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Antibiotic Resistance Is Associated With Longer Bacteremic Episodes and Worse Outcome in Febrile Neutropenic Children With Cancer

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Purpose. With the increasing emergence of multiresistant pathogens, better understanding of these infections is necessary. The aim of the present study was to evaluate the risk factors associated with isolating a multiresistant organism (MRO) from a positive blood culture in pediatric cancer patients with febrile neutropenia (F&N), and to study its impact on clinical course and outcome of febrile episodes. ***Patients and Methods.*** The association between MRO with underlying malignancy, age, disease status, hospitalization during episode, absolute neutrophil count, absolute monocyte count, clinical foci of infection, and pathogens isolated was assessed in bacteremic pediatric cancer patients. The MRO phenotype was defined as diminished susceptibility to ≥3 of the broad spectrum antibody classes. ***Results.*** Among 239 episodes of blood stream infections (BSI), Gram-positive, and Gram-negative organisms were detected in 180 (75%), and 59(25%) episodes, respectively; with 38% of isolates showing multiresistance (n = 92). Significant risk factors ($P < 0.05$) for MRO were hospitalization, Gram-negative organisms, presence of clinical focus of infection, reduced ANC, prolonged duration of neutropenia, and previous intake of antibiotics. Of the episodes with prolonged duration of fever extending for more than 7 days 62% (64|93) were associated with a multiresistant phenotype, while it accompanied 72% (18|25) of the cases with an unfavorable outcome; *P*-value <0.001. ***Conclusion.*** Isolation of MRO is more likely to be associated with a prolonged course and an unfavorable outcome. Continuous multidisciplinary surveillance of BSI is warranted to develop strategies for antimicrobial resistance control. Pediatr Blood Cancer 2011;57:283–288.

Key words: antibiotic resistance; bacteremia; febrile neutropenia; multiresistant organism (MRO); pediatric oncology

INTRODUCTION

Despite the widespread use and availability of powerful antibiotics, bacteremia/sepsis remains the most important independent prognostic marker for mortality in children with cancer who have febrile neutropenia (F&N). A diagnosis of sepsis or bacteremia conferred a 10-fold increase in the risk of death [1]. However, given the fact that empirical therapy remains the mainstay of supportive care of F&N [2], perhaps it is wise to consider its side effects.

The widespread use of antibiotics has had an enormous effect on the world of pathogens, promoting the emergence of resistant strains, with multiple drug resistant staphylococci as the leading example [3]. The World Health Organization (WHO) has identified antimicrobial resistance as one of the three greatest threats to human health. In general, nosocomial infections are increasingly associated with antibiotic resistance, which may lead to increased rates of morbidity and mortality as well as healthcare costs [4].

In F&N, new antimicrobial agents has made it possible to treat infectious complications more effectively, but their availability is also leading to an increased prevalence of highly resistant pathogens [5]. Available studies on antibiotic resistance in association with F&N are either limited to particular antibiotics [6,7] or to known resistant organisms, for example, methicillin resistant *Staphylococcus aureus*. Thus, our aim was to evaluate the frequency of resistant pathogens focusing on the presence of multiresistant phenotype as a whole rather than a separate look to individual antibiotics, in addition to investigating the risk factors associated with multiresistance in pediatric cancer patients with chemotherapy induced F&N, and its impact on clinical course and outcome.

PATIENTS AND METHODS

This prospective, single center cohort study was conducted at the Pediatric Microbiology Laboratory, Clinical Pathology and Pediatric Oncology Departments of National Cancer Institute (NCI), Cairo University. Cases were pediatric cancer patients treated with chemotherapy for a malignant disease and developing bacteremia while febrile neutropenic, in the period from first of July to end of December 2006. The study was approved by Ethics Committee of NCI and an informed consent was obtained from parents of participants.

During this period, 239 bacteremic episodes were recorded in 193 patients. Data recorded at first day of fever included age, diagnosis, state of disease, absolute neutrophil count (ANC), absolute monocyte count (AMC), platelet count, clinically documented infection (CDI), and febrile neutropenic episodes treated with broad spectrum antibiotics within 1 month preceding blood stream infection (BSI). Other data analyzed were chemotherapy received, standard or intensified protocols, and days between receiving chemotherapy and fever. If a patient developed fever ≥48 hr after hospitalization, the case was considered febrile neutropenic while hospitalized.

