ORIGINAL INVESTIGATION

Bacteremic Pneumonia in Neutropenic Patients With Cancer

Causes, Empirical Antibiotic Therapy, and Outcome

Jordi Carratalà, MD, PhD; Beatriz Rosón, MD; Alberto Fernández-Sevilla, MD, PhD; Fernando Alcaide, MD; Francesc Gudiol, MD, PhD

Background: Bacteremic pneumonia is a major cause of death among neutropenic patients with cancer.

Methods: We analyzed the causes, empirical antibiotic therapy, and outcome of 40 consecutive cases of bacteremic pneumonia identified among 408 episodes of bacteremia in adult neutropenic patients with cancer, prospectively documented from 1986 to 1995.

Results: The most frequent causative organisms were *Pseudomonas aeruginosa* (17 cases), *Streptococcus pneumoniae* (12 cases), *Escherichia coli* (5 cases), and *Streptococcus mitis* (3 cases). Overall, *P aeruginosa* and *S pneumoniae* caused 72.5% of all episodes of bacteremic pneumonia, compared with 11.4% of bacteremic episodes from other sources ($P<.001$). Thirty patients received ceftazidime and 10 patients received imipenem as the β-lactam component of the initial empirical treatment. All strains of *P aeruginosa* were susceptible to both agents. Forty-seven percent of streptococcal strains were penicillin resistant and showed a decreased susceptibility to ceftazidime (minimum inhibitory concentration ranged from 1 to 64 µg/mL). Five patients (12.5%) were considered to have received inappropriate empirical antibiotic therapy. Attributable mortality in patients with bacteremic pneumonia was higher than in patients with bacteremia from other sources; 22 (55%) of the 40 patients with bacteremic pneumonia died, whereas 39 (10.6%) of the 368 patients with bacteremia from other sources died ($P<.001$).

Conclusions: Our data suggest that bacteremic pneumonia in neutropenic cancer patients is associated with a poor outcome and that empirical antibiotic therapy for neutropenic patients with pneumonia should include agents active against both *P aeruginosa* and cephalosporin-resistant streptococci.

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From the Services of Infectious Disease (Drs Carratalà, Rosón, and Gudiol), Hematology (Dr Fernández-Sevilla), and Microbiology (Dr Alcaide), Ciutat Sanitària i Universitària de Bellvitge, University of Barcelona, Barcelona, Spain.

DESPITE advances in antibiotic therapy, pneumonia remains a major cause of morbidity and mortality.[1-3] In recent years, a change in the patient population with pneumonia, which includes an increasing number of patients immunosuppressed by human immunodeficiency virus infection, transplantation, immunosuppressive drugs, and cancer, has been noted.[4] However, investigators have excluded such patients from most prospective studies, and the American Thoracic Society has provided guidelines that exclude immunosuppressed patients.[5,6] Therefore, there is a need for studies dealing with pneumonia in the different groups of immunosuppressed patients.

Patients with cancer are at high risk of developing life-threatening bacteremic infections during episodes of severe neutropenia.[7] In this critically ill population, the prompt institution of adequate empirical antibiotic therapy for febrile episodes is essential.[8] The increasing number of gram-positive systemic infections observed in neutropenic patients along with the emerging problems of resistance to antimicrobial agents make this task a therapeutic challenge.[9-14] Thus, pneumonia, which has been pointed out as the most common cause of infectious death in cancer patients,[15,16] might be inadequately covered by most current regimens of empirical antibiotic therapy administered to febrile neutropenic patients. However, little attention has been focused on bacterial pneumonia in this patient population in recent years. The purposes of this study are to describe the causes, empirical antibiotic therapy, and outcome of bacteremic pneumonia in neutropenic patients with cancer.

RESULTS

During the 10-year study period, a total of 408 episodes of bacteremia in neutropenic patients with cancer were identi-

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PATIENTS AND METHODS

STUDY PATIENTS AND SOURCE OF DATA

This study was carried out in a 1000-bed teaching hospital for adults, with approximately 24 000 admissions annually. The hospital serves an urban area with a population of more than 1 million. A prospective surveillance of all cases of bacteremia is regularly performed at our institution. All neutropenic patients with cancer with bacteremia identified daily by our microbiology laboratory are visited by a staff member of the Infectious Disease Service, who fills out a computer-assisted protocol and provides medical advice when indicated. For the purposes of this study, we included all cases of bacteremic pneumonia documented from January 1, 1986, through December 31, 1995, in neutropenic patients with cancer (granulocyte count, $<500\times10^9$/L).

