both of these countries report cases of the disease in their citizens who have been travelling within their own countries. In 2003, 17 of the 18 clusters reported in France would not have been detected without internal reporting, and six of 14 clusters in Italy would also have been missed [1]. In other countries, such as Austria, data protection is often a welcome justification for impeding mandatory reporting of all cases to EWGLINET. Fear of being blamed as a 'nestbeschmutzer' (a person who spoils his/her own nest) is an additional obstacle to addressing national problems at a European level, with the result that relevant opportunities to prevent avoidable disease are missed. The cases of Legionnaires' disease associated with travel in Austria, both in foreigners and in Austrian citizens, highlight the need for implementation of the European guidelines [2], adapted to national conditions, so that the appropriate measures can be taken to control the risk of travel-associated Legionnaires' disease.

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RESEARCH NOTE

Clinical features and outcome of patients with community-acquired *Pseudomonas aeruginosa* bacteraemia

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ABSTRACT

Cases of community-acquired *Pseudomonas aeruginosa* bacteraemia (n = 39) that occurred at a tertiary-care hospital during a 5-year period were analysed retrospectively. The commonest underlying diseases were solid tumour (41%) and haematological malignancy (18%). Most (44%) of the patients were neutropenic, and 39% had septic shock at initial presentation. The 30-day attributable mortality rate was 39%. Two previously healthy patients were identified with fatal *P. aeruginosa* pneumonia with bacteraemia. *P. aeruginosa* bacteraemia is a fatal infection that should be considered in the differential diagnosis of patients presenting from the community with rapidly progressive sepsis.

Keywords Bacteraemia, community-acquired, pneumonia, *Pseudomonas aeruginosa*, sepsis, treatment outcome

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Pseudomonas aeruginosa is an important nosocomial pathogen [1,2], and can be difficult to treat because of resistance to many antibiotics, including antibiotics used commonly in the community. Community-acquired *P. aeruginosa* sepsis has been reported in previously healthy patients [3,4], but because the symptoms of bacteraemia are non-specific, the initial antibiotic therapy is almost always empirical, pending identification of the responsible pathogens [5]. It is therefore important to determine the likelihood that *P. aeruginosa* is the cause of a particular infection syndrome. Furthermore, there are limited data regarding community-acquired bacteraemia caused by *P. aeruginosa*. Thus, the present study investigated community-acquired cases of *P. aeruginosa* bacteraemia that presented at a tertiary-care hospital, in order to determine the potential risk factors for *P. aeruginosa* infection, and to examine the clinical features and outcome.

Clinical microbiology laboratory and medical records of individuals were reviewed from January 1998 to December 2002 at Seoul National University Hospital (Seoul, Korea), a 1500-bed tertiary-care university hospital and referral centre, to identify patients with clinically significant *P. aeruginosa* bacteraemia. Only the first bacteraemic episode for each patient was included in the analysis. Community-acquired bacteraemia was defined as a positive blood culture taken on or within 48 h of admission. The antimicrobial therapy was considered 'appropriate' when the initial treatment 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. As an aminoglycoside was not prescribed in high doses once-daily, which might be appropriate for *P. aeruginosa* bacteraemia, aminoglycoside monotherapy was considered inappropriate. The study methods and definitions were as described previously [6].

In total, 190 patients with *P. aeruginosa* bacteraemia were identified, of whom 39 (20.5%) had community-acquired infection. Among all cases of community-acquired Gram-negative bacteraemia (n = 886), 4.4% involved *P. aeruginosa*. Most (67%) patients were male, and the mean (± SD) age was 56 ± 14 years (range, 24–95 years). The commonest underlying diseases were solid tumour (n = 16; 41%) and haematological malignancy (n = 7; 17.9%). Most (44%) patients had neutropenia, and 38.5% had septic shock at initial presentation. Overall, 18% of patients had received antibiotics within the 30 days before the onset of bacteraemia. The commonest primary sites of infection were lung (n = 9; 23.1%), pancreaticobiliary tract (n = 8; 20.5%) and the urinary tract (n = 5; 12.8%). No primary site was identified for 14 (35.9%) patients. Two patients who were considered previously healthy, i.e., with no previous history of hospitalisation and no known underlying diseases, were identified. These patients had pneumonia with septic shock at the onset of bacteraemia, and died before the results of microbiological investigations were available.

