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RESEARCH ARTICLE

CAUSES OF NEUTROPENIA AND BACTERIAL INFECTIONS: A RETROSPECTIVE STUDY

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ABSTRACT: Neutropenia is characterized by an absolute neutrophil count less than 1,500 cells/µL and an increased risk of infection. Retrospective data of 267 inpatients (cases) with neutropenia and 333 inpatients without neutropenia (normal cases) were consecutively collected from laboratory database of the Italian Hospital of Desio. Subjects with neutropenia caused by chemo- or radiotherapy treatment, myelodysplastic syndromes, chronic liver diseases, and drug-induced had significantly higher rates of infection than normal cases ($p < 0.01$). Patients whose neutropenia was caused by autoimmune or idiopathic diseases showed no significant differences ($p > 0.4$). Subjects with neutropenia caused by myelodysplastic syndromes or chemo- or radiotherapy treatment had an increased risk of infections from mild and moderate to severe neutropenia (p trend < 0.0001). Patients affected by myelodysplastic syndromes had a significant shift from urinary to respiratory tract ($p = 0.008$) and to systemic infections with positive blood cultures (SI+PBC) ($p = 0.02$) compared to normal cases. Subjects with recent chemo- or radiotherapy treatment presented a significant shift only to SI+PBC ($p = 0.01$). Collectively, it is important to pay more attention to specific causes of neutropenia and the degree of neutrophils count, which are associated with different risks and sites of the infections.

KEYWORDS: Neutropenia, Infection, Absolute neutrophil count, hematological diseases

INTRODUCTION:

Neutropenia is diagnosed when the absolute neutrophil count (ANC) is less than 1,500 cells/µL. The most common causes of transient neutropenia are infections, both viral and bacterial, chemotherapy agents, drugs, and autoimmune diseases.[1] The causes of chronic neutropenia can be extrinsic, such as nutritional deficiencies of vitamin B12, folic acid, and copper, congenital immunological and systemic autoimmune disorders, or intrinsic, such as myelodysplasia, acquired and congenital bone marrow failures, which cause a reduction of circulating mature neutrophils.[1] Infection is the main complication of neutropenia, and severe sepsis and septic shock are

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consequences presenting high hospital mortality.[2] An ANC of 1,000-1,500 cells/µL, which describes a still not compromised host defense, justifies further investigation of the underlying cause; an ANC of 500-1,000 cells/µL enhances the risk of infection in the presence of altered immune system; an ANC of 200-500 cells/µL is associated with higher risk of infection based on specific clinical conditions. Last, an ANC < 200 cells/µL or less is related to the risk of life-threatening infections.[1] Neutrophils are critically involved in antimicrobial activity against bacteria and fungi, and in general, laboratory evidence indicate that, during infection, the neutrophil count can fluctuate considerably in blood.[3] Four decades ago, Bodey *et al.* demonstrated an inverse relationship between neutrophil count and infection in subjects affected by acute leukemia after chemotherapy.[4] The aim of the present retrospective study is to evaluate the risks and the sites of infection in subjects with different pathologies causing neutropenia.

MATERIALS AND METHODS :

Study design and Selection of participants

This retrospective study is based on a large medical and laboratory database. Data were collected from a sample of inpatients consecutively assessed from January 2010 to November 2016 in the Italian Hospital of Desio, Lombardy.

All inpatients aged > 3 years, non-pregnant, non-diabetic, without hematological diseases (except for myelodysplastic syndromes), with at least two complete blood counts (CBC) and at least one of C-reactive protein or procalcitonin values and one erythrocyte sedimentation rate (ESR) or fibrinogen measurement during hospitalization, were enrolled. Subjects with all the available ANC during hospitalization lower than 1,500 cells/µL and one of these diagnoses known to be cause of neutropenia, i.e. recent chemo- or radiotherapy for solid neoplasia treatment, myelodysplastic syndromes, chronic liver diseases, drug-induced, autoimmune, idiopathic, were named CASES. Subjects with all the available ANC values during hospitalization higher than 1,500 cells/µL, and without any diagnoses known to be cause of neutropenia described above, were named NORMAL CASES. The diagnoses known to be cause of neutropenia were recovered by medical record data according to ICD-9-CM codes (International Classification of Disease, 9th Revision, and Clinical Modification).

