Microbiological findings in febrile neutropenic patients in a tertiary hospital of Southern Brazil

Achados microbiológicos em pacientes neutropênicos febris em um hospital terciário do sul do Brasil

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ABSTRACT

Background: Neutropenia is a major risk factor for infection. The prevalence of Gram-negative bacteria decreased in the early nineties, while the frequency of Gram-positive bacteria increased from between 55 to 70% of all bacteremia episodes. Even more recently there has been a resurgence of Gram-negative infections. The aim of this report is to describe the microbiological findings in a cohort of febrile neutropenic patients in a tertiary teaching hospital of Southern Brazil.

Methods: This was a cohort study designed to evaluate the implementation of a clinical protocol for treatment of febrile neutropenic patients. Prospectively included in our study were patients with febrile neutropenia (FN) admitted between January 2004 and December 2005 at the Hospital de Clínicas of Porto Alegre. Historical controls were selected from patient visits recorded between March 2001 and April 2003 - or recorded before the clinical protocol was introduced.

Results: During the 2004-2005 and 2001-2003 study periods, 164 and 159 pathogens were documented, respectively. In 93 of 190 episodes (48.9%), and 84 of 193 episodes (43.5%) there were documented microbiological infections. Fungal infection was documented in very few episodes (6.1 vs. 5.7%). We also observed a 52.8% prevalence of Gram-positive and a 47.2% prevalence of Gram-negative bacteria in the 2001-2003 period. Observed in the 2004-2005 period were 38.1% Gram-positive and 61.9% Gram-negative bacteria (P=0.012). There was also a significant increase in *Pseudomonas aeruginosa* prevalence in the second study period (1.9 to 11.6%; P<0.001). Six isolates (31.6%) were discovered to be multi-resistant in the 2004-2005 period versus none in the first period. The prevalence of Oxacillin-resistant *Staphylococcus* was 53.5 and 65.8% in the first and second periods, respectively (P=0.23).

Conclusion: These documented pathogens are the most commonly observed in febrile neutropenic patients, but the emergence of multidrug-resistant *Pseudomonas aeruginosa* is of some concern.

Keywords: Neutropenia fever; microbiology; drug resistance; bacterial; Pseudomonas; Staphylococcus; epidemiology

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RESUMO

Introdução: Neutropenia é um forte fator de risco para infecção. A prevalência de bactérias Gram-negativas diminuiu no início da década de 90 e a frequência de bactérias Gram-positivas aumentou em 55 a 70% em todos os episódios de bacteremia. Porém, mais recentemente, infecções por bactéria Gram-negativas ressurgiram. O objetivo deste estudo é descrever os achados microbiológicos em uma coorte de pacientes neutropênicos febris em um hospital terciário de ensino do sul do Brasil.

Metodologia: Estudo coorte para avaliação da implementação de um protocolo clínico para o tratamento de pacientes neutropênicos febris. Foram incluídos prospectivamente pacientes com neutropenia febril (NF) admitidos entre janeiro de 2004 e dezembro de 2005 no Hospital de Clínicas de Porto Alegre. Controles históricos foram selecionados de visitas de pacientes entre março de 2001 e abril de 2003 ou antes do protocolo clínico ter sido implementado.

Resultados: Nos períodos do estudo de 2004-2005 e 2001-2003, foram documentados 164 e 159 patógenos, respectivamente. Em 93 de 190 episódios (48,9%) e 84 de 193 episódios (43,5%) foram documentadas infecções microbiológicas. Infecções fúngicas foram documentadas em poucos episódios (6,1 e 5,7%). Observou-se uma prevalência de 52,8% de bactérias Gram-positivas e 47,2% de bactérias Gram-negativas no período de 2001-2003. No período de 2004-2005, foram observadas 38,1% de bactérias Gram-positivas e 61,9% de bactérias Gram-negativas (P=0,012). Também houve um aumento significativo da prevalência de *Pseudomonas aeruginosa* no segundo período de estudo (1,9 para 11,6%; P<0,001). Em 2004-2005, seis isolados eram multirresistentes (31,6%). A prevalência de *Staphylococcus* resistente à oxacilina foi de 53,5 e 65,8% nos primeiros e segundos períodos, respectivamente (P=0,23).