PROPHYLACTIC AND THERAPEUTIC REGIMENS

Since January 1988, prophylactic norfloxacin was given orally (400 mg twice daily) to patients with cancer who were neutropenic or those who were likely to develop cytotoxic therapy–induced neutropenia lasting more than 7 days. No other antibacterial prophylaxis was given. Ceftazidime plus amikacin sulfate was the empirical antibiotic regimen most commonly used for febrile episodes that occurred during the study period. In cases in which infection was microbiologically documented, the initial antibiotic therapy was changed, when appropriate, according to the susceptibility results.

DEFINITIONS

Bacteremic pneumonia was defined as the presence of an acute respiratory illness and a pulmonary infiltrate on a chest radiograph in association with positive blood cultures. Pneumonia was considered to be nosocomially acquired if it was neither present nor incubating at the time of admission and it appeared at least 48 hours after admission. Neutropenia was considered severe when the granulocyte count was less than 100×10^9/L. Shock was defined as systolic blood pressure less than 90 mm Hg with clinical signs of peripheral hypoperfusion. Prophylactic antibacterial treatment was considered to be present when norfloxacin was administered for at least 3 days before bacteremia. Attributable mortality was defined as death during symptomatic infection or as a consequence of its complications. Overall mortality was defined as death within 30 days of bacteremia.

MICROBIOLOGIC STUDIES

Between 1986 and 1989, blood cultures were performed by means of manual biphasic media (Roche Septicheck System, Hoffmann-La Roche Inc, Nutley, NJ). From 1990 on, the samples were inoculated into culture vials (BACTEC PLUS 26 for aerobic cultures and BACTEC PLUS 27 for anaerobic cultures; Johnston Laboratories Inc, Towson, Md) and tested on a non-radiometric instrument (BACTEC NR 860; Johnston Laboratories Inc), which detects carbon dioxide by infrared analysis. The bottles were incubated for 7 days at 35°C before being discarded. Bacteria were identified by standard methods. Susceptibility testing was performed by microdilution. We used the National Committee for Clinical Laboratory Standards criteria to define penicillin and cephalosporin resistance for *Streptococcus pneumoniae* and other streptococci.[17] Empirical antibiotic treatment was considered inappropriate when isolates were resistant to the antimicrobial agents prescribed. Patients with pneumococcal bacteremic pneumonia caused by strains with a minimum inhibitory concentration (MIC) of ceftazidime of 2 μg/mL or more (accepted National Committee for Clinical Laboratory Standards breakpoint for other third-generation cephalosporins),[17] and who were treated with this β-lactam agent and amikacin, were considered to have received inappropriate empirical antibiotic therapy.

STATISTICAL ANALYSIS

We used the χ^2 test with Yates correction or Fisher exact test when appropriate for analysis of categorical variables. $P<.05$ was considered statistically significant.

fied. The sources of all episodes of bacteremia are summarized in **Table 1**. Pneumonia was the source of bacteremia in 9.8% of cases. Overall, there were 40 episodes of bacteremic pneumonia involving 39 patients. The characteristics of these episodes are shown in **Table 2**. A total of 26 patients (67%) were men and 13 (33%) were women. The mean age of patients was 56 years (range, 16 to 84 years). Twenty-six patients (67%) had hematologic malignant neoplasms, and 13 had solid tumors. Acute leukemia and lung cancer were the most frequent underlying conditions. Two patients had undergone bone marrow transplantation and another one had a splenectomy. No patient was infected with human immunodeficiency virus. In most cases, bacteremic pneumonia manifested as severe sepsis with marked systemic signs and symptoms, high fever, and a poor clinical condition. Symptoms at the time of initial examination included fever (38 patients [95%]), cough (19 [47.5%]), shortness of breath (9 [22.5%]), sputum (10 [25%]), and pleuritic chest pain (7 [17.5%]). Bilateral pneumonia and septic shock were observed frequently (9 patients [22.5%]).