Definitions

In the context of neutropenia, fever was defined as a single oral temperature of ≥38.3°C, or a temperature ≥38°C for 1 hour continuously or at two times with a minimum interval of 12 hours; rectal measurement was avoided in neutropenic patients. Neutropenia described an ANC <<0.5 × 10^9 or <<1.0 × 10^9/L, with decline

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Conflict of interest: Nothing to report.

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predicted over the next 2 days [2]. Lower respiratory tract infections (LRTI) was defined as any new infiltrate arising within 48 hr before or after the onset of the febrile episode. When the blood culture revealed a potential contaminant, another positive blood culture, or other clinical evidence of ongoing BSI, such as rigors, hypotension, or documented infection at a second site with the same organism, was required for confirmation of true infection.

Microbiology

Two blood culture sets were usually drawn from each patient within the first day of fever from two separate veins. If the cannula site, portacath, or CVC was suspected as the source of infection, a blood sample was obtained from it as well. Collected blood was directly injected into Bactec® (Becton Dickinsion, Franklin Lakes, NJ)

TABLE I. Characteristics of Patients (N = 193) and Episodes (N = 293) in Relation to Antibiotic Resistance

Parameters	Sensitive, N (%)	Resistant, N (%)	*P*-value
Age, years	5 (0.25–18)	5 (0.25–18)	0.843
Sex			
Male (n = 119)	72 (61)	47 (39)	0.676
Female (n = 38)	47 (64)	27 (36)	
Disease			
AML (n = 56)	28 (50)	28 (50)	0.065
ALL (n = 58)	36 (62)	22 (38)	
Lymphoma (n = 30)	18 (60)	12 (40)	
Solid tumors (n = 49)	37 (76)	12 (24)	
Disease status			
Induction (n = 64)	37 (58)	27 (42)	0.076
Maintenance (n = 45)	31 (69)	14 (31)	
Solid tumors (n = 36)	27 (75)	9 (25)	
Relapse (n = 48)	24 (50)	24 (50)	
Chemotherapy			
Intensified (n = 121)	68 (56)	53 (44)	0.088
Standard (n = 118)	79 (67)	39 (33)	
Days between chemotherapy and fever			
<7 days (n = 83)	44 (53)	39 (47)	0.049
≥7 days (n = 156)	103 (66)	53 (34)	
Hospitalized (n = 95)	49 (52)	46 (48)	0.010
Out-patient (n = 144)	98 (68)	46 (32)	
Fever degree			
<39°C (n = 116)	78 (67)	38 (33)	0.077
≥39°C (n = 123)	69 (560)	54 (44)	
Clinical infections			
Yes (n = 125)	67 (54)	58 (46)	0.009
No (n = 114)	80 (70)	34 (30)	
CVC infection			
Yes (n = 14)	5 (36)	9 (64)	<0.001
No (n = 225)	142 (63)	83 (37)	
Chest infection			
Yes (n = 63)	24 (38)	39 (62)	<0.001
No (n = 176)	123 (70)	53 (30)	
Blood counts, 10^9/L, median (range)			
ANC 0.049 (0.0–10.1)	0.05 (0.0–10.1)	0.03 (0.0–1.5)	0.128
AMC 0.040 (0.0–2.5)	0.07 (0.0–2.5)	0.03 (0.0–1.3)	0.025
Platelets 38.0 (3.0–905.0)	42 (4–905)	28.5 (3–433)	0.029
Organism			
Gram positive (n = 180)	121 (67)	59 (33)	0.002
Gram negative (n = 59)	26 (44)	33 (56)	
Fungi			
Yes (n = 35)	7 (20)	28 (80)	<0.001
No (n = 204)	140 (69)	64 (31)	
Duration of neutropenia	7 (0–30)	12 (0–32)	<0.001
Episode outcome on day 7[a]			
Recovered (n = 135)	108 (80)	27 (20)	<0.001
Fever (n = 93)	39 (38)	64 (62)	
Outcome			
Alive (n = 214)	140 (65)	74 (35)	<0.001
Dead (n = 25)	7 (28)	18 (72)	

[a]Missing data are in cases with early deaths.

