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# *Clinical characteristics and therapeutic outcome of patients with febrile neutropenia*: Our clinical experience

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## Abstract
Aim: The aim of this paper is to present our experience in the treatment of adult patients with malignant disease: breast cancer, digestive cancer, gynecological cancer, urological cancer and malignant disease of the lungs. Introduction: Neutropenia exists when there is an absolute decrease in the number of circulating neutrophils, less than 1.0 x10/9/l. Febrile neutropenia exists when a patient with a neutrophil count less than 1.0 x10/9/l has a temperature greater than or equal to 38,0 C. Patients and methods: From January 2000 to December 2013 in the oncology department of the General Hospital "Sveti returns" in Bijeljina were analyzed in 1594 patients with malignancies who are commonly treated in our hospital.We analyzed 270 (16,9%) patients with febrile neutropenia. Results: Most patients had received chemotherapy for breast carcinoma of 75, 66 of the patients had digestive carcinoma, 51 had a gynecological carcinoma, urological carcinoma had 36 and 42 patients had pulmonary carcinomas. Cultures were positive in only 36 patients (13,3%). Most were isolated: Staphylococcus epidermidis in 12 patients, Staphylococcus aureus in 5, Enterococcus faecalis in 5, E. coli in 3, Acinetobacter 2, Serratia spp. 2, Pseudomonas aeruginosa in 3, and Candida albicans in 4 patients. Three patients died due to sepsis. Conclusion: Febrile Neutropenia is a medical emergency and has a significant impact on morbidity and mortality. Treating febrile neutropenia is associated with high healthcare costs. Management of febrile neutropenia requires continuous monitoring and the prompt removal of the source of infection.

## 1. Introduction

Neutropenia exists when there is an absolute decrease in the number of circulating neutrophils, less than 1.0 x10/9/l. Febrile neutropenia exists when a patient with a neutrophil count less than 1.0 x10/9/l has a temperature greater than or equal to 38.0 C, or if a patient is systemically unwell with a clinical suspicion of sepsis. Neutropenia is a common adverse effect of chemotherapy, and it can put patients at risk of severe infection. Treatment of febrile neutropenia in patients with carcinoma must be based on knowledge of the most common types of microorganisms, and the frequency of antibiotic sensitivity of isolated bacterial strains. Neutropenia, and more specifically febrile neutropenia, are clinically

relevant issues with a negative impact on quality of life, causing increased morbidity and mortality rates, and elevating treatment costs. In patients with neutropenia are the 3rd and 4 degree, when the neutrophil count is less than 1 x 10/9/l, take a intravenous antibiotic therapy in hospital. Intravenous antibiotic therapy is better because patients with febrile neutropenia have and associated mucositis and is not possible to apply medication by oral. It is a condition that directly threatens the life of patients and represents absolutely indication for urgent hospital treatment (1,2,3).

Factors that determine the level of risk for the development of infectious complications was shown last international joint study with 1139 patients who received chemotherapy and had febrile neutropenia. This study determined the criteria for patients with low risk of complications: Patients with low risk for complications are younger than 60 years (children not included), a disease with partial or complete remission, a X-ray image of the lung, the absence of hypotension, no respiration less than 24/min, absence of chronic lung disease, absence of diabetes, the absence of mental confusion or other alteration, the absence of bleeding, the absence of dehydration, lack of fungal infections in anamnesis or the patient did not receive antifungal therapy 6 months before the occurrence of fever (4,5).

