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Letter to the Editor

Risk estimates and features of infectious events in subjects with different causes and level of neutropenia

E. Manuli*, J. Intra, G. Limonta, P. Brambilla

Dear Sir,

Neutropenia is diagnosed when absolute neutrophil count (ANC) is less than 1,500 cells/µL.[1] Specific causes and severity of neutropenia were directly related to the risk of infection. Four decades ago, Bodey et al. demonstrated an inverse relationship between neutrophils number and infection in subjects affected by acute leukemia after chemotherapy.[2] The risk of infection increased when ANC was less than 500 cells/µL for a long period, whereas it is decreased when ANC is greater than 500 cells/µL and the duration of neutropenia is reduced.[2]

In our study, we analyzed the relationship between causes and degree of neutropenia and occurrence of bacterial infection along with their features (site of infection and type of microorganism). Laboratory data of 675 subjects consecutively assessed from 2010 to 2016 in the Italian Hospital of Desio, aged between 2 to 96 years, non-pregnant and non-diabetic, with at least two complete cell blood counts (CBC) spaced at least 3 months, a measurement of C-reactive protein (CRP) or procalcitonin (PCT) and of erythrocyte sedimentation rate (ESR) or fibrinogen (FBG) between the first and the second CBC, and available for at least a minimum of one year later after the second CBC, were enrolled. Individuals affected by infectious diseases on the basis of ICD-9-CM (International Classification of Disease, 9th Revision, Clinical Modification), with white blood cells (WBC), absolute neutrophil count (ANC) and absolute lymphocyte count (ALC) higher than upper reference limits, with at least one of the following tests CRP, PCT, ESR and FBG with values higher than normal reference levels between the first and the second CBC were excluded.[3] Individuals are classified as Cases if they presented all these criteria: CRP >5.0 mg/L and/or PCT >0.5 ng/mL, ESR >20 mm/hr (if female) or >13 mm/hr (if male) and/or FBG >450 mg/dL, and/or positive microbiological tests or presence of a diagnosis of infection according to ICD-9-CM after the second CBC. Individuals are classified as Controls if they presented all these criteria: individuals with CRP ≤5.0 mg/L and PCT ≤0.5 ng/mL (or only one if they are not both present), ESR ≤20 mm/hr (if female) or ≤13 mm/hr (if male) and FBG ≤450 mg/dL (or only one if they are not both present), absent or negative microbiological tests, absence of a diagnosis of infection according to ICD-9-CM after the second CBC. Levels of neutropenia were defined as mild (ANC 1,000-1,500 cells/µL), moderate (500 to 1,000 cells/µL), and severe (<500 cells/µL), according to the Common Toxicity Criteria of the National Cancer Institute.[1] Causes of neutropenia were identified by medical record data.

Cases and controls groups included 225 and 450 subjects, respectively. The logistic regression analysis for the evaluation of the association between neutropenia-related conditions and infection was possible only for subjects with recent chemo-radiotherapy for solid neoplasia treatment (n = 68), myelodysplastic syndromes (n = 41), chronic liver diseases (n = 18), drug-induced neutropenia (n = 23), autoimmune diseases (n = 15), and idiopathic diseases (n = 102). The logistic regression model showed a significant progressive increment of risk of infection with the decrease of ANC level (p trend <0.0001) for individuals with recent chemo- radiotherapy for solid neoplasia treatment and myelodysplastic syndromes, as previously described.[4,5] In addition, drug-induced neutropenia is also associated with a high rate of infection, as previously observed.[4,5]

In our study, the most common drugs, known to be implicated in causing neutropenia, were acetylsalicylic acid, diazepam, chlorpromazine, haloperidol, risperidone, carbamazepine, valproate acid, spironolactone, ramipril, coumarin and omeprazole.[4,5] Moreover, we found that neutropenia caused by chronic liver diseases is associated with higher risk of infection.

In fact, in subjects affected by liver cirrhosis, neutropenia is possibly caused by malnutrition and a shortened neutrophils lifespan due to an increased apoptosis.[6] On the other hand, autoimmune and idiopathic-related neutropenia showed no significant higher risks of infection, confirming that in these conditions ANCs close to zero might exist for years without apparent susceptibility to infection.[4,5]

Then, we evaluated the 225 cases to find the relationship between ANC levels in neutropenic subjects, non-neutropenic individuals and different sites of infection. We know that it is problematic to relate type of patient and degree of neutropenia with site and type of infection. However, although this limitation, among all infectious events, we found three main sites of bacterial infections: urinary tract (51%), respiratory tract (21%) and

bloodstream (9%). Non-adjusted and adjusted odds ratios (ORs) with gender, age of the time of tests, and year of blood collection as covariates, showed a different relationship between site of bacterial infection and ANC values (Figure 1, Table 1).