We evaluated the presence of infection in cases and normal cases considering these criteria: C-reactive protein > 5.0 mg/L and/or procalcitonin > 0.5 ng/mL, and with at least one of these other criteria, ESR > 20 (if female) or > 13 (if male) mm/hr, fibrinogen > 450 mg/dL, positive microbiological tests, diagnosis of infection according to ICD-9-CM codes (Figure 1).[5] We evaluated the infection as absent in cases and normal cases considering these criteria: one of these two tests or both if present, C-reactive protein ≤ 5.0 mg/L, procalcitonin ≤ 0.5 ng/mL, and with one of these two tests or both if present, ESR ≤ 20 (if female) or ≤ 13 (if male) mm/hr, fibrinogen ≤ 450 mg/dL, with absent or negative microbiological tests and with absence of diagnosis of infection according to ICD-9-CM codes (Figure 1) (Henry et al., 2011).

Neutropenia levels classification

Neutropenia levels were classified as mild (ANC value ranged between 1,000-1,500 cells/µL), moderate (ANC value ranged between 500 to 1,000 cells/µL), and severe (ANC value < 500 cells/µL), according to the Common Toxicity Criteria of the National Cancer Institute.[6]

Laboratory analysis

WBC and differential leucocytes counts were measured by automated counter XE 2100 (Sysmex, Kobe, Japan). All measurements were performed on whole blood samples collected by vacuum into tubes containing EDTA as anticoagulant.

ESR and FBG (Clauss method) measurements were performed on whole blood samples collected by vacuum into tubes containing sodium citrate as anticoagulant using the fully automated analyzer Ves-Matic 60 (Diesse, Siena, Italy) and the Behring Coagulation System (BCS) analyzer (Siemens Healthcare, Erlangen, Germany) respectively.

CRPL3 3rd generation immunoturbidimetric method (Roche Diagnostics, Mannheim, Germany) was used for the quantitative determination of CRP. Analysis were performed using automated chemistry analyzers such as Modular SWA P-MODULE and Cobas C501 (Roche Diagnostics, Mannheim, Germany). Measurements were performed on plasma samples collected by vacuum into tubes containing lithium heparin as anticoagulant.

PCT level was measured on plasma samples in tubes with lithium heparin as anticoagulant by electrochemiluminescence immunoassay (ECLIA) using automated chemistry analyzer Modular SWA E170 and Cobas E602 (Roche Diagnostics, Mannheim, Germany).

Statistical analysis

A database using SAS software (version 9.4; SAS Institute Inc., Cary, NC, USA) was maintained. The logistic regression analysis was used to evaluate the distribution of infections in Cases and Normal cases, and then, within established ANC cut-points. The results were expressed as non-adjusted and adjusted odds ratio for covariates (gender, age during hospitalization, and year of blood collection). A p value of < 0.05 was considered statistically significant (Armitage, 1955).

Ethical statement

The local ethics committee did not require informed consent because all subjects data were retrospective and de-identified.

RESULTS :

