Eur J Clin Microbiol Infect Dis (1999) 18:539–544

Article

Prognostic Factors Influencing Mortality in Cancer Patients with Neutropenia and Bacteremia

E. González-Barca, A. Fernández-Sevilla, J. Carratalá, A. Salar, J. Peris, A. Grañena, F. Gudiol

Abstract The purpose of this study was to identify risk factors for mortality in neutropenic patients with cancer and bacteremia. A consecutive sample of 438 neutropenic patients (granulocyte count $<0.5\times10^9$/l) with cancer and bacteremia was studied to identify the clinical characteristics associated with mortality at the onset of bacteremia. The mean age of the subjects was 48 years (range, 15–87 years). Most cases of bacteremia (77%) were hospital-acquired and occurred in patients with acute leukemia (48%). Gram-positive organisms caused 233 (53%) episodes of bacteremia, gram-negative organisms caused 151 (34%) episodes, and 48 (11%) episodes were polymicrobial. The overall mortality within 30 days of the onset of bacteremia was 24.4%. The variables found to be independently associated with increased mortality using logistic regression techniques were as follows: shock at the onset of bacteremia (OR, 10; 95% CI, 4.2–23.8), pneumonia (OR,4.4; 95% CI, 1.9–10), uncontrolled cancer (OR,4.3; 95 %CI, 1.5–12.7), and absence of prophylaxis with norfloxacin (OR,2.4; 95%CI, 1.3–4.5). The prognostic factors ascertained in this study may help to identify those patients at higher risk of death. Medical intervention addressing some of these factors may improve the outcome of bacteremia in neutropenic patients with cancer.

Introduction

Infection continues to be a major complication in patients with cancer [1], and neutropenia is the main risk factor for developing a serious infection [2]. Most neutropenic patients with cancer experience fever, and a third of them have a microbiologically documented infection, primarily bacteremia [3]. Advances in supportive care of patients with cancer have improved long-term survival. Nevertheless, bacteremia still causes significant mortality (15–25%) among neutropenic patients despite new antimicrobial therapies [4–6].

The identification of prognostic factors amenable to medical intervention could be useful in improving the outcome for this population. However, information regarding the predictors of mortality at the onset of bacteremia is scarce [7, 8]. The aim of the present study was to identify at the onset of bacteremia the factors influencing mortality in a series of 438 consecutive episodes of bacteremia occurring in neutropenic patients with cancer.

E. González-Barca (✉), A. Fernández-Sevilla, A. Salar, J. Peris, A. Grañena
Department of Hematology, Institut Català d'Oncología, Hospital Duran i Reynals, Ciutat Sanitaria i Universitària de Bellvitge, Autovía de Castellfels Km 2,7, L'Hospitalet de Llobregat, E-08907 Barcelona, Spain
e-mail: e.gonzalez@csub.scs.es

J. Carratalá, F. Gudiol
Department of Infectious Diseases, Ciutat Sanitaria i Universitària de Bellvitge, Autovía de Castellfels Km 2,7, L'Hospitalet de Llobregat, E-08907 Barcelona, Spain

Patients and Methods

Setting and Source of Data. This study was carried out in a 1000-bed university hospital in Barcelona, Spain. The hospital serves as a referral center for adults and is located in an urban area with a population of approximately 1 million. Cancer patients undergoing cytoreductive chemotherapy are hospitalized in the hematology and oncology divisions, which consist of three 30-bed inpatient units and six isolation rooms. Prospective surveillance of all cases of bacteremia is regularly performed at our institution.

All neutropenic cancer patients with bacteremia identified daily by our microbiology laboratory are visited by a physician who fills out a computer-assisted protocol and gives medical advice when indicated. For the purpose of the study, we included all cases of bacteremia documented from January 1986 to August 1996.

Prophylactic and Antibiotic Therapy Regimens. Beginning in January 1988, prophylactic norfloxacin was given orally (400 mg twice daily) to patients with hematologic cancer who were neutropenic or who were likely to develop cytotoxic therapy-induced neutropenia lasting more than 7 days. Norfloxacin was discontinued when empiric antibiotic therapy was begun. No other antibacterial prophylaxis was given. Patients received nystatin (2×10^6 U) orally three times daily as a solution whenever possible.