culture vials and were incubated in the Bactec 9050® incubator. Identification of isolates was carried out utilizing MicroScan® dried Gram-negative MIC/Combo and dried Gram-positive MIC/Combo panels Siemens Healthcare Diagnostics Ltd (Sir William Siemens Sq. Frimley, Camberley, UK GU16 8QD) for Gram-negative and Gram-positive organisms, respectively. The panel of antibiotics used for Gram negative included amikacin, amoxicillin-clavulanate, ampicillin-sulbactam, aztreonam, cefepime, cefoperazone, ceftazidime, cefuroxime, ciprofloxacin, gentamycin, imipenim, meropenem, norfloxacin, piperacillin, piperacillin-tazobactam, ticarcillin-clavulanate and trimethoprim-sulfamethoxazole; clindamycin, erythromycin, gatifloxacin, gentamycin, levofloxacin, linezolid, moxifloxacin, oxacillin, synercid, tetracycline, and vancomycin were additionally included in the Gram-positive panel. Antimicrobial susceptibility testing was determined by using the criteria established by the National Committee for Clinical Laboratory Standards [8]. The multiresistant organism (MRO) phenotype was defined as diminished susceptibility to $\geq$3 of the following cephalosporins, fluoroquinolones, aminoglycosides, beta-lactamase inhibitor combinations, and carbapenems [9]. Blood cultures were performed in parallel with other cultures from existing clinical sites of infection whenever possible.

During this period, children presenting with F&N were routinely hospitalized and treated with empirical double agent broad spectrum parentral antimicrobial therapy. The empirical regimen of hospital guidelines included cefoperazone/sulbactam + amikacin or cefepime + amikacin; but sometimes change between third-generation cephalosporins according to hospital supplies was done. No antibiotic prophylaxis was used. An antifungal was added on day 5 if fever persisted with no clinical or microbiological documentation necessitating shift or addition of antibiotics or if clinically or microbiologically indicated. Antibiotic therapy was continued until the patient became a febrile and ANC exceeded 0.5×10^9/L. The episode was considered to be successfully controlled when fever and clinical signs resolved within 5–7 days. A prolonged episode was defined by persistent fever for more than 7 days, with other measures taken into consideration including the general condition of the patient as regards severity and duration of neutropenia, in addition to any associated clinical focus.

Invasive fungal infections (IFI) were defined according to the criteria defined by the European Organization for Research and Treatment of Cancer (EORTC) [10]. Episodes of fungemia were not counted as episodes of BSI.

Statistical Methods

Data were analyzed using SPSSwin statistical package version 15. Chi-square test or Fisher's Exact test were used for test relation between qualitative variables. Comparison between two groups regarding numeric variables was done using either Student's *t*-test or Mann–Whitney test as appropriate. Multivariate analysis was done using binary logistic regression by forward conditional method. A P-value <0.05 was considered significant. All tests were two tailed.

RESULTS

Patient Characteristics

In the period from July first to end of December 2006, bloodstream infections were detected in 239 febrile neutropenic episodes identified in 193 patients. Of the 239 BSI episodes, 95 (40%) cases developed F&N while hospitalized, whereas, 144 (60%) were receiving their chemotherapy as outpatients. The patients' age ranged from 3 months to 18 years, with a mean age of 6.7 $\pm$ 4.8 years. The patients' characteristics, their diagnoses, and the clinical features of the episodes are listed in Table I.

Clinical Features

Fever was the hallmark of episodes, with a mean of 38.9 $\pm$ 0.65. Respiratory tract infections were recorded in 63 (26%) episodes. Gastroenteritis manifested by diarrhea, with or without vomiting, and abdominal pain coincided with fever in 45 (19%) episodes. Skin infections (perianal cellulites, ulcers, facial cellulites, skin abscesses, and infected bed sores) and catheter-related infections; were recorded in 28 (12%) and 14 (6%) episodes, respectively. A CDI was considered positive whenever any of the above manifestations were detected; in addition, tonsillitis (n = 8), sinusitis (n = 2), and viral infection including herpetic lesions (n = 5), and chicken pox (n = 1). Collectively, a CDI was encountered in 125 (52%) episodes, whereas, 48% (n = 114) episodes lacked a focus.

A previous F&N with intake of empirical broad spectrum antibiotics was recorded in 105 episodes, while 134 episodes showed no previous F&N. Of those with no previous F&N 32% (n = 17) had an MRO, whereas, 52% (n = 55) of those with a prior F&N had an MRO ($P = 0.046$).