The 30-day mortality rate was 38.5%. Of the 15 patients who died as a result of *P. aeruginosa* bacteraemia, 13 died within 7 days of hospitalisation, and ten within 72 h. The mean time (± SD) to death was 4.0 ± 5.4 days. The infection-related attributable mortality rate was 35.9% (14/39). All patients received antimicrobial therapy, which in 95% of cases was a β-lactam agent with or without an aminoglycoside. Twenty-four patients, of whom ten (41.7%) died, received inappropriate initial antimicrobial therapy, whereas 15 patients, of whom five (33.3%) died, received appropriate initial antimicrobial therapy (p 0.603). Univariate analysis was performed to assess risk factors for mortality. Septic shock at initial presentation was a factor associated significantly with mortality (OR, 71.50; 95% CI, 8.96–570.28; $p < 0.001$). Patients with pneumonia had a higher, but not statistically significant, mortality rate (OR, 4.67; 95% CI, 0.95–22.90; p 0.063). Of 39 *P. aeruginosa* isolates, only two were resistant to one or more anti-pseudomonal antibiotics such as ceftazidime, piperacillin or ciprofloxacin. Clinical details of all patients with community-acquired *P. aeruginosa* bacteraemia are summarised in Table 1.

To supplement a previous report focusing on all cases of *P. aeruginosa* bacteraemia [6], the present study focused exclusively on community-acquired infections over a longer period of time. Although rare, *P. aeruginosa* bacteraemia is often rapidly progressive, and can occur with a high mortality rate in previously healthy patients [3,4]. *P. aeruginosa* should be considered in the differential diagnosis of any patient presenting with rapidly progressive sepsis, particularly in patients with pneumonia. The present study confirmed the adverse prognostic potential of *P. aeruginosa* in patients with community-acquired infection.

Table 1. Clinical features and outcome of patients with community-acquired *Pseudomonas aeruginosa* bacteraemia