## 2. Patients and Methods

Since January 2000 to December 2013 in the oncology department of the General Hospital "Sveti Veračevi" in Bijeljina has treated 1594 patients with various carcinoma. We analyzed 270 (16, 9%) patients with febrile neutropenia (Table1). All patients were careful history and physical examination including: type of carcinoma and recent treatment, temperature, pulse, respiratory rate, blood pressure and oxygen saturation. ]

***Table 1.*** *Patients characteristics.*

| Malignity | Number patients with FN | Female | Male |
|---|---|---|---|
| Breast | 75 | 73 | 2 |
| Digestive | 66 | 38 | 28 |
| Gynecological | 51 | 51 | 0 |
| Urological | 36 | 27 | 9 |
| Pulmonar | 42 | 28 | 14 |
| Summary | 270 | 217 | 53 |

The laboratory processed by determining the count of blood cells, serum values of urea, creatinine and transaminases, coagulation profile, C reactive protein (CRP), central line blood cultures (if patient has a central venous access device), mid stream urine sample, sputum if patient has a productive cough. Physical exam focusing on: chest, mucous membranes, skin, venous access devices, peri-anal area, urinary tract, gastrointestinal tract. All patients were routinely made before the application of chemotherapy and chest X-ray image. CT abdomen was undertaken in patients with a questionable collection bodies in the abdomen or retroperitoneum. Thirty-six patients (13.3%) had isolated microorganisms in culture. Chemotherapy dose reduction/delay is not the only strategy available for reducing FN-related morbidity and mortality. Another option is FN prevention through prophylactic treatment with G-CSF, granulocyte–macrophage colony-stimulating factors (GM–CSF) and/or antibiotics, hematopoietic cell growth factors stimulate the proliferation and survival of neutrophils and their precursors, and thereby reduce the severity and duration of chemotherapy-induced neutropenia and FN (Table 2.).

## 3. Results

Most patients had received chemotherapy for breast carcinoma of 75, 66 of the patients had digestive carcinoma, 51 had a gynecological carcinoma, urological carcinoma had 36 and 42 patients had pulmonar carcinomas

Peripheral blood smear showed a significant neutropenia. Large cells left the band form leukocytes, and the right is myelocyte. Both cells show toxic granulation (Figure 1.) The second picture shows the normal think of blood (Figure 2.) Thirty-six patients (13.3%) had isolated microorganisms in culture (Figure 3.)

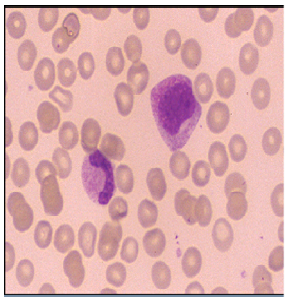

***Figure 1.*** *Large cell to the left is a "band form" of leukocytes, and the right is myelocytes. Both cells showed toxic granulation.*

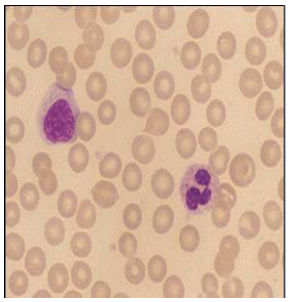

***Figure 2.*** *Normal form leukocytes.*

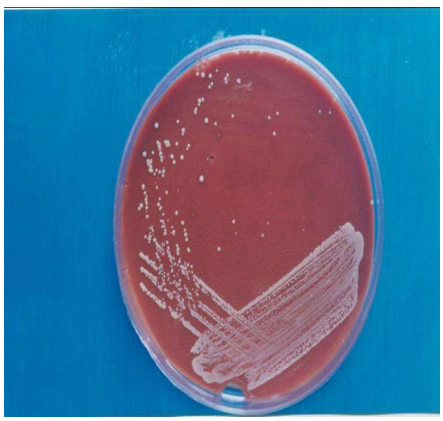

***Figure 3.*** *Culture of microorganisms.*

Most were isolated: Staphylococcus epidermidis in 12 patients, Staphylococcus aureus in 5, Enterococcus faecalis in 5, E. coli in 3, Acinetobacter 2, Serratia spp. 2, Pseudomonas aeruginosa in 3, and Candida albicans in 4 patients.