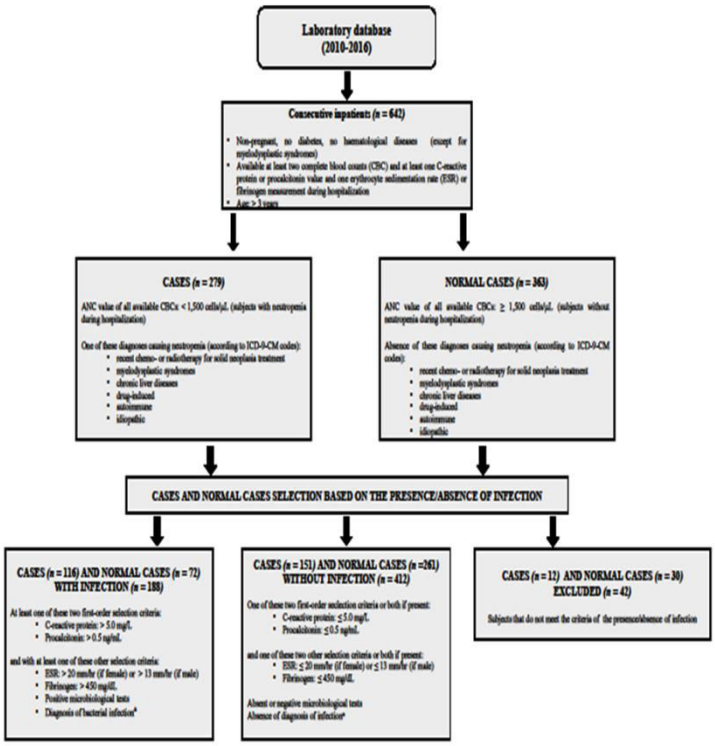

Figure 1: Flow diagram of the study for case-control selection. [a]Diagnosis of infection was made by codification according to the International Classification of Disease, Ninth Revision, Clinical Modification (ICD-9-CM) or by the presence of positive microbiological test.

From 2010 through 2016, we retrospectively enrolled 600 consecutive inpatients admitted to the Italian Hospital of Desio (Figure 1). Cases and Normal cases groups included 267 and 333 subjects, respectively. We evaluated the presence of infection between cases, distinguished by pathologies causing neutropenia and ANC levels, and normal cases (Figure 1). The characteristics of

participants are shown in Table 1. Females in cases group showed older age compared to those of the normal cases group ($p < 0.0001$). Cases and normal cases with infections showed older age compared to cases and normal cases without infections both in females and males ($p < 0.05$) (Table 1).

Table 1: Characteristics of study population.

	Total	Cases[a]	Normal cases[a]	p[b]
Number	600	267	333	
Age[c]	48 (14-77)	58 (11-80)	42 (17-74)	< 0.0001
Males (*n*)	270	105	165	
Age	45 (13-76)	55 (11-80)	43 (17-74)	0.11
Females (*n*)	330	162	168	
Age	49 (15-78)	61 (12-81)	42 (15-72)	< 0.0001
Subjects with infectious disease (*n*)	188	116	72	
Age	61 (14-81)	66 (5-84)	52 (17-78)	0.0005
Males (*n*)	69	43	26	
Age	61 (3-81)	66 (3-82)	60 (3-78)	0.58
Females (*n*)	119	73	46	
Age	60 (17-83)	67 (26-87)	47 (17-78)	< 0.0001
Subjects without infectious disease (*n*)	412	151	261	
Age	43 (15-75)	50 (11-76)	41 (18-72)	0.001
Males (*n*)	201	62	139	
Age	40 (15-74)	41 (11-76)	40 (18-74)	0.92
Females (*n*)	211	89	122	
Age	45 (15-75)	55 (11-78)	41 (15-68)	< 0.0001

[a]See Materials and methods for Cases and Normal cases enrolment.
[b]*p*-values obtained comparing Cases and Normal cases.
[c]Age during hospitalization expressed as years (median (5^{th}-95^{th} percentile)).

Subjects with neutropenia induced by chemo- or radiotherapy for solid neoplasia treatment had significantly higher rates than matched normal cases ($p = < 0.0001$). However, there was no significant difference found between neutropenic individuals and matched normal cases in subjects whose neutropenia was caused by an autoimmune or idiopathic diseases ($p > 0.4$) (Table 2).

Table 2: The association between different causes of neutropenia and infection.