Table 3 shows the causative pathogens of the episodes of bacteremic pneumonia according to the place of acquisition. A total of 43 organisms were isolated in the 40 episodes of pneumonia; 25 (58%) of the isolates were gram-negative organisms and 18 (42%) were gram-positive organisms. Three episodes (7.5%) were polymicrobial. The most frequently isolated pathogens were *Pseudomonas aeruginosa* (17 cases), *Streptococcus pneumoniae* (12 cases), *Escherichia coli* (5 cases), and *Streptococcus mitis* (3 cases). Overall, *P aeruginosa* and *S pneumoniae* caused 72.5% of all episodes of bacteremic pneumonia, compared with 11.4% of bacteremic episodes from other sources ($P<.001$). Regarding the place of acquisition, no significant differences in causative agents were observed among community-acquired and nosocomially acquired cases.

All patients with bacteremic pneumonia were given empirical antibiotic therapy. Altogether, 30 patients

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Table 1. Source of Infection in 408 Episodes of Bacteremia in Neutropenic Patients With Cancer

Source of Bacteremia	No. (%)
Unknown*	218 (53.4)
Catheter	62 (15.2)
Oral mucositis	44 (10.8)
Pneumonia	40 (9.8)
Skin and soft tissue	21 (5.1)
Other	23 (5.6)

*Endogenous bacteremia.

Table 2. Characteristics of 40 Episodes of Bacteremic Pneumonia in 39 Neutropenic Patients With Cancer

	No. (%) of Episodes
Mean age (range), y	56 (16-84)
Male sex*	26 (67.0)
Underlying disease*	
Hematologic malignant neoplasms	26 (67.0)
Acute leukemia	15
Non-Hodgkin lymphoma	6
Hodgkin lymphoma	3
Other	2
Solid tumors	13 (33.0)
Lung cancer	8
Breast cancer	3
Other	2
Prophylaxis with norfloxacin	12 (30.0)
Severe neutropenia ($<100\times10^9$/L)	26 (65.0)
Clinical manifestation	
Fever	38 (95.0)
Cough	19 (47.5)
Shortness of breath	9 (22.5)
Sputum	10 (25.0)
Pleuritic chest pain	7 (17.5)
Septic shock	9 (22.5)
Chest radiograph	
Segmental	8 (20.0)
Lobar unilateral	16 (40.0)
Multilobar unilateral	6 (15.0)
Bilateral	9 (22.5)
Patchy	1 (2.5)
Pleural effusion	4 (10.0)
Inappropriate empirical antibiotic therapy	5 (12.5)
Outcome	
Attributable mortality	22 (55.0)
Overall mortality	25 (62.5)

*The denominator for these is the number of patients rather than episodes.

received ceftazidime and 10 patients received imipenem as the β-lactam component of the initial empirical treatment. Vancomycin hydrochloride was included in the regimen of empirical therapy in 3 cases. Five patients (12.5%) were considered to have received inappropriate empirical antibiotic therapy. These cases are detailed in **Table 4**. Three patients with bacteremic pneumonia caused by cephalosporin-resistant pneumococci who were empirically treated with ceftazidime plus amikacin died of infection. Two patients with cephalosporin-resistant streptococcal pneumonia (*S pneumoniae* in 1 case and *S mitis* in 1 case) who were treated with imipenem survived.

Table 3. Causative Agents of 40 Episodes of Bacteremic Pneumonia in 39 Neutropenic Patients With Cancer*

Pathogens	Community-Acquired (16 Episodes), No.	Nosocomially Acquired (24 Episodes), No.	Total No. (%) of Isolates
Gram-negative	**10**	**15**	**25** (58)
Pseudomonas aeruginosa	6	11	**17** (42.5)
Escherichia coli	3	2	**5** (12.5)
Moraxella catarrhalis	1	0	**1** (2.5)
Haemophilus influenzae	0	1	**1** (2.5)
Klebsiella pneumoniae	0	1	**1** (2.5)
Gram-positive	**7**	**11**	**18** (42)
Streptococcus pneumoniae	5	7	**12** (30.0)
Streptococcus mitis	1	2	**3** (7.5)
CNS†	1	1	**2** (5.0)
Staphylococcus aureus	0	1	**1** (2.5)

*Three episodes were polymicrobial.
†CNS indicates coagulase-negative staphylococci. The CNS were also isolated from sputum.