Neutropenia is reported on average 9.5 days after the application of chemotherapy, but that in 64 patients (23,7%) reported after the I and II cycles, while the other occurred after the third and sixth cycles of chemotherapy. The average value of absolute neutrophil count was 0.43x10/9/l. In 210 patients (78%) reported the anemia, and in 140 (51.8%) thrombocytopenia. One hundred twenty (44.4%) had pancitopenia.

Antibiotic therapy undertaken for patients of low risk of complications consisted of oral application of ciprofloxacin plus amoxicillin-clavulanate. Intravenous antibiotic therapy was applied in patients with high risk of complications of the three protocols:

1. Monotherapy a third or fourth generation cephalosporin (ceftazidime or cefepime) or a carbapenem (imipenem-cilastatin or meropenem).

2. The combination of the two antibiotics (aminoglycosidi plus antipseudomonas penicillin, cephalosporin (cefepime or ceftazidime), or a carbapenem.

3. Therapy with glycopeptides (vancomycin) plus (1) or (2).

Patients in whom is the neutrophil count was greater than 0.5 x10/9/l two days, the culture was positive, when the afebrile patient was more than 48 hours of application antibiotic therapy is stopped. If the neutrophil count was less than 0.5 x10/9/l patient initially had a low risk of complications application antibiotic therapy is stopped if the patient was afebrile more 5-7 days. If the patient initially had a high risk of complications antibiotic therapies apply continuously. Application of antiviral drugs and blood transfusion granulocytes are not undertaken routinely. Routine antibiotic prophylaxis is not used except for trimethoprim-sulfamethoxazole for prevention of pneumocystis carinii pneumonitis. Antifungal and antiviral prophylaxis fluconazol and acyclovir or ganciclovir was routinely used. Patients were assigned to receive filgrastim (12 μg/kg of body weight per day) ($n$ = 109) beginning within 12 hours of empiric therapy with tobramycin and piperacillin. Patients received treatment and remained in the study until the neutrophil count was greater than 0.5 x10/9/L and until 4 days without fever (temperature <37.5 C) had elapsed.

***Table 2.*** *Characteristics of patients at risk for complications from febrile neutropenia.*

| **Low risk (most of the factors listed below)** | **High risk (*any* of the factors listed below)** |
|---|---|
| no high risk factors | |
| outpatient status at time of development of fever | inpatient status at time of development of fever |
| no associated acute comorbid illness independently indicating inpatient treatment or close observation | significant clinical comorbidity or medically unstable, including:<br>• Hemodynamic instability<br>• Oral/GI mucositis impairs swallowing, causes severe diarrhea<br>• New onset abdominal pain , nausea, vomiting or diarrhea<br>• Neurologic changes/confusion<br>• Intravascular catheter infection |
| anticipated short duration of severe neutropenia (≤100 cells/mcL for <7 days) | anticipated prolonged severe neutropenia (≤100 cells/mcL and ≥7 days) |
| good performance status (ECOG 0-1) | uncontrolled/ progressive cancer; pneumonia or other complex infections at clinical presentation; alemtuzumab therapy; mucositis grade 3-4 |
| no hepatic insufficiency | hepatic insufficiency (five times ULN for aminotransferases) |
| no renal insufficiency | renal insufficiency |
| MASCC risk index score ≥21 41,42 (see Appendix A) | MASCC risk index score less than 21 41,42 (see Appendix A) |
| <60 years | |
| Cancer partial or complete remission | |
| No focal findings of infection | |
| Temp <39 C | |
| Normal chest x ray | |
| Absence hypotension | |
| Respiratory rate ≤ 24 | |
| No chronic lung disease or diabetes | |
| No dehydration/ confusion | |
| No history of fungal infection or antifungal therapy in past six months | |

## 4. Discussion

The risk of developing febrile neutropenia depends on the degree and duration of chemotherapy-induced neutropenia and on a number of patient factors, including age, comorbidity and serum albumin levels (6,7).