Microbiology

Gram-positive organisms (GPC) were the predominant causative agents of BSI, constituting 75% (n = 180) of isolated organisms, while 25% of infections were caused by Gram-negative organisms (GNR) (n = 59). The organisms isolated are summarized in Table II. Of the *S. aureus* isolated, 59.3% were oxacillin resistant. Among the GNR, non-fermenters were predominant (n = 36) and

TABLE II. Pattern of Isolated Organisms From 239 Bactermic Episodes in Pediatric Cancer Cases With Febrile Neutropenia

Organisms	Number (%)
Gram-positive organisms	180
Coagulase negative *Staphylococci*	116(48.5)
Streptococcus spp.	29(12.1)
Stapylococcus aureus	23(9.6)
Micrococci	6(2.5)
Gram-positive bacilli	6(2.5)
Gram-negative organisms	59
Non-fermenters	36
Acinetobacter sp.	20(8.4)
Pseudomonas sp.	13(5.4)
Stenotrophomonas maltophilia	1(0.4)
Chryseobacteria meningosepticum	1(0.4)
Rolastonia picketti	1(0.4)
Enterobactericae	23
E. coli	9(3.8)
Klebsiella spp.	6(2.5)
Enterobacter spp.	2(0.8)
Salmonella spp.	1(0.4)
Serratia spp.	1(0.4)
Yersenia spp.	1(0.4)
Kluyvera ascorbata	2(0.8)
Unidentified GNR	1(0.4)

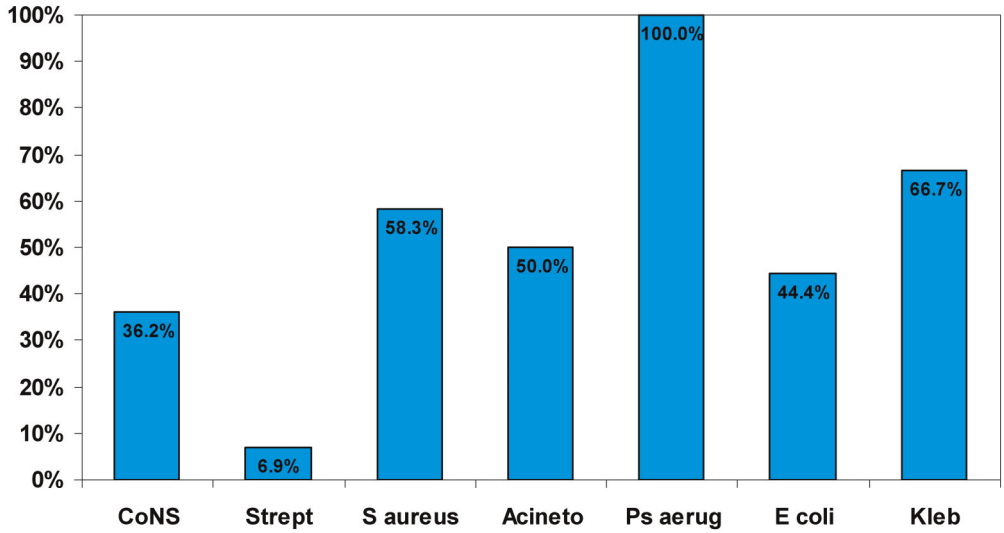

Fig. 1. Percentage of multiresistance among isolated organisms. CoNS, coagulase negative *Staphylococci*; Strept, *Streptococcal* sp; *S. aureus*, *Staphylococcus aureus*; Acineto, *Acinetobacter* sp; Ps aerug, *Pseudomonas aeruginosa*; *E. coli*, *Escherechia coli*; Kleb, *Klebsiella* sp. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com]

Enterobactericae were isolated from 23 cases (9.6%). Antibiotic resistance was encountered in 92/239 episodes (38.4%). The relation between antibiotic resistance and different parameters studied are summarized in Table I. Figure 1 demonstrates the percentage of resistance in major groups of isolates. Thirty-five episodes (15%) were identified as proven or probable IFI according to EORTC criteria.