Conclusão: Os patógenos documentados neste estudo são os mais comuns em pacientes neutropênicos febris, mas a emergência de *Pseudomonas aeruginosa* resistente a multidrogas é uma preocupação.

Palavras-chave: Neutropenia; febre; microbiologia; resistência a medicamentos; bacteriano; Pseudomonas; Staphylococcus; epidemiologia

Approximately 10 to 50% of patients with solid tumors, and more than 80% of these with hematologic malignancies, will develop febrile neutropenia (FN) after chemotherapy (1). The mortality rate associated with FN is decreasing but is still a concern (1-4). The prevalence of Gram-negative bacteria (*Escherichia coli, Pseudomonas aeruginosa, and Klebsiella spp*), represented 60 to 70% of all documented infections in the seventies and eighties but decreased in the early 1990's. At the same time, frequency of Gram-positive bacteria (*Staphylococcus aureus*, *Streptococcus viridans and Streptococcus pneumoniae*) increased to a level of between 55 - 70% of all bacteremia episodes (5). This change may be attributed to prophylaxis with fluoroquinolones, the toxicity associated with more intensive chemotherapy and the higher usage rates of intravenous catheters (6). On the other hand, other studies have shown that there has been resurgence of Gram-negative infections (7,8). Non-bacterial infections are caused mostly by fungi. Thus, more than 20% of all neutropenic patients may develop systemic fungal infections - 90% of which consist of the *Candida spp., Aspergillus spp., Fusarium spp., or Scedosporium spp.* (5).

The rates of documented microbiological infections are between one-third to one-half of all febrile neutropenic episodes (8,9), and the majority of microbiologically infected patients need empirical broad-spectrum antibiotic therapy for fevers of unknown origins. Currently, much attention is being paid to resistance issues, and resistant strains are now considered a serious public health concern. Thus, special care concerning specific pathogens is needed including: methicillin-resistant *Staphylococcus aureus* (MRSA), coagulase-negative staphylococci, vancomycin-resistant enterococci, viridans group streptococci, ciprofloxacin-resistant *Escherichia coli*, and *Pseudomonas aeruginosa* (10). Considering the importance of local characteristics in the pattern of microorganisms causing infections, it is important to know their epidemiology. Institutional clinical guidelines are developed to aid in the choice of the most effective treatment based on the local pathogenic profile and the epidemiologic pattern of resistance (4,11). Adherence to proposed recommendations seems to be associated with

better clinical outcomes (3). In view of the importance of such pathogenic profiles, then, it is our purpose to describe the microbiological findings in a cohort study of febrile neutropenic patients in a tertiary teaching hospital of Southern Brazil. Further, our study is designed to evaluate the clinical protocol for implementing treatment of such neutropenic patients (3).

METHODS

Patients hospitalized from January 2004 to December 2005, and who presented with febrile neutropenia at the Hospital de Clínicas of Porto Alegre (HCPA), were prospectively included in our study. Historical controls were selected from the records including those from March 2001 to April 2003 - a period before the clinical protocol was introduced. HCPA is a general and public, tertiary teaching hospital in Southern Brazil with 742 beds. The Hematology Unit admits neutropenic patients who are then submitted to high-dose chemotherapy and/or hematopoietic stem cell transplants (HSCT). Our study was approved by the institution's Review and Ethics Committee.

Patients with a granulocyte count up to 1,000/mm³ or neutrophils up to 500/mm³ were identified by the hospital's computerized system and had their registration records revised so as to be included in the study. These identified neutropenic febrile patients were then followed until either hospital discharge or death. Only the first episode of febrile neutropenia in each hospitalization was considered. Exclusion criteria included: patients who were less than 18 years old, those who were HIV positive, and patients with their neutropenic episode secondary to infection.

Before antimicrobial therapy was initiated, culture specimens were obtained routinely according to the suspected focus of infection. Beyond merely blood tests, the origin of these cultures might include peripheral blood in the catheter, urine, and sputum, among other sources. All isolated culture specimens were identified at the microbiological laboratory of HCPA by routine methods. Species identification was confirmed with standard reference methods, and susceptibility testing was performed through disk diffusion method (Kirby Bauer).

