Clinical Analysis of Patients with *Pseudomonas aeruginosa* Bacteremia

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ABSTRACT. Eighty-six cases with *Pseudomonas aeruginosa* bacteremia during last five years were analyzed with regard to predisposing factors and clinical manifestations. We divided these cases into two groups to compare clinical features; 27 cases from 1994 to 1995 (group A) and 59 cases from 1991 to 1993 (group B), because the susceptibility of *Pseudomonas aeruginosa* to antibiotics has recently been changed and β-lactam- or new quinolone-resistant strains has increased.

The main underlying diseases of group A were hematological diseases in 8 cases, traumatic diseases in 7 cases and gastrointestinal diseases in 6 cases. In group B, there were 21 patients with hematological diseases, 10 with gastrointestinal diseases and 6 with cardiovascular diseases.

The primary source of bacteremia in group A was the urinary tract with 13 episodes, followed by the respiratory tract with 7 (pharyngeal swab 4, sputum 3). In group B, the primary source was distinctly the respiratory tract with 37 episodes (sputum 21, throat swab 16), followed by the urinary tract with 20 episodes. An IVH catheter was inserted in 15 cases but *Pseudomonas aeruginosa* was detected in only one case by a culture from the IVH catheter tip in group A, and in 6 out of 35 cases in group B.

Antibiotics were used prior to the onset of *Pseudomonas aeruginosa* bacteremia in 50 episodes in both groups but most of them were not active effective against *Pseudomonas aeruginosa*. The prognosis was comparatively good in group A, that is, the clinical effect was good in 20 episodes (efficacy rate: 71%), fair in 1 and poor in 7. All the patients of the 7 poor cases died of septic shock (mortality rate: 27%) and antibiotics were not administered in five of these cases because the culture results were reported after the death of the patients. In group B, however, the prognosis was poor, that is, the clinical effect was good in 29 episodes (efficacy rate: 46%), fair in 3 and poor in 32. In these 32 poor cases, 26 patients died of septic shock, other 5 died of pneumonia and 1 died of multiple organ failure. No antibiotics were administered in 15 cases of these 32 poor cases for the lack of culture results.

β-lactam antibiotics were still effective against *Pseudomonas aeruginosa* isolated from group A, while new quinolones were resistant in many cases of both groups.

Key words: *Pseudomonas aeruginosa* bacteremia — underlying diseases — antibiotics

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Pseudomonas aeruginosa bacteremia is a clinically severe and often fatal infectious disease for immunocompromised hosts in hospitals. *Pseudomonas aeruginosa* is the most dominant causative agent of bacteremia among gram-negative species of nosocomial origin.[1] Therefore, we reviewed the patients who had experienced *Pseudomonas aeruginosa* bacteremia in our hospital during the past five year period and analyzed them with regard to predisposing factors and clinical manifestations. We divided these patients into two groups; cases from 1994 to 1995 and cases from 1991 to 1993, and compared clinical features each other in order to study the change over time in *Pseudomonas aeruginosa* bacteremia.

MATERIALS AND METHODS

Cases: Twenty-seven cases with 28 episodes in which blood culture was positive with *Pseudomonas aeruginosa* were collected in Kawasaki Medical School Hospital as group A, from January 1994 to December 1995. Fifty-nine of the cases, with 64 episodes of *Pseudomonas aeruginosa* bacteremia occuring in the same hospital from January 1991 to December 1993 as group B were collected to analyze differences in clinical features between the above groups.

Methods: The epidemiological data was obtained from the medical records of a total of 86 patients with *Pseudomonas aeruginosa* bacteremia and categorized according to age, sex, underlying diseases, laboratory findings, the primary source of bacteremia (we decided the primary source of bacteremia only when the isolate of the specimen had the same pattern of drug sensitivity with the isolate of the blood culture), monomicrobial or polymicrobial infection, antibiotics administered prior to the onset of bacteremia, clinical effects and the antibiotics used, complications and the prognosis applying standard criteria for both periods.[2,3] Testing for the antimicrobial activity of *Pseudomonas aeruginosa* was carried out for both periods by the optic disc method in vitro as previously described.[4] The antimicrobial activity was graded into four degrees: (−), (+), (++) and (+++). The percentage of the number of (+++)/ total tested number was calculated and registered.

