosa* bacteriemia in 17 hematology patients.

Characteristic	Value
Temperature °C[1], median (range)	39 (37.8-40.5)
Type of infection, no. of patients (%)	
Bacteriemia	18 (100)
Pneumonia	8 (44)
Perirectal area	5 (28)
Skin lesion	3 (17)
Digestive tract	1(6)
Central nervous system	1(6)
Co-infection, no. of patients (%)	8 (44)
Others bacteriemia	5 (28)
Pulmonary aspergillosis	2 (11)
Cytomegalovirus	2 (11)
Septic shock[1], no. of patients (%)	5 (28)
Peripheral blood counts,[1] median (range)	
Neutrophil, 10^9 cells/L	105 (30-2500)
Albumin g/L	30 (25-39)
C-reactive protein mg/L	177,5 (6-539)
Procalcitonin* ng/mL	0.8 (0-39.6)
Fibrinogen g/L	6.2 (2.6-10.6)

[1]*on the day of positive blood culture;* [*]*values available for 14 patients*

>1500 CFU/L) and the tap water points of two nursing rooms in the conventional (*P. aeruginosa spp.*=1000 CFU/L) and protected sectors (*P. aeruginosa spp.*=1000 CFU/L, non typeable=30 CFU/L, type 010=100 CFU/L). Fourteen clinical strains and two environmental strains were studied by PFGE which identified multiple clones, suggesting that the cases were not epidemiologically linked. No samples were cultured from health care workers.

Standard precautions were reinforced with an emphasis on the use of hand rubbing alcoholic solutions. Terminal filters were installed on tap water points. The frequency of toilet and lavatory disinfection was increased. The outbreak has not recurred after a 15-month follow up. Few outbreaks of *P. aeruginosa* infections have been described in adult hematology units.[6-10] When bacteriemic, the infections were associated with a 40% to 87.5% mortality rate. This can be explained by the severe immunesuppression of these patients and the lack of therapeutic options against multidrug resistant strains. In our study, as previously reported,[3,11-12] failure and death occurred in patients with septic shock (4/5) and pneumonia (5/8). Surprisingly, we did not find inappropriate initial empirical therapy (50% of cases) to be a poor prognostic factor, but our study lacks power. We observed an overall high rate of clinical resolution (67%) compared to that in previously published reports. Factors contributing to the outcome might be the use of combination antimicrobial therapy, colistin and/or the close management of these patients resulting in early antibiotic therapy. All but one of our patients received a combination regimen following our institutional guidelines on the management of febrile neutropenia. Despite these guidelines, adapted annually to our microbial ecology, only half the patients had an empirical therapy comprising at least one active drug.

The use of combination antimicrobial therapy against *P. aeruginosa* is controversial[13-14] but generally supported. It is also supported by *in vitro* data demonstrating a synergistic effect of combining two beta-lactams with an aminoglycoside even when the strains are resistant to the individual antibiotics.[15,16] At the height of the epidemic, colistin became a part of our empirical regimen for febrile neutropenia in severely immunocompromised patients, i.e., those admitted to the isolation sector.

Colistin[17] is an old antibiotic of the polymixin class which was discovered in 1947 and became clinically available in 1959. It is active against most Gram-negative bacilli, particularly *P. aeruginosa*, *Acinetobacter spp*, *Klebsiella spp.* and *Enterobacter spp*. Its use has been minimal in the last 20 years, excepted in cystic fibrosis, due to reports of substantial nephrotoxicity and neurotoxicity. The rise in severe infections due to multiple drug-resistant Gram negative bacilli led to a revival of its use. Recent studies[2,5] of intensive care unit patients treated with systemic colistin showed both efficacy against multidrug-resistant strains of *P. aeruginosa* and tolerable safety. Colistin-resistant *P. aeruginosa* have been reported[18] in patients exposed to colistin. This has not been observed in our institution. In our study, colistin was used in ten cases, including seven in which it was the only active drug: of these seven cases, four (57%) were cured. Furthermore, no significant toxicity was observed.

The origin of the outbreak was not conclusively demonstrated. *P. aeruginosa* strains were isolated from the hospital water system but the outbreak was polyclonal. This did not support an environmental or a hand carriage hypothesis. We did not check health care workers for *P. aeruginosa* carriage this would have been considered had the outbreak persisted. The increase in the incidence of *P. aeruginosa* bacteremia parallels an increase in isolation of the bacteria from stool samples (*data not shown*). This suggests bacteriemias occur following translocation of the bacteria from the gastro-intestinal tract. The transformation from susceptible to resistant strains might be due to genetic mutations under antibiotic selective pressure[1,19] or the acquisition of resistance genes.[20] One limitation of our work is the lack of PGFE typing of the strains isolated from the stools. We cannot, therefore, distinguish superinfection from mutation of a previously susceptible strain.

The departmental antibiotic policy was reviewed as selective pressure might have led to this increase in *P. aeruginosa* isolation. The policy had been instituted in 2000 following a close collaboration between hematologists and infectious diseases physicians. No significant changes in recommended first line beta-lactams was observed in 2004. Furthermore, in 2005, the same guidelines were used (with a slight adaptation due to a shortage of cefepim in France) without a similar increase in *P. aeruginosa* isolation. Since this outbreak, colistin has been added to our empirical regimens in patients colonized with resistant *P. aeruginosa*.

Case fatality in multidrug resistant *P. aeruginosa* bacteriemia can be reduced to below 50%, even in patients with hematologic malignancies. Colistin appears to be safe and as effective as other anti-pseudomonal drugs in curing bacteriemia.

SA had full access to all the data in the study and takes responsibility for the integrity of the data; SA, SdB, RG, JBM: study concept and design; SA, FB, GB, SdB, SD, VC, RD, OL, JBM, IY-A: analysis and interpretation of data; SA, SdB, VC, OL, JBM: drafting of the manuscript: Critical revision of the manuscript for important intellectual content; approval of the final version of the manuscript: all authors. Manuscript received February 23, 2006. Accepted June 7, 2006.

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