A sample size of 200 episodes per period was calculated for the primary objective of the study, not included in this paper. Data were analyzed with the Statistical Package for the Social Sciences 13.0 (SPSS Inc.), Chicago, IL, USA, and a level of significance of 0.05 was considered for our study. Chi-square statistics were used in the comparison of categorical variables, and Student's t-test was applied to compare continuous variables.

RESULTS

We identified 630 patients from the computerized hospital system for the 2001-2003 period and 530 patients for the 2004-2005 period. One hundred ninety three in the first and 190 in the second period met the inclusion criteria. The characteristics of the studied sample are shown in Table 1.

Patients included after the clinical protocol implementation in the 2004-2005 period were younger than those from the 2001-2003 control period. There were also more patients after the protocol implementation with multiple myeloma and fewer patients with diseases other than leukemia, lymphoma, solid tumors, and other hematological diseases. Finally, there were more skin and intravenous catheter infections from the 2004-2005 period.

In the 2004-2005 study period 691 blood cultures were performed, while there were 740 for the 2001-2003 period. Respectively, there were 164 (23.7%) and 159 (21.0%) pathogens documented. There were microbiological infections documented in 93 of 190 episodes (48.9%) from the first period and 84 of 193 episodes (43.5%) from the second. Pathogens isolated from neutropenic patients are presented in Table 2. Fungal infection was also documented in a few episodes. The rate of non-fermentative Gram-negative rods (18.3%) was documented in the 2004-2005 period and was higher than the finding in the 2001-2003 period (6.9%) (P=0.002). Computing only 291 pathogens identified as Gram-positive or Gram-negative bacteria, we observed a change from a predominance of Gram-positive bacteria before the clinical protocol implementation to that of the Gram-negative bacteria following: 52.8% Gram-positive and 47.2% Gram-negative versus 38.1% and 61.9%, respectively (P=0.012). The rate of Gram-positive cocci clusters from the 2001-2003 period was 22.6% (N=159) and 33.3% (N=164) in the 2004-2005 period (P=0.031).

We found a significant increase in the prevalence of *Pseudomonas aeruginosa* in the 2004-2005 period (P<0.001). Among the three cases of *Pseudomonas* documented in 2001-2003, one was found to be amikacin resistant (33.3%) and non-multidrug-resistant. The prevalence of resistance in the 2004-2005 period was not statistically different (31.6%), but six isolates were multi-resistant (31.6%). The prevalence of *Staphylococcus* oxacillin-resistant was 53.5% for the first period and 65.8% for the 2004-2005 period (P=0.230).

Table 1 - Sample characteristics before and after implementation of the protocol for treatment of febrile neutropenia.

Characteristics	2004/2005 (n = 190)	2001/2003 (n = 193)	P - value*
Male – n (%)	100 (52.6)	116 (60.1)	0.170
Age - mean (DP)	44.9 (14.9)	49.0 (15.6)	0.009†
Underlying disease – n (%)			
Leukemias	94 (49.5)	90 (46.6)	0.650
Lymphomas	38 (20.0)	40 (20.7)	0.961
Other hematological diseases	6 (3.2)	8 (4.1)	0.808
Solid tumors	21 (11.1)	30 (15.5)	0.253
Multiple Myeloma	30 (15.8)	17 (8.8)	0.054
Other diseases	1 (0.5)	8 (4.1)	0.045
Neutropenia Causes – n (%)			1.000
Acute disease	23 (12.1)	24 (12.4)	
Chemotherapy	167 (87.9)	169 (87.6)	
Infection site – n (%)			
Pulmonary	21 (10.3)	22 (11.3)	0.751
Urinary Tract	23 (11.3)	16 (8.2)	0.303
Gynecological	0 (0.0)	1 (0.5)	0.489
Gastrointestinal Tract	9 (4.4)	3 (1.5)	0.952
Skin	11 (5.4)	3 (1.5)	0.037
Catheter	21 (10.3)	10 (5.1)	0.054
Superior Air Ways	8 (3.9)	5 (2.6)	0.446
Other	4 (2.0)	4 (2.1)	1.000
Unknown	107 (52.5)	131 (67.2)	0.003

Table 2 - Pathogen distribution during the periods before and after implementation of the protocol for treatment of febrile neutropenia.