The most frequent empiric antibiotic therapies for febrile episodes were ceftazidime plus amikacin in 264 (60%) episodes and imipenem plus amikacin in 63 (14%) episodes. Vancomycin was subsequently added to the initial treatment because fever persisted for more than 3 days in 105 (24%) patients. Once the microorganism was identified, the initial antibiotic therapy was changed according to the results of susceptibility tests. Antibacterial therapy was continued until bone marrow recovery.

Definitions. Bacteremia (clinical symptoms and positive blood cultures) was considered to be nosocomially acquired if it appeared 48 h after admission and no evidence of infection was present on admission. Episodes of polymicrobial bacteremia were those in which more than one organism was isolated from one or more blood cultures within a 72 h period. Bacteremia caused by coagulase-negative staphylococci (CNS) was considered significant when CNS grew in at least two blood cultures or in one blood culture and in one other site. Mortality was defined as death within 30 days of the onset of bacteremia. All the following variables were evaluated at the onset of bacteremia: neutropenia was defined as a granulocyte count of $< 0.5 \times 10^9$/l and severe neutropenia as a granulocyte count of $< 0.1 \times 10^9$/l; prophylactic antibacterial treatment was considered to be present when norfloxacin was administered for at least 3 days before the onset of bacteremic episode; empiric antibiotic therapy was considered adequate when the microorganism(s) isolated showed sensitivity to the antibiotic(s) administered; shock was defined as systolic blood pressure < 90 mmHg with signs of peripheral hypoperfusion; the source of bacteremia was defined according to previously published criteria [9]; bacteremic pneumonia was defined as the presence of acute respiratory illness and a pulmonary infiltrate on a chest radiograph in association with positive blood cultures (in 1 case of CNS pneumonia, CNS was also isolated from sputum); and uncontrolled cancer was defined as the absence of complete remission in patients with leukemia plus the development of new lesions, enlargement of a measurable lesion while on chemotherapy, or premature termination of chemotherapy due to other evidence of failure.

Microbiological Studies. Between 1986 and 1989, blood cultures were performed using the Roche Septicheck System (Hoffmann-La Roche, Germany) with trypticase soy broth and thioglycolate broth media for aerobic and anaerobic cultures, respectively. Beginning in 1990, blood samples were inoculated into Bactec bottles and tested on a Bacter NR-860 instrument (Johnson Laboratories, USA), which detects carbon dioxide by infrared analysis. The bottles were incubated for 7 days at 35 °C before being discarded. Bacteria were identified using standard methods [10].

Statistical Analysis. Crude and adjusted odds ratios (OR) were calculated using univariate and multivariate unconditional logistic regression techniques [11]. All logistic regression models were fitted by means of the maximum likelihood estimation of parameters [11]. All variables were entered in the regression analysis as categorical variables with two categories coded 0 (absent) or 1 (present). Statistical significance was established at an alpha value of 0.05, and, accordingly, 95% confidence intervals (CI) around the ORs are presented.

Results

During the study period, 438 episodes of bacteremia in neutropenic patients with cancer were documented. Sixty-two percent of the episodes occurred in men. The mean age of the patients was 48 years (range, 15–87 years). Most cases of bacteremia (77%) were hospital-acquired and involved patients with acute leukemia (48%). The general characteristics and underlying conditions of patients are outlined in Table 1. Overall mortality was 24.4%, and most deaths occurred within the first week of the onset of bacteremia (Figure 1).

Gram-positive organisms caused 233 episodes of bacteremia, gram-negative organisms caused 151 episodes, and 48 episodes were polymicrobial (Table 2). The most frequently isolated gram-positive organisms were CNS and viridans group streptococci; the gram-negative organisms most frequently isolated were *Escherichia coli* and *Pseudomonas aeruginosa.*

One hundred eighty-nine episodes of bacteremia occurred while patients were on norfloxacin prophylaxis (mortality rate, 22/189, 12%). Two hundred forty-nine episodes of bacteremia developed in patients not receiving prophylaxis: 164 occurred in patients with solid tumors (mortality rate, 61/164, 37%) and 85 in patients with hematologic cancer (mortality rate, 24/85, 28%), 63 of whom were already on antibiotics because of a previous febrile episode during the same period of neutropenia. Two hundred eighty-nine episodes of bacteremia received adequate empiric treatment

Table 1 General characteristics of 438 neutropenic patients with cancer and bacteremia (mean age 48 years, range 15–87 years)