RESULTS

The 27 cases with *Pseudomonas aeruginosa* bacteremia in group A, 22 males and 5 females, ranged in age from 5 to 90 years old with the average 61.2 years old. The 59 cases in group B, 45 males and 14 females, ranged in age from 7 to 88 years old with the average 61.9 years old. The underlying diseases of the patients with *Pseudomonas aeruginosa* bacteremia are shown in Fig 1. In group A, 8 cases had hematological disease, 7 had trauma (including 2 with burn), and 6 had gastrointestinal disease. The percentages of these three underlying diseases was almost the same each other. Only one case of respiratory disease was observed in group A. In group B, 21 cases had hematological disease (note a high percentage of leukemia) and 10 had gastrointestinal disease, and the percentage of cases with respiratory disease was also low. Urinary tract complications, such as acute renal failure and neurogenic bladder existed in the most of these cases in both groups. Otherwise, a high percentage of malignant diseases, including leukemias, existed

in group B, with 33 cases (56%) as compared with 12 cases (44%) in group A. The symptoms and main laboratory findings in group A are shown in Fig 2. There were many patients who had poor general conditions (Performance status 3-4) and all patients had forms of nosocomial infection. The peak fever ranged over 38°C and the WBC count ranged over 9000/ul in most cases except for 8 cases with hematological diseases, in whom the WBC count was below 500/ul. The patients' nutritional condition was also poor; namely serum protein, albumin and cholineesterase were in the low figures in over 70 percent of the patients. This is the case also in group B.

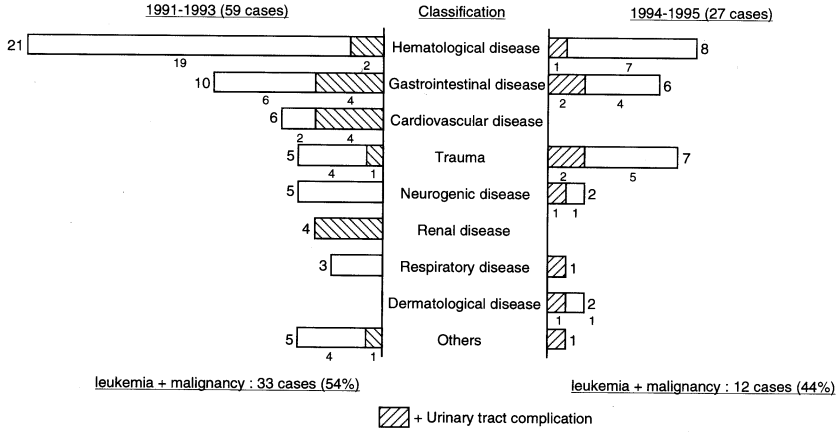

Fig 1. Underlying diseases of *Pseudomonas aeruginosa* bacteremia

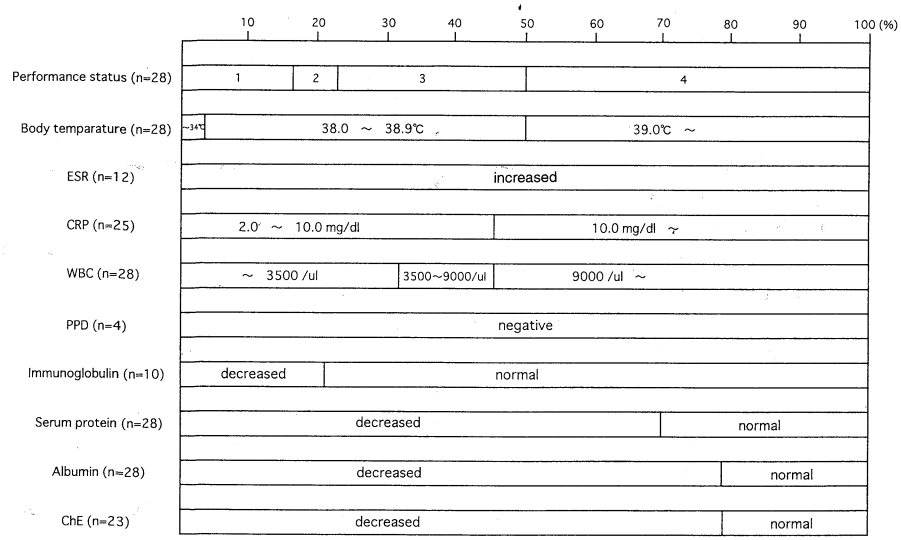

Fig 2. Clinical symptoms and main laboratory findings of *Pseudomonas aeruginosa* bacteremia (27 cases, 28 episodes)