Pathogens - n (%)	2001/2003 (n = 159)	2004/2005 (n = 164)	P - value *
Non fermenting Gram-negative rods	**11 (6.9)**	**30 (18.3)**	0.002
Pseudomonas aeruginosa	3 (1.9)	19 (11.6)	
Acinetobacter spp.	6 (3.8)	7 (4.3)	
Stenotrophomonas spp.	2 (1.2)	4 (2.4)	
Fermenting Gram-negative rods	**42 (26.4)**	**52 (31.7)**	0.295
Klebsiella pneumoniae	11 (6.9)	14 (8.5)	
Escherichia coli	19 (11.9)	20 (12.2)	
Proteus spp.	3 (1.9)	1 (0.6)	
Salmonella spp.	0	1 (0.6)	
Citrobacter spp.	0	1 (0.6)	
Serratia spp.	2 (1.3)	1 (0.6)	
Haemophilus spp.	2 (1.3)	2 (1.2)	
Alcaligenes spp.	0	1 (0.6)	
Enterobacter spp.	5 (3.1)	11 (6.7)	
Other rods**	**22 (13.8)**	**15 (9.1)**	0.186
Gram-negative	15 (9.4)	9 (5.5)	
Gram-positive	7 (4.4)	6 (3.6)	
Gram-positive cocci clusters	**53 (33.3)**	**37 (22.6)**	0.031
S. aureus	25 (15.7)	18 (11)	
S. coagulase negative	28 (17.6)	19 (11.6)	
Gram-positive cocci chain	**16 (10.1)**	**13 (7.9)**	0.502
Streptococcus spp. (other than *S. pneumoniae*)	10 (6.3)	8 (4.9)	
S. pneumoniae	0	1 (0.6)	
Enterococcus species	6 (3.8)	4 (2.4)	
Other cocci	**6 (3.8)**	**7 (4.3)**	0.821
Fungi	**9 (5.7)**	**10 (6.1)**	0.867
Pneumocistis jiroveci	2 (1.3)	2 (1.2)	
Candida spp.	6 (3.8)	7 (4.3)	
Aspergillus spp.	1 (0.6)	1 (0.6)	

DISCUSSION

This paper describes the microbiological findings for patients with febrile neutropenic episodes conducted in a tertiary teaching hospital in Southern Brazil. A great number of culture specimens were obtained, and one half of the episodes were microbiologically documented. These results are among the best reported in other studies (8,12). A shift was recorded from Gram-positive bacteria to Gram-negative infections from the 2001-2003 period to the 2004-2005 period.

In both periods studied, only 6.0% of identified pathogens were fungi, and these findings were similar to those identified in a Brazilian multicenter study (7) as well as those reported in other countries (13). As we expected, *Candida* was the most frequently documented invasive fungal infection (7). Fungal

infections represent a major concern given the relatively insensitive diagnostic methods and the poor associated outcome.

Several observational studies have demonstrated a shift from Gram-negative to Gram-positive organisms in documented microbiological infections with neutropenic patients (12) - findings such as those observed for the 2001-2003 period. But the shift back to Gram-negative predominance observed in 2004–2005 seems also to be a change described by other authors (9,12,14). Higher rates of Gram negative infections were also observed among neutropenic cancer patients in HCPA during the 2006-2008 period (from personal communication). Bow et al. suggest a reason for this movement might be a decline in the use of fluoroquinolones (6). In the 2004-2005 period we recorded a lower use of fluoroquinolones (data not shown), and the observed change in microbiology was attributed mainly to the decrease in *Staphylococcus aureus* bacteria and *Staphylococcus* coagulase-negative, not including the increase in non-fermentative Gram-negative bacilli (especially *P. aeruginosa*) (table 2). In 2011, according to the HCPA Infectious Control Committee, the prevalence of Gram-positive bacteria represented 58.6% of documented infections in neutropenic cancer patients from HCPA. This shift back to Gram-positive predominance was also described in others studies (15). These changes are important, for they guide the policy of antimicrobial prophylaxis as well as treatment of neutropenic cancer patients.