	Number (*n*)	Odds ratio (95 % CI)	Adjusted odds ratio (95 % CI)	p[a]
Normal cases[b]				
	333	1.00	1.00	ref.
Cases[b]				
Recent chemo- or radiotherapy for solid neoplasia treatment	68	8.11 (4.56-14.44)	6.37 (3.40-11.94)	< 0.0001
Myelodysplastic syndromes	41	5.12 (2.61-10.04)	4.49 (2.07-9.71)	0.002
Chronic liver diseases	18	7.25 (2.63-19.99)	6.99 (2.31-21.15)	< 0.0001
Drug-induced	23	2.79 (1.17-6.62)	3.49 (1.36-8.92)	0.008
Autoimmune diseases	15	1.32 (0.41-4.26)	1.43 (0.41-4.99)	0.59
Idiopathic diseases	102	0.83 (0.47-1.46)	1.21 (0.66-2.19)	0.46

[a]*p*-values arise from logistic regression analysis adjusting for the covariates gender, age during hospitalization, and year of blood collection.
[b]Normal cases: subjects without neutropenia; Cases: subjects with neutropenia (See *Materials and methods* for details).
Abbreviations: CI: Confidence Interval; ref: reference.

Then, we evaluated the correlation between risk of infection and different ANC levels in pathologies known to be cause of neutropenia with a sufficient number of subjects, such as recent chemo- or radiotherapy for solid tumors treatment ($n = 68$),

myelodysplastic syndromes (n = 41), and idiopathic diseases (n = 102). In individuals whose neutropenia was caused by myelodysplastic syndromes or chemo- or radiotherapy for solid neoplasia treatment had an increased risk of infection from mild and moderate to severe neutropenia was observed (p trend < 0.0001). There was no significant increased risk of infections in subjects whose neutropenia was caused by an idiopathic disease (p trend = 0.50) (Table 3).

Table 3: The association between different causes and levels of neutropenia and infection.

	ANC (cells/µL)	Number (n)	Odds ratio (95 % CI)	Adjusted odds ratio (95 % CI)	p^a
Normal cases					
	≥ 1,500	333	1.00	1.00	*ref.*
Recent chemo- or radiotherapy for solid neoplasia treatment					
Mild	1,000 - < 1,500	34	6.65 (3.14-14.07)	4.98 (2.12-11.71)	0.0002
Moderate	500 - < 1,000	9	4.53 (1.19-17.31)	1.91 (0.46-7.88)	0.37
Severe	< 500	25	14.50 (5.26-39.98)	12.98 (4.06-41.47)	< 0.0001
***p* trend: < 0.0001**					
Myelodysplastic syndromes					
Mild	1,000 - < 1,500	19	3.26 (1.28-8.33)	2.59 (0.81-8.33)	0.11
Moderate	500 - < 1,000	13	5.80 (1.84-18.27)	2.46 (0.65-9.25)	0.18
Severe	< 500	9	12.69 (2.58-62.40)	20.49 (3.75-111.92)	0.0005
p trend: < 0.0001					
Idiopathic diseases					
Mild	1,000 - < 1,500	67	0.71 (0.35-1.43)	1.01 (0.48-2.13)	0.98
Moderate	500 - < 1,000	27	0.82 (0.30-2.25)	1.81 (0.60-5.48)	0.29
Severe	< 500	8	2.18 (0.51-9.32)	3.99 (0.78-20.45)	0.10
p trend: 0.50 (NS)					

[a] *p*-values arise from logistic regression analysis adjusting for the covariates gender, age during hospitalization, and year of blood collection.
Abbreviations: ANC: Absolute Neutrophil Count; CI: Confidence Interval; ref: reference; NS: not significant.

Finally, we evaluated the differences in the site of infection between normal cases and cases based on diseases causing neutropenia. The most common sites of infection were urinary tract (64%), respiratory tract (23%), and SI+PBC (13%) (Table 4). In subjects with recent chemo- or radiotherapy for solid neoplasia treatment, our data showed a higher risk of systemic infections and lower risk of urinary tract infections compared to normal cases (Table 4). Moreover, in subjects with neutropenia caused by myelodysplastic syndromes, a higher risk of systemic and respiratory tract infections and a lower risk of urinary tract infections, compared to normal cases, were observed (Table 4).

Table 4: Causes of neutropenia and sites of bacterial infection[a].