Characteristic	No. (%) of patients
Sex	
Male	272 (62)
Female	166 (38)
Underlying disease	
Hematological malignancy	
Acute leukemia	211 (48)
Lymphoma	86 (20)
Other	64 (15)
Solid tumors	77 (17)
Bone marrow transplantation	56 (13)
Hospital acquisition	336 (77)
Central venous catheter	262 (60)
Prophylaxis with norfloxacin	193 (43)
Fever	427 (97)
Shock	37 (8)
Septic metastases	18 (4)
Mortality	107 (24)

Table 2 Organisms isolated in 438 episodes of bacteremia, and associated mortality rates

	No. of episodes	No. (%) of deaths
Gram-positive organisms	233	42 (18)
CNS	102	13 (13)
Viridans group streptococci	61	13 (21)
Staphylococcus aureus	24	3 (13)
Streptococcus pneumoniae	14	6 (43)
Enterococci	13	4 (41)
Corynebacteria	3	1 (33)
Other	16	2 (13)
Gram-negative organisms	151	48 (32)
Escherichia coli	70	20 (29)
Pseudomonas aeruginosa	48	19 (40)
Klebsiella pneumoniae	11	3 (27)
Enterobacter cloacae	6	1 (17)
Other	16	5 (31)
Multiple organisms (polymicrobial episode)	48	15 (31)
Anaerobes (*Fusobacterium*)	6	2 (33)

CNS, coagulase-negative staphylococci

according to the subsequent microbiologic results, 111 received inadequate empiric therapy, and 38 episodes of bacteremia were not treated empirically because the patients were already on antibiotics for a previous febrile episode. The most frequent causative agents in the 111 episodes treated with inadequate empiric therapy were CNS in 55 cases of bacteremia, *Staphylococcus aureus* in 14 episodes, and viridans group streptococci in ten episodes.

The following variables influencing mortality were analyzed in the univariate analysis: the patient's age and sex; the presence of acute leukemia, uncontrolled cancer, or bone marrow transplantation; nosocomial acquisition of bacteremia; severity of neutropenia; presence of shock; the type of causative agent (gram-positive, gram-negative, or polymicrobial); the bacteria isolated (CNS, viridans group streptococci, *Staphylococcus aureus, Streptococcus pneumoniae, Escherichia coli,* or *Pseudomonas aeruginosa*); the source of bacteremia (pneumonia, catheter, oral mucosa, skin); prophylaxis; and adequacy of empiric treatment (according to microbiologic results). The variables found to be significantly associated with prognosis are shown in Table 3. The following variables were analyzed by a multivariate logistic regression model: the patient's age and sex; presence of acute leukemia or uncontrolled cancer; the acquisition of bacteremia; the presence of shock, gram-negative bacteremia, *Pseudomonas aeruginosa* bacteremia, or pneumonia; and prophylaxis with norfloxacin. In the multivariate analysis, shock (OR,10), pneumonia (OR,4.4), uncontrolled cancer (OR,4.3), and absence of fluoroquinolone prophylaxis (OR,2.4) were the only variables independently associated with increased mortality (Table 4). When the multivariate analysis was repeated omitting the variable prophylaxis, the other three variables and only those three were still significantly associated with death: shock (OR,10.2; 95% CI, 4.4–23.6; $P=0.00001$), pneumonia (OR,4.1; 95% CI, 1.9–9.2; $P=0.0004$), and uncontrolled cancer (OR,5.8; 95% CI, 2–16.8.2; $P=0.001$).

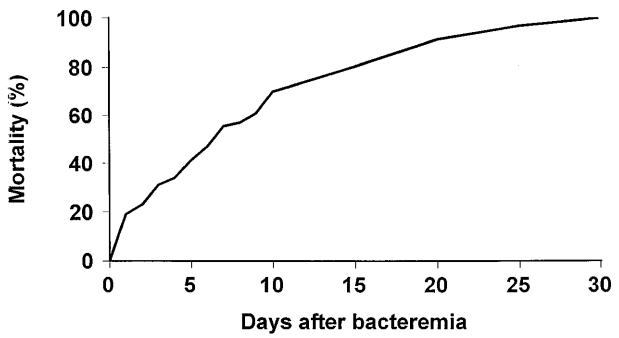

Figure 1 Cumulative mortality among 110 neutropenic cancer patients who died of bacteremia

Discussion

In our study, which involved a large number of patients with bacteremia documented prospectively over a 10-year period, the mortality rate within 30 days of the onset of bacteremia was 24.4%. The main risk factors for mortality were shock, pneumonia, uncontrolled cancer, and absence of fluoroquinolone prophylaxis. Shock at the onset of bacteremia was found to be the main risk factor associated with mortality. This finding is in agreement with previous studies, which have also pointed out the ominous prognosis of shock [7, 8]. Eight percent of the patients presented shock at the onset of bacteremia in our study. The poor prognosis of these patients highlights the urgent need for more adequate care. Different strategies to improve their outcome have been studied, such as the use of monoclonal antibodies and different cytokines, but the results continue to be discouraging [12–15].