The SENTRY Program (19) reported that the most significant resistance problems in Latin American countries are the multidrug resistant non-fermentative Gram-negative bacilli like *P. aeruginosa* and *Acinetobacter species* - pathogens that appear relatively frequently in our study. *Klebsiella pneumoniae* and *E.coli* are among the most frequently isolated Gram-negative organisms in our 2001-2003 sample, as they were in other settings (20). They persist as major pathogens, but *P. aeruginosa* emerged in 2004-2005 as one of the most common Gram-negative bacilli.

Two of the most common pathogens isolated in Brazilian Hospitals between the years 2007 to 2010 were *Klebsiella spp* and *Acinetobacter spp* (7). That condition does not seem to be restricted to neutropenic patients since the Mystic Program Brazil 2003 (21) recorded *P. aeruginosa* to be the leading Gram-negative bacilli among all isolates from twenty Brazilian centers. The prevalence of the resistant *Pseudomonas species* in the Mystic Program was 36.6% for amikacin and 36.0% for meropenem. The emergence of multidrug-resistant Gram-negative rods as frequently reported pathogens in neutropenic patients is of increasing concern. This trend is likely a consequence of antibiotic selection pressure resulting from the use of some antibiotics like carbapenems (22).

As reported in other studies (23), among the Gram-positive microorganisms the foremost identified pathogens were *S. aureus* and *Staphylococcus* coagulase-negative. Gram-positive cocci clusters are chiefly linked with intravascular catheter infections - infections that were more frequently found in the 2004-2005 period as compared to the 2001-2003 period. The incidence of oxacillin-resistant *Staphylococcus* was also higher during 2004-2005, although the difference is not statistically significant and may well be the result of the low statistical power (65%) of our study. The prevalence data of the HCPA Infectious Control Committee for 2001-2005, on oxacillin-resistant S. aureus and *Staphylococcus* coagulase-negative were 58 and 71%, respectively, thereby indicating that the pattern of neutropenic patient infections followed nosocomial epidemiology. This finding is similar in two Brazilian teaching hospitals where oxacillin-resistant *S. aureus* was responsible for 64.3% of hospital-acquired *S. aureus* cases of infection (24). In the SENTRY Antimicrobial Surveillance Program between 2005-2008, the Gram-positive organisms most frequently isolated were S.aureus (20%), *Staphylococcus* coagulase-negative (14,7%), and *Enterococcus spp*. Resistance to oxacillin was 31% for *S. aureus*, and vancomycin resistance significantly increased among enterococci (23).

Antimicrobial resistance is associated with increases in mortality, morbidity, length of hospital stay, and cost of health care (25). Therefore, there is concern that the emergence of multidrug-resistant pathogens as frequent aggressors in neutropenic patients may contribute to the failure of empirical treatment. At one time, the institutional clinical protocol recommended cefepime, or cefepime combined with amikacin, as the initial empirical therapy. These regimens were effective against most bacteria documented in this study. In case of *Staphyloccus* oxacillin-resistant, vancomycin persists as the most available alternative, but antimicrobial resistance among *P. aeruginosa* may yet complicate the treatment thereby limiting therapeutic choices.

This study has limitations that must be taken into account. It was not sufficiently powered to compare the prevalence rates of pathogens, and it also had insufficient statistical power to detect small differences in resistant prevalence between the two periods. Further, because of the observational design, we were not able to attribute the changes in the microbiological patterns solely to the implementation of the clinical protocol.

And finally, there are many other factors not addressed by the protocol such as: antimicrobial prophylaxis for neutropenia episodes, local epidemiology, and institutional policy for antimicrobial use. These other unexplored issues may also play an important role.

CONCLUSION

The microbiological pathogens documented in this cohort study are chiefly those expected for neutropenic patients who develop a febrile episode. However, the emergence of multidrug-resistant *P. aeruginosa* is of serious concern. Data suggests, after the clinical protocol for treatment of febrile neutropenia was implemented, there was a perceived shift toward prominent Gram-negative infections. Therefore, continuous surveillance is recommended to identify changes in microbiologic patterns for the purpose of guiding antimicrobial use.

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