During the study period, 5 (42%) of the 12 pneumococcal strains that caused bacteremic pneumonia were penicillin resistant and had decreased sensitivity to other β-lactam agents. The MICs of penicillin ranged from 0.12 to 4 μg/mL, and MICs of ceftazidime ranged from 1 to 64 μg/mL. Forty percent of these resistant strains were intermediately resistant to penicillin (MIC, 0.12-1 μg/mL), and 60% were resistant (MIC, ≥2 μg/mL). Two of the 3 strains of *S mitis* were highly resistant to penicillin (MIC, 4 μg/mL) and to ceftazidime (MICs, and 64 μg/mL). Overall, 7 (47%) of the 15 streptococcal strains were penicillin resistant. All of these strains were susceptible to imipenem and vancomycin. All strains of *P aeruginosa* and *E coli* were susceptible to ceftazidime and imipenem.

Attributable mortality was 55% and overall mortality reached 62.5%. Attributable mortality of gram-positive bacteremic pneumonia was 53%, whereas that of gram-negative bacteremic pneumonia was 54.2%; the difference was not significant. Attributable mortality in patients with bacteremic pneumonia was higher than that in patients with bacteremia from other sources; 22 (55%) of the 40 patients with bacteremic pneumonia died, whereas 39 (10.6%) of the 368 patients with bacteremia from other sources died ($P<.001$). No significant differences in attributable mortality were found among patients who received appropriate or inappropriate empirical antimicrobial therapy. Three of the 5 patients considered to have received inappropriate empirical therapy died (Table 4).

COMMENT

Pulmonary complications in immunocompromised patients have been investigated in several previous studies.[18-22] However, to our knowledge, no study has systematically examined the cause, empirical antibiotic therapy, and outcome of bacteremic pneumonia in neutropenic patients with cancer. We describe herein 40 consecutive episodes of bacteremic pneumonia in cancer

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Table 4. Characteristics of Neutropenic Patients With Cancer and Bacteremic Pneumonia Considered to Have Received Inappropriate Empirical Antibiotic Therapy*

Age, y/ Sex	Underlying Disease	Isolated Pathogens	Empirical Treatment	MIC, µg/mL		Definitive Treatment	Outcome	Time to Death, d
				PEN	CTZ			
77/M	AML	*Streptococcus pneumoniae*	Ceftazidime, amikacin sulfate	2.00	32.00	No	Died	1
52/F	Non-Hodgkin lymphoma, splenectomy	*S pneumoniae*	Ceftazidime, amikacin	0.25	2.00	No	Died	2
77/F	AML	*S pneumoniae*	Ceftazidime, amikacin	2.00	32.00	Imipenem†	Died	5
59/M	Multiple myeloma	*Staphylococcus aureus, Haemophilus influenzae*	Ceftazidime, amikacin	. . .	. . .	Amoxicillin-clavulanate potassium	Cured	. . .
52/F	Breast cancer	CNS‡	Ceftazidime, amikacin	. . .	. . .	Ciprofloxacin hydrochloride, rifampin	Cured	. . .

**MIC indicates minimum inhibitory concentration; PEN, penicillin; CTZ, ceftazidime; AML, acute myelocytic leukemia; and CNS, coagulase-negative staphylococci. Ellipses indicate not applicable.*

†*The MIC of imipenem was 0.5 µg/mL.*

‡*Also isolated from sputum.*

patients with neutropenia prospectively documented during a 10-year period.