Pneumonia as the source of bacteremia in neutropenic patients with cancer was associated with a higher risk of mortality in our study. The poorer prognosis of patients with bacteremic pneumonia was compared with the prognosis of patients with bacteremia due to other sources has been described by other authors [8]. The outcome of this group of patients with standard antibiotic regimens is disappointing. In previous studies, we found that the most frequent causative agents of bacteremic pneumonia were *Pseudomonas aeruginosa* and *Streptococcus pneumoniae* [6, 16], which are pathogens associated with high mortality. In these studies, all *Pseudomonas aeruginosa* strains causing bacteremic pneumonia were susceptible to the β-lactam antibiotic included in empiric therapy, but approximately half of the streptococci were penicillin resistant and had decreased susceptibility to all β-lactam agents,

Table 3 Prognostic factors for mortality in 438 episodes of bacteremia in neutropenic patients with cancer, as determined by univariate analysis

Variable	No. of deaths/ no. of episodes (%)	Odds Ratio (95% CI)	*P* value
Age in years			
≤45	29/179 (16)	1.0	
>45	81/259 (31)	1.5 (1.2–1.9)	0.001
Type of neoplasia			
Acute leukemia	35/211 (17)	1.0	
Other	72/227 (32)	2.3 (1.5–3.7)	0.0003
Uncontrolled cancer			
No	4/87 (5)	1.0	
Yes	103/351 (30)	8.6 (3.1–24)	0.00001
Place acquired			
Hospital	69/336 (20)	1.0	
Community	38/102 (37)	2.3 (1.4–3.7)	0.0007
Neutropenia			
$<0.1\times10^9$/l	71/330 (22)	1.0	
$0.1–0.5\times10^9$/l	36/108 (33)	0.7 (0.6–0.9)	0.02
Shock			
No	79/401 (20)	1.0	
Yes	28/37 (76)	12.7 (5.8–28)	0.00001
Gram-positive bacteremia			
No	65/205 (32)	1.0	
Yes	42/233 (18)	0.5 (0.3–0.7)	0.001
Gram-negative bacteremia			
No	59/287 (21)	1.0	
Yes	48/151 (32)	1.8 (1.2–2.8)	0.009
CNS bacteremia			
No	94/336 (28)	1.0	
Yes	13/102 (13)	0.4 (0.2–0.7)	0.002
P. aeruginosa bacteremia			
No	88/390 (23)	1.0	
Yes	19/48 (40)	2.2 (1.2–4.2)	0.01
Pneumonia			
No	85/401 (21)	1.0	
Yes	22/37 (59)	5.4 (2.7–11)	0.00001
Catheter			
No	99/371 (27)	1.0	
Yes	8/67 (12)	0.4 (0.2–0.8)	0.01
Absence of norfloxacin prophylaxis			
No	2/189 (12)	1.0	
Yes	85/249 (34)	4.0 (2.3–6.6)	0.00001

CNS, coagulate-negative staphylococci

especially ceftazidime [16]. Therefore, the empiric antibiotic therapy in neutropenic cancer patients suspected to have pneumonia should be reconsidered.

Patients with uncontrolled cancer have an increased risk of death due to bacteremia, a fact related to the low performance status frequently present in these patients [2, 7, 17]. Today, more intensive therapeutic regimens are used to treat neoplastic diseases, and overall the prognosis of cancer patients is improving. However, complications of infection constitute one of the most frequent causes of death in patients with resistant cancer.

The use of norfloxacin prophylaxis was associated with a lower risk of mortality in our study. It is clear that the use of prophylaxis with norfloxacin prevents gram-negative bacteremia [18–21], but there are discordant results regarding its influence on infection-related mortality. A recent meta-analysis of 19 randomized studies involving 2112 patients failed to demonstrate a better outcome for patients receiving fluoroquinolone prophylaxis [22]. These discordant results may be partially explained by the different populations analyzed, since few patients in these studies had bacteremia. In our study, mortality was high in neutropenic patients with solid tumors who developed bacteremia caused mainly by gram-negative bacilli. It is widely accepted that patients with solid tumors do not receive prophylaxis because they usually do not experience prolonged neutropenia. Our data, however, suggest that this strategy should be reconsidered. Therefore, prospective randomized studies including patients with solid tumors who receive ambulatory hematotoxic chemotherapy should be performed.