Our data comply with results reported in other previous works where urinary tract infections are a common complication during chemotherapy in subjects affected by hematological malignancies.[7] Furthermore, the frequent insertion of Foley catheters in neutropenic oncology individuals exposes them to urinary pathogens. Among twenty bloodstream infections, seven subjects were affected by severe sepsis, and out of these, three presented an ANC value less than 500 cells/µL.

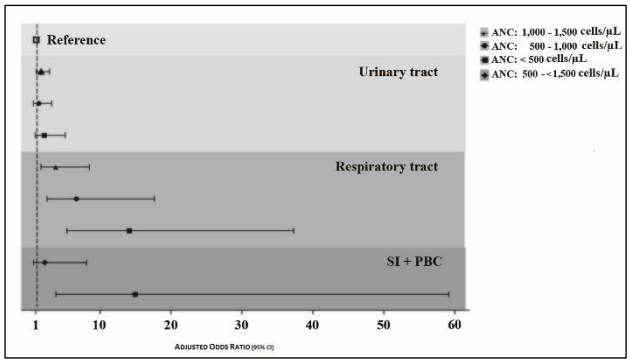

Figure 1: Plot of odds ratios and 95% confidence intervals obtained by logistic regression: the association between neutropenia and site of infection.

Table 1: Association between neutropenia and sites of bacterial infection.

Site of infection	ANC (cells/µL)	Number (n)	Odds ratio (95 % CI)	Adjusted odds ratio (95 % CI)	P[a]
Urinary tract					
Non-neutropenia[b]	≥ 1,500	49	1.00	1.00	ref
Neutropenia[b]					
Mild	1000 - < 1,500	43	1.79 (1.13-2.84)	1.70 (1.00-2.87)	0.06
Moderate	500 - <1,000	11	1.54 (0.74-3.22)	1.38 (0.59-3.19)	0.36
Severe	< 500	11	2.55 (1.17-5.56)	2.10 (0.87-5.09)	0.06
					P Trend: NS
Respiratory tract					
Non-neutropenia[b]	≥ 1,500	11	1.00	1.00	ref
Neutropenia[b]					
Mild	1000 - < 1,500	16	2.97 (1.34-6.58)	3.74 (1.65-8.49)	0.0074
Moderate	500 - <1,000	9	5.62 (2.19-14.45)	6.67 (2.51-17.67)	0.0003
Severe	< 500	11	11.35 (4.44-29.00)	14.12 (5.34-37.31)	< 0.0001
					P Trend: <0.0001
SI+PBC					
Non-neutropenia[b]	≥ 1,500	4	1.00	1.00	ref
Neutropenia[b]					
Mild-moderate	500 - < 1,500	8	3.15 (0.93-10.61)	2.22 (0.61-8.09)	0.29
Severe	< 500	8	22.70 (6.35-81.11)	14.94 (3.77-9.16)	< 0.0001
					P Trend: <0.0001

[a]p-values arise from logistic regression analysis adjusting for the covariates gender, age of the time of tests, and year of blood collection. [b]Neutropenia defined as an absolute neutrophil count <1.5x103 cells/µL [1]. Abbreviations: ANC: Absolute Neutrophil Count; SI+PBC: Systemic infection with positive blood cultures; CI: Confidence Interval; ref: reference; NS: not significant

Finally, we evaluated the relationship between neutropenia and type of microorganisms causing bacterial infection. Both Gram-negative and Gram-positive bacteria are responsible for infections in neutropenic subjects, but, during the last years, a shift from Gram-negative rods to Gram-positive cocci has been observed.8 In our study, 54 % of infections were due to Gram-negatives, 35 % to Gram-positives, and 11 % presented polymicrobial infection. The most observed Gram-negative microorganism was *Escherichia coli*, while *Streptococcus pneumoniae* among Gram-positives. Our data indicated that subjects with severe neutropenia showed a significant increment of infection due to Gram-positives versus Gram-negatives compared to non-neutropenic group (adjusted OR 3.03, 95 % CI: 1.09-8.40, p = 0.03). This difference was not observed in mild-moderate neutropenia (adjusted OR 0.70, 95 % CI: 0.32-1.51, p = 0.36).

As retrospective and monocentric study, a larger number of individuals is needed in order to improve the accuracy of our estimates of the relationship between neutropenia and infection.

In conclusion, our findings are in agreement with previous results that focused attention on neutropenia. This study suggests paying more attention on the cause and the degree of neutropenia because it is often linked to different type of infection and worst clinical conditions.

E. Manuli*, J. Intra, G. Limonta, P. Brambilla

Department of Laboratory Medicine, University of Milano-Bicocca, Desio Hospital, Milan, Italy

*Correspondence to
Dr. E. Manuli,
E-mail: elisa.manuli1@gmail.com

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