The primary sources of *Pseudomonas aeruginosa* bacteremia are shown in Fig 3. The urinary tract might be the source in 13 episodes, and the respiratory tract in 7 (pharyngeal swab 4, sputum 3) in group A. However, in group B, the primary source was most frequently the respiratory tract, that is, in 37 episodes (sputum 21, throat swab 16), followed by the urinary tract in 20 episodes. An IVH catheter was inserted in 15 cases but *Pseudomonas aeruginosa* was detected in only one case by a culture from the IVH catheter tip in group A. In group B, *Pseudomonas aeruginosa* was detected by cultures from the IVH catheter tip in 6 cases out of 35 cases.

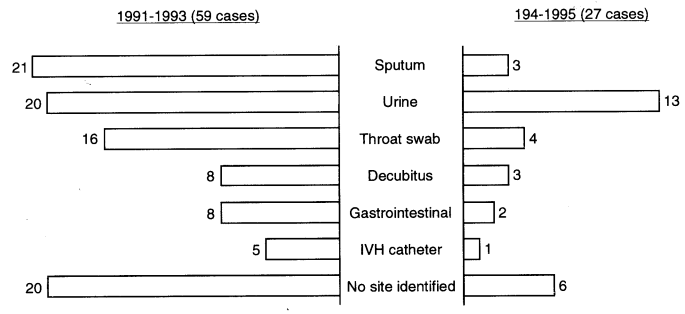

Fig 3. Origin of *Pseudomonas aeruginosa* bacteremia

The bacteremic types of *Pseudomonas aeruginosa* was monomicrobial bacteremia in 21 episodes (75%) and polymicrobial bacteremia in 7 episodes (25%). In cases of polymicrobial bacteremia, excluding *Pseudomonas aeruginosa*, one spece was detected in five episodes (MRSA : 3, *Bacillus cereus* : 1, *Staphylococcus epidermidis* : 1) and two species were detected in two episodes (MRSA+*Enterococcus faecalis* : 1, *Escherichia coli*+B group *B-streptococcus* : 1) in group A. In group B, on the other hand, there were 47 episodes of monomicrobial bacteremia (73%) and 17 episodes of polymicrobial bacteremia (27%).

As for the use of antibiotics prior to the onset of *Pseudomonas aeruginasa* bacteremia antibiotics were not administered in 15 episodes (53%), but were administered in 13 episodes (47%). However, in almost all cases antibiotics were not effective against *Pseudomonas aeruginosa* (for example; two drugs VCM+MINO, one drug CEZ, FMOX) in group A. In group B, on the other hand, prior the onset of bacteremia antibiotics were not administered in 27 episodes (43%), but were administered in 37 episodes (57%). However, they were not effective against *Pseudomonas aeruginosa*. The antibiotics used for *Pseudomonas aeruginosa* and the clinical effects are shown in Table 1. The prognosis was comparatively good in group A, that is, because the clinical effect was good in 20 episodes (efficacy rate : 71%), fair in 1 episode and poor in 7 episodes. In the cases with a good clinical effect, appropriate antibiotics such as IPM/CS, CAZ, PIPC were administered. In the 7 poor cases, the patients died of septic shock (mortality rate : 27%) and antibiotics were not administrated in 5 of these cases because the finding of *Pseudomonas aeruginosa* bacteremia was reported after the death of the patients. On the other hand, in group B the prognosis was poor, that is, the clinical effect was

poor in 32 episodes, fair in 3 episodes and good in 29 episodes (efficacy rate: 46%). In most cases of group B, as in group A, antibiotics with anti-pseudomonal activity such as IPM/CS, CAZ, PIPC, SBT/CPZ were administered, but no antibiotics were administered in 16 episodes. Among the 32 cases of group B, 26 died of septic shock, 5 died of pneumonia and 1 died of multiple organ failure. The major complications of *Pseudomonas aeruginosa* bacteremia were as follows; septic shock 11 cases (39%), disseminated intravas-