No.	Age/Sex	Underlying diseases	Co-morbid condition	Septic shock[a]	Site of infection[b]	Empirical antibiotics[c]	Definitive antibiotics	Outcome
1	43/M	Lymphoma	Corticosteroid use, neutropenia		Lung	CTX, AMK	CAZ, AMK, CIP	Progression to lung empyema; died on 50th day of treatment
2	24/F	Leukaemia	Neutropenia		Unknown	PIP, TOB	PIP, TOB	Cured
3	55/M	Leukaemia	Neutropenia		Unknown	PIP, TOB	PIP, TOB	Cured
4	67/F	Leukaemia	Neutropenia		Unknown	PIP, TOB	PIP, TOB	Cured
5	62/M	DM	Neutropenia		Unknown	PIP, TOB	PIP, TOB	Cured
6	48/M	Lymphoma	Corticosteroid use, neutropenia	Yes	Unknown	PIP, TOB	PIP, TOB	Died on 1st day of treatment
7	57/F	Aplastic anaemia	Neutropenia	Yes	Unknown	PIP, TOB	PIP, TOB	Died on 4th day of treatment
8	55/M	Aplastic anaemia	Neutropenia	Yes	Unknown	PIP, TOB	IPM	Died on 9th day of treatment
9	54/M	Leukaemia	Central venous catheterisation, neutropenia		Unknown	CRO, AMK	CAZ, AMK	Cured
10	66/M	Aplastic anaemia	Neutropenia	Yes	Unknown	PIP, TOB	PIP, TOB	Cured
11	24/F	Hyperthyroidism	Agranulocytosis		Eyeball (eyelid)	AMS	CIP	Cured
12	67/F	Lung cancer	Neutropenia	Yes	Unknown	PIP, TOB	PIP, TOB	Died on 2nd day of treatment
13	61/M	Lung cancer	Neutropenia		Lung	PIP, TOB	CAZ, AMK	Cured
14	45/F	Ovarian cancer	Neutropenia		Unknown	PIP, TOB	PIP, TOB	Cured
15	62/M	Sarcoma	Neutropenia	Yes	Lung	CTX, AMK	CTX, AMK	Died on 1st day of treatment
16	51/F	ACUP	Neutropenia	Yes	Unknown	CTX, AMK, MTZ	CTX, AMK	Died on 2nd day of treatment
17	52/M	Maxillary cancer	Neutropenia	Yes	Unknown	PIP, TOB	PIP, TOB	Died on 2nd day of treatment
18	33/M	None	None	Yes	Lung	CXM, CM	CXM, CM	Died on 1st day of treatment
19	95/F	None	None	Yes	Lung	CTX, CM	CTX, CM	Died on 3rd day of treatment
20	63/M	CBD stone	None		Pancreaticobiliary tract	CTX	CAZ, AMK	Cured
21	59/F	CBD stone	PTBD		Pancreaticobiliary tract	CTX, AMK, MTZ	CTX, AMK, MTZ	Cured
22	66/M	IHD stone	None		Pancreaticobiliary tract	CTX, AMK	CAZ, AMK	Cured after PTBD
23	56/M	CBD stone	Prior ERCP	Yes	Pancreaticobiliary tract	CTX, AMK	CTX, AMK	Died on 5th day of treatment
24	62/F	Cerebral infarct	Neurogenic bladder		Urinary tract	CIP	CIP	Cured
25	57/F	DM	None		Urinary tract	CAZ, AMK	CAZ, AMK	Cured
26	81/F	Cerebral infarct	Indwelling urinary catheter	Yes	Urinary tract	CTX, AMK	CTX, AMK	Died on 4th day of treatment
27	27/F	Toxic epidermal necrolysis	Corticosteroid use		Skin	CFZ	CAZ	Cured
28	71/M	ESRD	Central venous catheterisation, haemodialysis		Catheter-related	CFZ, CM	CIP	Cured with catheter removal
29	65/M	Multiple myeloma	Corticosteroid use	Yes	Unknown	CTX	CTX	Died on 1st day of treatment
30	58/M	Stomach cancer	L-tube feeding	Yes	Lung	CTX, AMK	CTX, AMK	Died on 1st day of treatment
31	41/M	Stomach cancer	PTBD		Pancreaticobiliary tract	CTX	CIP	Cured with PTBD tube change
32	50/M	Stomach cancer	Percutaneous nephrostomy		Urinary tract	CIP	CIP	Cured
33	56/M	GB cancer	None		Pancreaticobiliary tract	CTX	CAZ, AMK	Cured with biliary-stent insertion
34	65/M	CBD cancer	Prior ERCP	Yes	Pancreaticobiliary tract	CTX, MTZ	CAZ, AMK	Cured after PTBD
35	51/M	Pancreatic cancer	None		Pancreaticobiliary tract	CTX, MTZ	CAZ	Cured after PTBD
36	49/M	Lung cancer	None		Lung	CTX	CTX	Died on 2nd day of treatment
37	51/M	Bladder cancer	None		Urinary tract	CTX	CTX	Cured
38	69/M	Larynx cancer	Tracheostomy		Lung	CTX, CM	CAZ, AMK	Cured
39	59/M	Sarcoma	None		Lung	CXM, AZM	CAZ, AMK	Died on 22nd day of treatment