	Number (%)[b]	SI+PBC (*n* (%)) (1)	Respiratory tract (*n* (%)) (2)	Urinary tract (*n* (%)) (3)	Odds ratio (95 % CI) (*p*-value)[c]		
					1 vs 2	1 vs 3	2 vs 3
All subjects	133 (100)	17 (13)	31 (23)	85 (64)			
Normal cases	64 (48)	4 (3)	11 (8)	49 (37)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)
Cases:	69 (52)	13 (10)	20 (15)	36 (27)			
Chemo- or radiotherapy for solid neoplasia	37 (28)	9 (7)	7 (5)	21 (16)	3.5 (0.8-16.0) ($p = 0.10$)	5.3 (1.5-18.9) ($p = 0.01$)	1.5 (0.5-4.4) ($p = 0.86$)
Myelodysplastic syndromes	19 (14)	4 (3)	8 (6)	7 (5)	1.4 (0.3-7.2) ($p = 0.71$)	7.0 (1.4-34.5) ($p = 0.02$)	5.1 (1.5 - 17.0) ($p = 0.008$)
Idiopathic diseases	13 (10)	0 (0)	5 (4)	8 (6)	ND	ND	2.8 (0.8-10.2) ($p = 0.12$)

[a]These groups with low number of subjects with causes of neutropenia were not considered for analysis: unspecified site of infection, ≥ 2 sites of infection, chronic liver diseases, drug-induced neutropenia, autoimmune diseases, digestive and genital sites of infection.
[b]Percentage calculated referred to the total number of subjects.
[c]*p*-values arise from logistic regression analysis between cases and normal cases.
Abbreviations: SI+PBC: Systemic infection with positive blood cultures; CI: Confidence Interval; ref: reference; ND: not determinable.

DISCUSSION:

White blood cell count, absolute neutrophil and lymphocyte counts are traditional infection markers.[8-11] The relationship between the occurrence of infection and neutropenia has been recognized for many years.[1] In 1966, for the first time, Bodey and coauthors examined the quantitative relationship between the degree and duration of granulocytopenia and the presence of infection in individuals affected by acute leukemia after chemotherapy. They demonstrated that the risk of infection increases, while the level of circulating granulocytes and lymphocytes decreases.[4]

In our study, we evaluated the association between different pathologies known to be cause of neutropenia and the presence of bacterial infections, with or without different degrees of neutropenia.

The logistic regression analysis showed a significant higher risk of infection in individuals affected by chronic liver diseases where neutropenia is related to a shortened neutrophil lifespan due to an increased apoptosis.[12] In addition, neutropenia induced by drugs is also associated with a higher risk of infection, as previously observed.[12-14] The most common drugs used in our study known to be implicated in causing neutropenia were acetylsalicylic acid, diazepam, chlorpromazine, haloperidol, risperidone, carbamazepine, valproic acid, spironolactone, ramipril, coumarins and omeprazole.[12-13] Moreover, we also found progressive increment of risk of infection with the decreasing of ANC levels in subjects with chemo- or radiotherapy for solid neoplasia treatment and myelodysplastic syndromes, as previously

described.[13-14] On the contrary, autoimmune- and idiopathic-related neutropenia showed no significant higher risks of infections, confirming that, in these conditions, ANCs closed to zero might exist for years without apparent susceptibility to infections.[13-16]

Neutropenic subjects are predisposed to a wide spectrum of infectious agents: fungi, viruses and bacteria.[17] Bacteria predominantly cause infections that occur during the early stages of a neutropenic episode.[18] The most common sites of infections include bloodstream, respiratory tract, urinary tract, hepato-biliary and intestinal tracts, skin and surgical sites.[19] In the present study, 43 % of neutropenic subjects developed an infection. Among all infectious episodes, we found three main sites of bacterial infection: urinary tract (63%), respiratory tract (26%) and bloodstream (11%). Our data comply with previous results reported in other works, where urinary tract infections are a common complication during chemotherapy.[20,21] Chemotherapy can damage the urinary bladder mucosa and reduce the body's ability to fight infection.[20] Moreover, in neutropenic oncology individuals, the frequent use of foreign medical devices, e.g. catheters, exposes them to urinary pathogens.[22] Conversely, other studies reported that urinary tract and bloodstream infections accounted for 10-15 % and 20-25 % of neutropenic subjects enrolled, respectively.[23] These differences were most probably due to the groups of subjects used in the studies, and by other factors, such as prophylactic antimicrobial therapy and antimicrobial stewardship.