TABLE 1. Clinical effects and antibiotics for *Pseudomonas aeruginosa* patients

		1991-1993 (64 episodes)		1994-1995 (28 episodes)	
Clinical effect	Good	Two drugs	15 episodes	Two drugs	5 episodes
		IPM/CS+PIPC 3	IPM/CS+AMK 1	IPM/CS+CAZ 2	
		CAZ+PIPC 2	IPM/CS+CFS 1	SBT/CPZ+PIPC 1	
		IPM/CS+CAZ 1	ISP+CAZ 1	IPM/CS+MINO 1	
		SBT/CPZ+PIPC 1	ISP+SBT/CPZ 1	ISP+PIPC 1	
		IPM/CS+MINO 1	SBT/CPZ+MINO 1		
			VCM+CAZ 1		
		One drug	13 episodes	One drug	15 episodes
		IPM/CS 5	PIPC 3	CAZ 5	
		CAZ 4	CPFX 1	PIPC 4	
				SBT/CPZ 2	
		Not done	1 episode	ISP 2	
				Cefpirome 1	
				IPM/CS 1	
	Fair	One drug	3 episodes	One drug	1 episode
		PIPC 1		CAZ 1	
		SBT/CPZ 1			
		CEZ 1			
	Poor	Two drugs	9 episodes	One drug	2 episodes
		IPM/CS+MINO 2	CLDM+PIPC 1	IPM/CS 2	
		PIPC+CZON 2	CAZ+PIPC 1		
		VCM+AMK 1	SBT/CPZ+AMK 1		
		IPM/CS+AMK 1			
		One drug	8 episodes	Not done	5 episodes
		IPM/CS 4	AMK 1		
		SBT/CPZ 1	VCM 1		
		CMX 1			
		Not done	15 episodes		

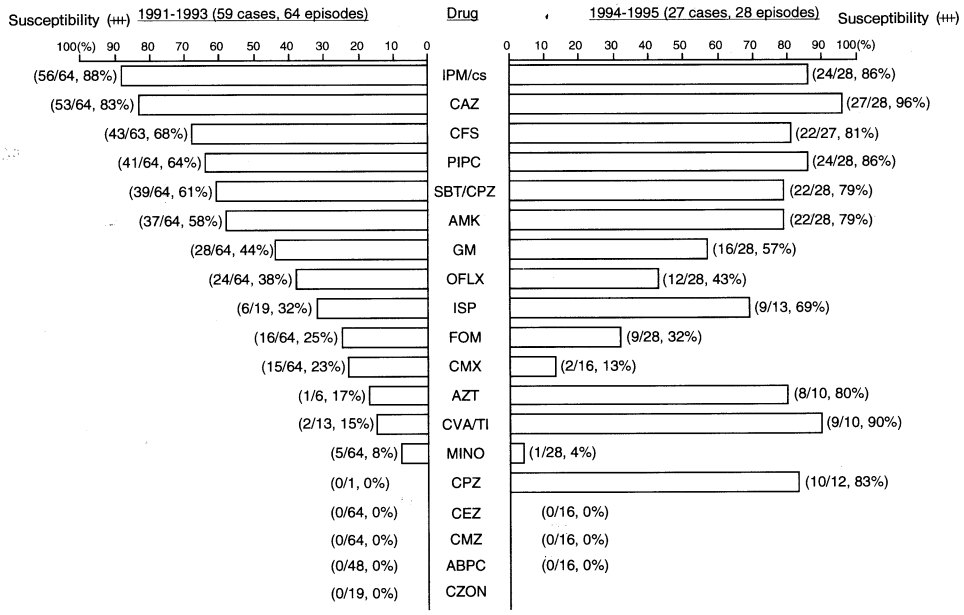

Fig 4. Drug sensitivity of *Pseudomonas aeruginosa* isolated from clinical materials

cular coagulation (DIC) 2 cases (7%), and acute respiratory distress syndrome (ARDS) 1 case (4%) in group A and septic shock 27 cases (42%), DIC 9 cases (14%), ARDS 9 cases (14%) in group B.

Antibiotic activity of administered drugs against *Pseudomonas aeruginosa* was measured by the optic disc method in vitro and the results are shown in Fig 4. The antibiotic activity of β-lactam antibiotics was still effective against *Pseudomonas aeruginosa*, while that of new quinolone was not resistant in both groups. As a whole, the antibiotic activity in both groups had not significant difference in the statistical analysis.