[a]Septic shock at initial presentation.
[b]The site of infection was either documented or presumed on the basis of clinical findings.
[c]Cases 2, 3, 4, 5, 6, 7, 8, 10, 12, 13, 14, 17, 24, 25 and 32, who received piperacillin, ceftazidime or ciprofloxacin, were considered to have received appropriate empirical antimicrobial therapy.
DM, diabetes mellitus; ACUP, adenocarcinoma of unknown primary site; CBD, common bile duct; IHD, intrahepatic duct; GB, gall bladder; ERCP, endoscopic retrograde cholangiopancreaticography; PTBD, percutaneous transhepatic biliary drainage; ESRD, end-stage renal disease; CTX, cefotaxime; CAZ, ceftazidime; CRO, ceftriaxone; CXM, cefuroxime; CFZ, cefazolin; PIP, piperacillin; AMK, amikacin; TOB, tobramycin; CIP, ciprofloxacin; IPM, imipenem; AMS, ampicillin–sulbactam; CM, clindamycin; AZM, azithromycin.

When compared with the mortality rate of community-acquired *Klebsiella pneumoniae* bacteraemia in the same institute during the same period, the mortality rate of *P. aeruginosa* bacteraemia was significantly higher (35.9% vs. 16.2%; p 0.002).

Only 38% of patients with *P. aeruginosa* bacteraemia received appropriate initial empirical antibiotics. Moreover, as reported previously [6], there was a significant association between survival and administration of an antimicrobial agent to which the strain was susceptible *in vitro*. These data may explain, at least in part, the high mortality rates among *P. aeruginosa*-infected patients. Although inappropriate initial antimicrobial therapy was not an independent predictor of death in the present study, this may simply have been a result of the small number of cases.

The present data also provide information regarding the clinical features of patients infected by *P. aeruginosa*, which may help to predict patients who are particularly at risk and to modify initial empirical antimicrobial therapy. These data suggest that initial empirical antimicrobial cover for *P. aeruginosa* should be considered seriously for patients with septic shock at initial presentation when community-acquired

Gram-negative bacteraemia is suspected, and particularly for patients with neutropenia, haematological malignancy or solid tumour, or who have recently received antibiotics.

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RESEARCH NOTE

Continuous infusion β-lactams for intensive care unit pulmonary infections

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ABSTRACT

This study evaluated the pharmacodynamics of continuous infusion β-lactams against pulmonary isolates of Gram-negative bacteria from patients managed in intensive care units (ICUs) in the USA. Multiple 10 000-patient Monte Carlo simulations were performed by integrating pharmacokinetic data from healthy individuals with 2408 MICs from the 2002 Intensive Care Unit Surveillance System database. These pharmacodynamic simulations suggested that continuous infusion regimens of cefepime, aztreonam, ceftazidime and piperacillin–tazobactam 13.5 g have the greatest likelihood of achieving pharmacodynamic targets against isolates of Enterobacteriaceae in the ICU. β-Lactams are unlikely to achieve pharmacodynamic targets against *Pseudomonas aeruginosa* or *Acinetobacter baumannii* when administered as monotherapy.

Keywords *Acinetobacter baumannii*, β-lactams, Enterobacteriaceae, Monte Carlo simulations, pharmacodynamics, *Pseudomonas aeruginosa*

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The threat of antibiotic resistance, coupled with a lack of new antibiotics active against Gram-negative bacteria in the industrial pipeline, necessitates more effective use of existing therapies. β-Lactams are one of the most diverse and clinically useful antibiotic classes, and are active against a wide array of bacterial species *in vitro* [1]. Unfortunately, in-vitro activity alone is not sufficient to ensure clinical success [2]. Clinical effectiveness depends on the interplay between in-vitro activity, pharmacokinetics, host immune status, tolerability and patient compliance.

In the absence of clinical trial data, pharmacodynamic models satisfy a critical need by enabling the scientific community to predict the likelihood of clinical success based on mathematical models that integrate antimicrobial susceptibility patterns and antimicrobial pharmacokinetics. Animal studies have demonstrated previously that clinical success is best predicted by one of three pharmacodynamic indices: the percentage of time for which the concentration remains above the MIC (%T > MIC); the ratio of peak concentration to MIC (C_{max}/MIC); and the ratio of area under the concentration–time curve to MIC (AUC/MIC) [1]. It has been demonstrated

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