Considering neutropenic subjects with chemo- or radiotherapy for solid neoplasia treatment, our data showed a significant shift of risk of bacterial infections from urinary tract to bloodstream (p = 0.01). It is currently assumed that sepsis is the first of the comorbidities in cancer patients and is related to the immune deficiency due to the intensive anticancer therapies, the increasing age of subjects, and the widespread use of monoclonal antibodies.[24-25] Therefore, our results confirm that bacterial bloodstream infection is a severe complication in cancer patients during neutropenia.

Considering individuals affected by myelodysplastic syndromes, our data indicated a significant shift of risk of bacterial infections from urinary to respiratory tract (p = 0.008) and bloodstream (p = 0.02). In a retrospective study, Dayyani et al. reported that among subjects affected by myelodysplastic syndromes who died in the period from 1980 to 2004, pneumonia and sepsis were responsible for 40 % and 38 % of deaths, respectively.[26] Moreover, recently, pulmonary infections were reported to be often related to the use of 5-azacytidine or decitabine, two demethylating agents widely used as reference therapy to treat subjects affected by myelodysplastic syndromes.[27,28] In fact, although the matter is under debate, treatments with these drugs seem to increase the risk of respiratory infections, since the neutrophils count decreases after hypomethylation agent therapy.[27,28]

Our work presents a limitation that should be considered. The study is retrospective and performed in a single hospital. A larger number of individuals is needed in order to improve the accuracy of our estimates of the relationships between diseases causing neutropenia, ANC levels and infections.

CONCLUSION:

Collectively, our findings comply with previous results that focused attention on neutropenic host because vulnerable to a wide range of bacterial infections. This study highlights the importance to carefully evaluate the specific pathologies causing neutropenia and its degrees, since they are often both associated with different risks and types of infection.

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REFERENCES:

1. Newburger PE, Dale DC. Evaluation and management of patients with isolated neutropenia. *Semin Hematol* 2013; **50:**198-206.
2. Legrand M, Max A, Schlemmer B, Azoulay E, Gachot B. The strategy of antibiotic use in critically ill neutropenic patients. *Ann Intensive Care* 2011; **1:**22.
3. Dale DC, Alling DW, Wolff SM. Application of time series analysis to serial blood neutrophil counts in normal individuals and patients receiving cyclophosphamide. *Br J Haematol* 1973; **24:**57-644.
4. Bodey GP, Buckley M, Sathe YS, Freireich EJ. Quantitative relationships between circulating leukocytes and infection in patients with acute leukemia. *Ann Intern Med* 1966; **64:**328-40.
5. Henry JB, McPherson RA, Pincus MR. *Henry's clinical diagnosis and management by laboratory methods.* Philadelphia: Elsevier/Saunders, 2011.
6. National Cancer Institute. Common Toxicity Criteria for Adverse Events. Version 4.03. Available at https://www.eortc.be/services/doc/ctc/ctcae_4.03_2010-06-14_quickreference_5x7.pdf
7. *Armitage, P. Tests for Linear Trends in Proportions and Frequencies. Biometrics 1955; **11:** 375–86.*
8. Loonen AJ, de Jager CP, Tosserams J *et al.* Biomarkers and molecular analysis to improve bloodstream infection diagnostics in an emergency care unit. *PLoS One* 2014; **9:**e87315
9. Yoon NB, Son C, Um SJ. Role of the neutrophil-lymphocyte count ratio in the differential diagnosis between pulmonary tuberculosis and bacterial community-acquired pneumonia. *Ann Lab Med* 2013; **33:**105-10.
10. Bozbay M, Ugur M, Uyarel H *et al*. Neutrophil-to-lymphocyte ratio as a prognostic marker in infective endocarditis: in-hospital and long-term clinical results. *J Heart Valve Dis* 2014; **23:**617-23.
11. Dogruel F, Gonen ZB, Gunay-Canpolat D, Zararsiz G, Alkan A. The Neutrophil-to-Lymphocyte ratio as a marker of recovery status in patients with severe dental infection. *Med Oral Patol Oral Cir Bucal* 2017; **22**:e440-5.
12. Minemura M., Tajiri K., Shimizu Y. Systemic abnormalities in liver disease. *World J Gastroenterol* 2009; **15(24):** 2960-2974. Review.
13. Boxer LA. How to approach neutropenia. *Hematology Am Soc Hematol Educ Program* 2012; **2012**:174-82.
14. Fioredda F, Calvillo M, Bonanomi S, Coliva T, Tucci F, Farruggia P, et al. Congenital and acquired neutropenia consensus guidelines on diagnosis from the Neutropenia Committee of the Marrow Failure Syndrome Group of the AIEOP (Associazione Italiana Emato-Oncologia Pediatrica). *Pediatr Blood Cancer* 2011; **57**(1):10-7.
15. Lindqvist H, Carlsson G, Moell J, Winiarski J, Sundin M. Neutropenia in childhood: a 5-year experience at a tertiary center. *Eur J Pediatr* 2015; **174(6):**801-7.
16. Andersen CL, Tesfa D, Siersma VD, Sandholdt H, Hasselbalch H, Bjerrum OW, et al. Prevalence and clinical significance of neutropenia discovered in routine complete blood cell counts: a longitudinal study. *JIM* 2016; **279(6):**566-575.
17. Puri S, Bery A, Sekhon JS, Amandeep. Pattern of Infections in patients with Neutropenia and their Outcome. *JIMSA* 2010; **23**: 219-21.