On the other hand, mortality was significant in neutropenic patients with hematologic malignancies who were not receiving prophylaxis when their bacteremia developed. This finding raises the question of whether it would be better to continue fluoroquinolone prophylaxis until resolution of neutropenia, even

Table 4 Prognostic factors for mortality in 438 episodes of bacteremia in neutropenic patients with cancer, as determined by multivariate analysis

Variable	Adjusted odds ratio (95% CI)	*P* value
Shock	10 (4.2–23.8)	0.00001
Pneumonia	4.4 (1.9–10)	0.0004
Uncontrolled neoplasia	4.3 (1.5–12.7)	0.007
No fluoroquinolone prophylaxis	2.4 (1.3–4.5)	0.005

though this approach may put patients at an increased risk of infection caused by multiresistant organisms. Moreover, the use of fluoroquinolone prophylaxis has been associated not only with an increase in gram-positive infections but also with the emergence of fluoroquinolone-resistant strains of *Escherichia coli* causing bacteremia [23–26]. As this study was not designed specifically to evaluate prophylaxis with norfloxacin, and since the prophylactic use of fluoroquinolones is highly controversial, we repeated the multivariate analysis omitting this variable, which did not change the other risk factors.

We found that inadequate empiric antibiotic therapy was not associated with a poorer outcome. Nevertheless, it should be noted that most bacteremic episodes in patients receiving inadequate therapy were caused by CNS. These organisms are frequently resistant to the usual empiric treatment used in our study (ceftazidime plus amikacin), but they rarely cause death [27].

In conclusion, the prognostic factors found in this study may help to identify those patients at higher risk of death. Medical intervention addressing some of these factors may improve the outcome of bacteremia in neutropenic patients with cancer.