Our study found that *P aeruginosa* and *S pneumoniae* caused the great majority of episodes of bacteremic pneumonia, whereas these organisms were isolated much less frequently in cases of bacteremia from other sources. A remarkable result of our study was that 42% of the causative agents of bacteremic pneumonia were gram-positive organisms. This finding notably differs from previous studies in which gram-positive pathogens were rarely isolated.[18,23] Nevertheless, sputum culture was used as a means of diagnosing pneumonia in many cases included in the previous studies, and the accuracy of this diagnostic technique has been questioned. In contrast, all patients described in this study had positive blood cultures, which offer a definite proof of the cause of pneumonia. Moreover, it should be noted that most previous studies dealing with pneumonia in the setting of cancer and neutropenia were carried out in the 1970s. In later years, gram-positive organisms have been recovered at a notably increased rate from neutropenic patients with cancer in most institutions.[9,24-26] Risk factors that have been associated with the increasing incidence of gram-positive infections include the use of more aggressive antineoplastic chemotherapy, which causes profound neutropenia and extensive mucositis, the universal use of central venous catheters, and the use of prophylaxis with fluoroquinolones, which is quite effective in preventing gram-negative bacteremia.[25-29] In particular, the presence of severe oral mucositis is likely a significant predisposing factor for streptococcal pneumonia. However, despite the high incidence of bacteremic pneumonias caused by gram-positive organisms observed in our study, the incidence of gram-negative pneumonias was still higher; *P aeruginosa* was the leading causative agent.

The prompt administration of empirical antimicrobial therapy to neutropenic patients who become febrile is now accepted as standard therapy.[30] The usual approach has been to use a combination of intravenous antibiotics consisting of an aminoglycoside and an antipseudomonal penicillin or a cephalosporin for all patients.[8] Nevertheless, despite this therapeutic strategy, infectious complications remain a significant problem and account for substantial mortality. Thus, some authorities have suggested that several types of infection probably deserve a more targeted approach.[30,31] In particular, the outcome of neutropenic patients treated for pneumonia with most standard antibiotic regimens is disappointing, and there is a need for more effective regimens. It should be noted that all gram-negative bacilli causing bacteremic pneumonia during the study period were susceptible to the β-lactam antibiotic used in the initial empirical therapy. Conversely, we found that approximately half of strains of streptococci were penicillin resistant and had decreased sensitivity to all β-lactams. In particular, ceftazidime, which is frequently administered as empirical therapy for febrile episodes in neutropenic patients with cancer, shows poor activity against these resistant streptococcal strains. In fact, we observed 3 patients with bacteremic pneumonia caused by cephalosporin-resistant pneumococci who were empirically treated with ceftazidime plus amikacin and died of infection. The important causative role of gram-positive organisms in bacteremic pneumonia documented in our study along with the increasing frequency of resistance to penicillin and cephalosporins among streptococci isolated worldwide may have major clinical implications when empirical antibiotic therapy is selected.[10-14] Currently, we believe that imipenem or a new extended-spectrum cephalosporin, such as cefepime and cefpirome sulfate, combined with an aminoglycoside offers adequate coverage for neutropenic cancer patients with pneumonia. These β-lactam antibiotics are active against *P aeruginosa* and also remain active against most penicillin-resistant streptococci. The clinical experience with vancomycin for the treatment of streptococcal pneumonia is limited, and the routine use of this drug presents some concerns because of the potential for emergence of resistance.[32]

Our study shows that bacteremic pneumonia in neutropenic patients with cancer is a serious infection that often terminates fatally. Although the mortality rates of

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gram-positive bacteremia in neutropenic patients are considered to be relatively low,[24] it is important to note that we did not find significant differences in mortality between gram-positive and gram-negative bacteremic pneumonia cases. The high frequency and significant mortality of pneumococcal pneumonia suggest the need for vaccination. However, the degree of protection afforded to immunocompromised patients by pneumococcal vaccination remains unclear.

Our results demonstrate that response rates for neutropenic patients with pneumonia are poorer than for those with bacteremia from other sources. It should be emphasized that a substantial number of patients described herein had bilateral pneumonia and septic shock. These findings concur with those of previous studies that have found that pneumonia is the most common cause of infectious death in patients with cancer.[15,16]

In summary, our study shows that bacteremic pneumonia in neutropenic patients with cancer is associated with a poor outcome and suggests that initial empirical antibiotic therapy for neutropenic patients with pneumonia should include agents active against both *P aeruginosa* and cephalosporin-resistant streptococci.

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Reprints: Jordi Carratalà, Infectious Disease Service, Hospital de Bellvitge, Feixa Llarga sn, 08907 L'Hospitalet, Barcelona, Spain (e-mail: jcarrata@redestb.es).

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