18. Naumenko V, Turk M, Jenne CN, Kim SJ. Neutrophils in viral infection. *Cell Tissue Res* 2018; **371:**505-16.
19. Rolston KV. Infections in Cancer Patients with Solid Tumors: A Review. *Infect Dis Ther* 2017; **6**(1):69-83.
20. Tancheva S, Micheva I, Marinova I, Bojchev B, Marinov M, Nenov K, et al. Infection in urinary tract of patient with hematological malignancies undergoing anti-neoplastic therapy. *Journal of IMAB Annual* 2009; **15:**95-7.
21. Sandoval C, Sinaki B, Weiss R, Munoz J, Ozkaynak MF, Tugal O, et al. Urinary tract infections in pediatric oncology patients with fever and neutropenia. *Pediatr Hematol Oncol* 2012; **29:**68-72.
22. Oude Nijhuis CS, Daenen SM, Vellenga E, van der Graaf WT, Gietema JA, Groen HJ, et al. Fever and Neutropenia in Cancer Patients: The Diagnostic Role of Cytokines in Risk Assessment Strategies. *Crit Rev Oncol Hematol* 2002; **44:** 163-74.
23. Purewal SS Singh RP, Kahlon R.S. Study of Bacterial Pathogens and Viral Infections in Neutropenic Cancer Patients. *International Journal of Educational Planning & Administration* 2011; **1**:15-22.
24. Staudinger T, Pène F. Current insights into severe sepsis in cancer patients. *Rev Bras Ter Intensiva* 2014; **26**(4):335-8.
25. Gustinetti G., Mikulska M. Bloodstream infections in neutropenic cancer patients: A practical update. *Virulence* 2016; **7**(3): 280–297.
26. Dayyani F, Conley AP, Strom SS, Stevenson W, Cortes JE, Borthakur G, et al. Cause of death in patients with lower-risk myelodysplastic syndrome. *Cancer* 2010; **116**(9):2174-9.
27. Latagliata R, Niscola P, Aloe Spiriti MA, Carmosino I, Cesini L, Sarlo C, et al. Pulmonary Infections in Patients with Myelodysplastic Syndromes Receiving Azacytidine Treatment. *Blood* 2016 128:5544.
28. Leone G, Pagano L. Infections in Myelodysplastic Syndrome in Relation to Stage and Therapy. *Mediterr J Hematol Infect Dis* 2018; **10**(1):e2018039.

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