References

1. Pizzo PA, Thaler M, Hathorn J: New beta-lactam antibiotics in granulocytopenic patients. American Journal of Medicine (1985) 79, Supplement 2:75–82
2. Bodey GP, Buckley M, Sathe YS, Freireich EJ: Quantitative relationship between circulating leukocytes and infection in patients with acute leukemia. Annals of Internal Medicine (1966) 64:328–340
3. EORTC International Antimicrobial Therapy Project Group: Three antibiotic regimens in the treatment of infections in febrile granulocytopenic patients with cancer. Journal of Infectious Disease (1988) 137:14–29
4. Singer C, Kaplan MH, Armstrong D: Bacteremia and fungemia complicating neoplastic disease. American Journal of Medicine (1977) 62:731–742
5. Whimbey E, Kiehn TE, Brannon P, Blevins A, Armstrong D: Bacteremia and fungemia in patients with neoplastic disease. American Journal of Medicine (1987) 82:723–730
6. González-Barca E, Fernández-Sevilla A, Carratalá J, Grañena A, Gudiol F: Prospective study of 288 episodes of bacteremia in neutropenic cancer patients in a single institution. European Journal of Clinical Microbiology & Infectious Diseases (1996) 15:291–296
7. Hovgaard D, Skinhoj P, Bangsborg J, Bruun B, Mork Hansen M, Nissen NJ: Bacteremia and candidemia in hematological malignancies: clinical findings. Scandinavian Journal of Infectious Diseases (1988) 20:495–501
8. Elting LS, Rubenstein EB, Rolston KVI, Bodey P: Outcomes of bacteremia in patients with cancer and neutropenia: observation from two decades of epidemiological and clinical trials. Clinical Infectious Diseases (1997) 25:247–259
9. Centers for Disease Control: National nosocomial infections study site definitions manual. Centers for Disease Control, Atlanta (1972) pp 82–84
10. Miller JM, O'Hara CM: Substrate utilization systems for the identification of bacteria and yeasts. In: Murray PR, Baron EJ, Pfaller MA, Tenover FC, Yolken RH (eds) Manual of clinical microbiology. American Society for Microbiology, Washington DC (1995) pp 103–109
11. Breslow NE, Day NE: The analysis of case-control studies. Statistical methods in cancer research. Scientific publication 32. International Agency for Research of Cancer, Lyon (1980)
12. Glauser MP: The inflammatory cytokines. New developments in the pathophysiology and treatment of septic shock. Drugs (1996) 52, Supplement 2:9–17
13. Zeni F, Pain P, Vindimian M, Gay JP, Gery P, Bertrand M, Page Y, Page D, Vermesch R, Bertrand JC: Effects of pentoxifylline on circulating cytokine concentrations and hemodynamics in patients with septic shock: results from a double-blind, randomized, placebo-controlled study. Critical Care Medicine (1996) 24:207–214
14. Fisher CJ Jr, Agosti JM, Opal SM, Lowry SF, Balk RA, Sadoff JC, Abraham E, Schein RM, Benjamin E: Treatment of septic shock with the tumor necrosis factor receptor:Fc fusion protein. New England Journal of Medicine (1996) 334:1697–1702
15. Siedlar M, Szczepanik A, Wieckiewicz J, Pituch-Noworolska A, Zembala M: Vancomycin down-regulates lipopolysaccharide-induced tumour necrosis factor alpha (TNF alpha) production and TNF alpha-mRNA accumulation in human blood monocytes. Immunopharmacology (1997) 35:265–271
16. Carratalá J, Rosón B, Fernández-Sevilla A, Alcaide F, Gudiol F: Bacteremic pneumonia in neutropenic patients with cancer: causes, empirical antibiotic therapy, and outcome. Archives of Internal Medicine (1998) 158:868–872
17. Talcott JA, Siegel RD, Finberg RD, Goldman L: Risk assessment in cancer patients with fever and neutropenia: a prospective, two center validation of a prediction rule. Journal of Clinical Oncology (1992) 10:316–322
18. Winston DJ, Ho WG, Nako SL, Gale PR, Champlin RE: Norfloxacin versus vancomycin-polymixin for prevention of infections in granulocytopenic patients. American Journal of Medicine (1986) 80:884–890
19. Karp JE, Merz WG, Hendricksen C, Laughon B, Redden T, Bamberger BJ, Barlett JC, Saral R, Burke P: Oral norfloxacin for prevention of gram-negative bacterial infections in patients with acute leukemia and granulocytopenia. A randomized, double-blind, placebo-controlled trial. Annals of Internal Medicine (1987) 106:1–7
20. Bow EJ, Rayner E, Louie TJ: Comparison of norfloxacin with cotrimoxazole for infection prophylaxis in acute leukemia. The trade off for reduced gram negative sepsis. American Journal of Medicine (1988) 84:847–854
21. Archimbaud E, Guyotat D, Maupas J, Ploton C, Nageotte A, Devaux Y, Thomas X, Fleurette J, Fiere D: Pefloxacin and vancomycin vs gentamicin, colistin sulphate and vancomycin for prevention of infections in granulocytopenic patients: a randomized double-blind study. European Journal of Cancer (1991) 27:174–178

22. Cruciani M, Rampazzo R, Malena M, Lazzarini L, Todeschini G, Messori A, Concia E: Prophylaxis with fluoroquinolones for bacterial infections in neutropenic patients: a meta-analysis. Clinical Infectious Diseases (1996) 23:795–805
23. Carratalá J, Fernández-Sevilla A, Tubau F, Callis M, Gudiol F: Emergence of quinolone-resistant *Escherichia coli* bacteremia in neutropenic patients with cancer who have received prophylactic norfloxacin. Clinical Infectious Diseases (1995) 20:557–560
24. Carratalá J, Fernández-Sevilla A, Tubau F, Dominguez MA, Gudiol F: Emergence of fluoroquinolone-resistant *Escherichia coli* in fecal flora of cancer patients receiving norfloxacin prophylaxis. Antimicrobial Agents and Chemotherapy (1996) 40:503–505
25. Kern WV, Andriof E, Oethinger M, Kern P, Hacker J, Marre R: Emergence of fluoroquinolone-resistant *Escherichia coli* at a cancer center. Antimicrobial Agents and Chemotherapy (1994) 38:681–687
26. Cometta A, Calandra T, Bille J, Glauser MP: *Escherichia coli* resistant to fluoroquinolones in patients with cancer and neutropenia. New England Journal of Medicine (1994) 330:1240–1241
27. Wade JC, Schimpff SC, Newman KA, Wiernik PH: *Staphylococcus epidermidis*: an increasing cause of infection in patients with granulocytopenia. Annals of Internal Medicine (1982) 97:503–508