The first challenge in the diagnosis of febrile neutropenia is to make sure that patients will recognize signs suggesting that they are seriously ill – and take the necessary action (8,9). It is essential to inform all patients receiving chemotherapy for malignancy about the risk of febrile neutropenia, and to explain what to look out for, before

they start their treatment. Typical signs include a temperature higher than 37.0 C, flu-like symptoms, mouth ulcers or a sore mouth that prevents eating (10,11).

Patients who receive chemotherapy are sensitive to bacteria, fungi, viruses and protozoans. They are chronically myelocytes and immunosuppression, and during heavy myelosuppression as a consequence of chemotherapy, intensified exposed nosocomially acquired infections. Most of these patients have venous catheters, and damage mucosal membrane as a result of chemotherapy, which damages the integrity of the defensive barriers. Malnutrition plays a significant role in susceptibility to infection. Prophylaxis of infections is one of the most important measures supporting treatment of patients with carcinomas, because it reduces mortality and morbidity from infection. In our institution the greatest attention is paid to preventive measures just. General measures include avoidance of many people, wearing masks, washing hands, good nutrition, dental hygiene and implementation of hygiene perianal region.

Prior use of empirical antibiotics bacteriemia is the neutropenic patients had mortality more than 80% (12,13).

In our study frequency and severity of infection correlates with the degree of neutropenia. The incidence is highest when the absolute neutrophils count of less than 0.5 x10/9/l. The choice of which antibiotic(s) to use needs to be established as a local policy, in consultation with the clinical teams managing patients on chemotherapy, and the microbiologists who monitor local patterns of infection and resistance. A combination of an amino glycoside and a broad-spectrum antibiotic was established as the standard first-line therapy of febrile neutropenia in a series of randomized clinical trials from the European Organization for Research and Treatment of Cancer (14,15). However, there are data suggesting that broad-spectrum antibiotic monotherapy can be effective, particularly in low-risk patients (usually defined as those without comorbidity, organ dysfunction and localized or deep-seated sites of infection, who are normotensive and whose neutropenia is expected to be brief) (16). Similarly, there are at least two randomized trials that have shown that combination oral antibiotics are at least as effective as standard intravenous combinations. In some protocols, the presence of an indwelling device, such as a Hickman line, influences the choice of first-line antibiotic therapy; as such a device can change the distribution of likely causative organisms (17).

Empirical broad spectrum antibiotic usage is significantly reduced mortality and morbidity in these patients. Selecting empirical antibiotics is not easy and depends on the experience of hospital facilities, the specific incidence of infection and type of resistance. It also occurs as a problem to do when the patient despite the first line empirical antibiotic therapy is still febrile, with a negative hemocultures. Most hospital facilities have their own protocols for changing the antibiotic therapy that includes better coverage of “Gram positive microorganisms” (18). It is important to recall that the need for review of the patient, re-taking hemocultures, and is often required radiological treatment. If no response after a further 48 h, patients with high risk, it is necessary to introduce antifungal therapy. Pneumocystis infection cleared the danger with large immunosuppression patients; you need spend prophylaxis trimethoprim-sulfametoxasol (19).

## 5. Conclusion

In analyzing our results, we conclude that febrile neutropenia (FN) is a serious complication of chemotherapy for patients with malignancy, with significant morbidity and mortality, and important implications for patients and healthcare resources. As a result of locally agreed and implemented policies for the management of febrile, neutropenia, healthcare professionals will become more confident in their ability to manage patients with the condition, and the public’s confidence in healthcare services will be enhanced. Achieving this goal will require education of all healthcare professionals, including those not directly involved in frontline cancer care, both at a national and local level. Febrile Neutropenia is a medical emergency and has a significant impact on morbidity and mortality. Treating febrile neutropenia is associated with high healthcare costs. Management of febrile neutropenia requires continuous monitoring and the prompt removal of the source of infection.

## Authors’ Contribution

Conception and design: SM; Acquisition, analysis and interpretation of data: SM; Drafting the article: SM ; Revising it critically for important intellectual content: SM and AS.

## Conflict of Interest

The authors declare that they have no conflict of interest

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