Course and Outcome

Recovery at day 4 of fever was recorded in 106 (44%) episodes. Recovery in $\leq$7 days was documented in 135/239 (57%) episodes. Antibiotics were still administered after 7 days in 124 (52%) episodes, and an antifungal was added by day 5 in 112 (47%) episodes. Crude mortality was 10.4% (25/239), with 60% infection attributable mortality, 15/25. Figure 2 illustrates the relation between course and outcome of episodes with antibiotic resistance. Factors significantly related to multidrug resistance on univariate analysis were entered in a multivariate logistic regression model to identify independent factors influencing MIC. These factors were infection with Gram-negative organism, time between chemotherapy and onset of episode $<$7 days and presence of chest and fungal infections with an odds ratio and 95.0% confidence interval of 3.25(1.64–6.46), 2.37(1.21–4.62), 2.76(1.35–5.68), and 6.83(2.62–17.79), respectively.

DISCUSSION

In this prospective cohort study, it was evident that MRO isolated from blood cultures of febrile neutropenic cancer patients is a major concern, as MRO constituted approximately 40% (38%) of causative agents of BSI. Multiresistant isolates were significantly associated with fever at day 4, persistent fever at day 7, and longer episode duration with patients staying more time in the hospital with substantial added risks. In addition MRO were significantly associated with increased overall mortality. Thus, multiresistant pathogens were accompanied with higher morbidity and mortality in bacteremic pediatric cancer patients with chemotherapy-related neutropenia.

There is substantial evidence on a global scale for a significant shift towards more Gram-positive isolates from blood-cultures [2,11]. This was confirmed in the present study as GPC constituted 75% of causative agents of BSI. However, multiresistance was twice as common with GNR compared to GPC (56% of GNR vs. 33% of GPC). In addition, Gram-negative organisms were significantly associated with morbidity and mortality in the present study. However, there is a recent trend of increasing GNR with an increased trend of GNR developing resistance to commonly used antibiotics in some centers [12,13]. In the latter study, 46% of causes of BSI were GNR with more than 40% of enterobacteria showing an extended-spectrum beta-lactamase phenotype, and 20% of non-fermenting Gram-negative bacilli were multiresistant to tested antibiotics [14].

In the current study, there was a change in pattern of GNR compared to previous surveillance studies in the same institution [15]; with a recent predominance of *Acinetobacter* species. Nowadays, multiresistant *Acinetobacter* species are among the challenging pathogens in critically ill patients [16]. Thus, continuous surveillance studies should be done to detect changes in pattern of pathogens in a given healthcare facility as modifications in the guideline practice of empirical therapy should be guided by the local pathogen profile.

The relationship between MRO and antimicrobial use was investigated in a study done over a 13-year period and demonstrated that the significant rise in resistant GNR was significantly correlated with increased consumption of broad spectrum antibiotics; namely extended-spectrum cephalosporins, beta-lactam-beta-lactamase inhibitor combinations, carbapenems, fluoroquinolones, and aminoglycosides [17]. Similarly, the findings of the present study revealed that a previous F&N with intake of broad spectrum antibiotic therapy was an important predisposing factor for multiresistance.

It is suggested that combination therapy given as empirical therapy to patients with F&N might increase the likelihood of antibiotic resistance. A meta-analysis compared clinical outcomes for beta lactam-aminoglycoside combination therapy versus beta lactam monotherapy for sepsis including 64 trials, randomizing