DISCUSSION

Pseudomonas aeruginosa has recently been the most dominant causative agent of bacteremia among gram-negative species of nosocomial origin. The frequency of *Pseudomonas aeruginosa* bacteremia was 0.7 episodes per 1000 patients in 1990 in Govadonga Hospital, Oviedo, Spain and composed 3.2% of the total number of bacteremia cases.[5]

With regard to underlying diseases of *Pseudomonas aeruginosa* bacteremia, hematological disease, traumatic disease, including burns, and malignant disease were dominant in group A, while hematological disease was dominant in group B. The reasons for this difference would be explained by the prior use of antibiotics such as new quinolones and induction of G-CSF drugs at the time of neutropenia after anticancer chemotherapy, especially for leukemia patients. Recently, especially in the division of hematological diseases, new quinolones such as CPFX and TFLX are often administered to leukemia patients during anticancer chemotherapy before the suspicion of nosocomial infection. In fact, high antimicrobial activity of CPFX and TFLX against *Pseudomonas aeruginosa* has been reported in many in vitro studies.[6] Also the availability of new agents with antipseudomonal activity, such as the broad-spectrum cephalosporins and new quinolones, introduce the possibility of more effective treatment than the conventional regimens of antipseudomonal antibiotics.[7]

The primary sources of bacteremia are shown in Table 3. In our study, the urinary tract was the main primary source in group A, but the respiratory tract (sputum and throat swab) was the most often the source in group B. However, there was not any difference in the frequency of the primary source of bacteremia between the two groups. In several other studies,[8,9] the respiratory tract was also the most common primary source of entry followed by the urinary tract. However, in Spanish hospitals, the urinary tract ranks as the most common primary source of entry.[10,11] As the underlying disease, urinary tract complications, such as acute renal failure and neurogenic bladder, were recognized in high percentages and uretheral catheters were inserted in many cases. Although these two factors were considered to be related to the primary source of entry in group A, in group B, a similar tendency was recognized and we could not find the reason for the difference.

Regarding antibiotic therapy performed for *Pseudomonas aeruginosa* bacteremia patients, the appropriate antibiotics were not administered as prior antibiotics for about half of the total cases in both groups as prior antibiotics. However, the clinical effect was quite different between the two groups, the efficacy rate being 71% in group A vs 46% in group B. In group A especially,

both the advance in the therapy for complications (septic shock, DIC, ARDS) and quick recovery of the neutrophil count by utilization of G-CSF drugs are suspected to have produced this efficacy especially. Furthermore, no antibiotics were administered for *Pseudomonas aeruginosa* bacteremia in many cases of group B as compared with group A and the antibiotics activity for *Pseudomonas aeruginosa* in group B was low as compared with group A. Hilf *et al*[12] recommended the administration of combination therapy (for example; β-lactam antibiotics + aminoglycoside antibiotics) since the use of combination therapy was even more important in determining the ultimate outcome than were underlying disease and the degree of neutropenia.

Finally, the antibiotic activities of β-lactam antibiotics were comparatively preserved in both groups, where for *Pseudomonas aeruginosa* as those of previously produced new quinolones, such as OFLX, were comparatively resistant in both groups. New quinolones had been expected to be effective drugs for *Pseudomonas aeruginosa* which had been resistant to β-lactam and aminoglycoside antibiotics. However, resistance of *Pseudomonas aeruginosa* to the new quinolone drugs existed because of mutations of the gene on the chromosome of the bacteria[13] and we experienced this phenomenon frequently. This tendency was especially strong for NFLX and OFLX had its tendency strongly, while for CPFX and TFLX, which have been suspected to have high antimicrobial activity for *Pseudomonas aeruginosa* it is presently comparatively preserved.[14] In several recent studies, *Pseudomonas aeruginosa* has been reported to show resistance for β-lactam antibiotics; *e.g.*, IPM/CS or CAZ.[15,16]

Presently, although some β-lactam and new quinolones with high antipseudomonal activity have been developed, *Pseudomonas aeruginosa* bacteremia still exists as big hazard for patients with hematological diseases. To resolve this problem, we administer appropriate antibiotics as soon as possible so that patients recover their immunity for infection. After obtaining information from surveillance cultures,[17] we consider treatment methods: *i.e.*, the administration of G-CSF,[18] antipseudomonal r-globulin drugs and early recovery of the neutrophil count using monoclonal antibodies for various kinds of pathogenetic factors containing endotoxin.

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