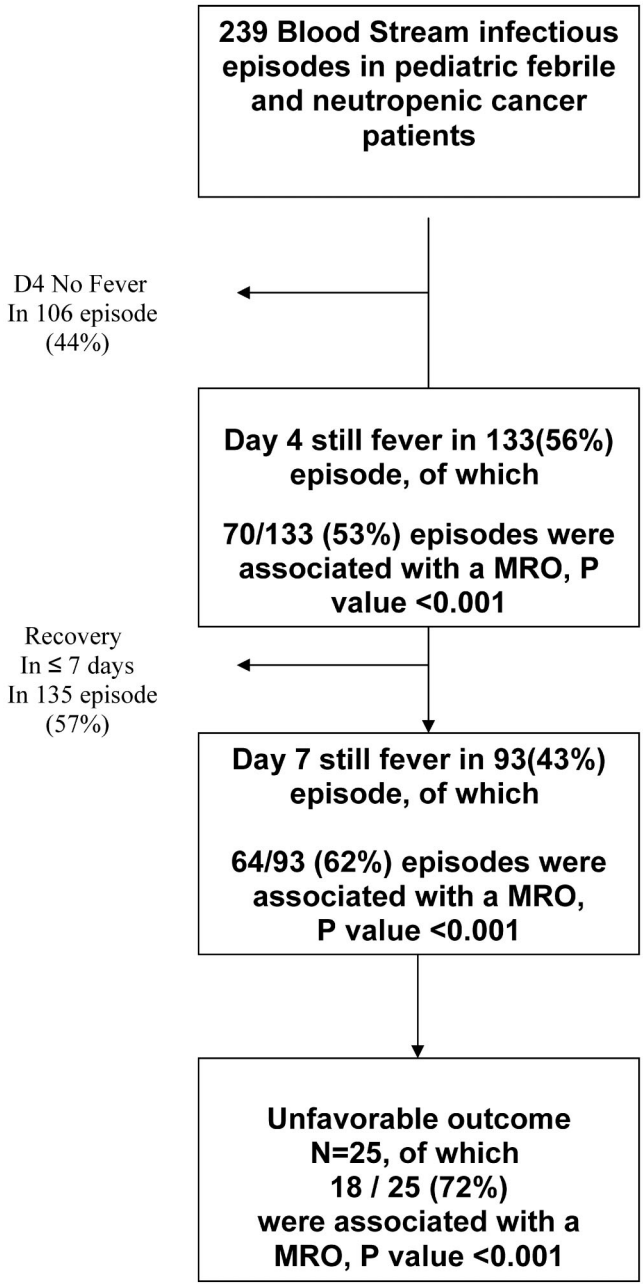

Fig. 2. The relation between course and outcome of bacteremic episodes with antibiotic resistance. MRO, multiresistant organisms.

7,586 patients [18]. This study concluded that the addition of an aminoglycoside to beta lactams for sepsis offered no advantage to beta-lactams alone, with; however, an increased risk of renal damage associated with combination therapy [18]. Further studies exploring the effect of monotherapy versus combination empirical therapy on development of antibiotic resistance in F&N may help clarify this question.

Other risk factors significantly associated with an MRO included hospitalization prior to developing F&N, the presence of a clinically documented focus of infection, especially CVC infections and respiratory tract infections, reduced counts, and longer duration of neutropenia. Similarly, antibiotic resistance to fluoroquinolone was associated with prolonged neutropenia and CVC infections; the use of levofloxacin prophylaxis was the most significant risk factor predisposing to antibiotic resistance on multivariate analysis [6]. In addition, patients with cancer often require recurrent hospitalization with prolonged exposure to hospital environment and antibiotics. Thus, they are more susceptible not only to different bacterial infections but also to infection with antibiotic resistant organisms [19].

By multivariate analysis, pneumonia, GNR bacteremia, <7 days between chemotherapy and fever, and fungal infections were significantly associated with MRO in the current study. Similarly, in a study to evaluate risk factors for longer length of stay and mortality among hospitalized febrile neutropenic children with cancer, pneumonia and fungal infections were associated with eight- and fivefold increase in the risk of death, respectively [1]. In the present study, 45% (28/59) of the multiresistant GPC were accompanied by documented fungal infection. This finding, in addition to the afore-mentioned risk factors, stress the necessity of searching for an explanation to multiresistance in pediatric neutropenic patients with BSI.

The present study demonstrated that MRO isolated from blood cultures of febrile neutropenic cancer patients significantly contributed to adverse outcome in patients with fever and neutropenia. The MRO phenotype had a direct impact on course and outcome of bacteremic episodes in our patients. Previous intake of antibiotics, hospitalization, clinically documented infection besides bacteremia, lower counts, longer duration of neutropenia, and type of incriminated organisms were all significantly associated with higher incidence of multiresistance. Of these risk factors, infection with Gram-negative organisms, time between chemotherapy and onset of an episode <7 days and presence of chest and fungal infections were significantly associated with a multiresistant phenotype on multivariate analysis.

Close follow-up of the emergence of resistance with better understanding of underlying mechanisms of resistance should provide key data to circumvent this problem. In addition, expansion of risk-based therapy in neutropenia together with possible use of monotherapy whenever practical, should be studied further.

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