

## **Chemotherapy-Related Neutropenia, Risks of Neutropenic Fever and Antibacterial Prophylaxis**

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### **Abstract**

**Introduction:** Most antineoplastic agent used in oncology are cytotoxic. Excessive amounts needed to treat cancer patients adversely affect myelopoiesis leading to severe and sometimes prolonged neutropenia, which may result in potentially fatal infection.

**Aim of Work:** In this review, we will discuss the last available evidence about the risk of neutropenic fever in patient treated with chemotherapy and the antibacterial agent to prevent the condition.

**Methodology:** We conducted a systematic search on PubMed search engine and Google Scholar search engine for all studies examining neutropenic febrile syndrome.

**Conclusion:** The predictor of neutropenic fever could be related to the patient, the disease, and the cytotoxic agent used. Female gender, concomitant active comorbidity negatively affecting patient's performance as cardiovascular, renal, endocrine, or pulmonary conditions, higher body surface area, and bad nutritional status are associated with higher risk of neutropenic fever and its complication.

Antimicrobial prophylaxis aims to prevent or reduce the risk of neutropenic fever and its complication. It is not clear what is the optimal time for initiating is and discontinuing antibacterial prophylaxis due to lack of evidence. Gram-negative bacilli especially *Pseudomonas aeruginosa* are among most incriminated pathogens. Fluoroquinolone prophylaxis reduced the risk for all-cause mortality as well as infection-related mortality.

**Keywords:** *Neutropenic Febrile Syndrome; Chemotherapy-Related Neutropenia; Risks of Neutropenic Fever; Prevention; Antimicrobial Agent with Chemotherapy*

### **Introduction**

Most antineoplastic agent used in oncology are cytotoxic. Excessive amounts needed to treat cancer patients adversely affect myelopoiesis leading to severe and sometimes prolonged neutropenia, which may result in potentially fatal infection. In addition, the cytotoxic effects alters the integrity of gastrointestinal (GIT) mucosa. The disruption of such integrity increase risk of invasive infection caused by colonizing bacteria and/or fungi. As a consequences of neutropenia, the inflammatory response could be compromised in the magnitude and a fever may be the earliest and only sign of infection [1]. Other symptoms and signs are usually minimal or even absent. Nevertheless, infections in cancer patient with neutropenia can progress rapidly, leading to life-threatening complications, shock, and even death. It is

important to prevent and early recognize neutropenic fever and initiate empiric systemic antibacterial therapy to prevent these complications. Thus, it is consensual that all febrile neutropenic patients should be managed empirically with antibiotics even if they were receiving prophylaxis antibiotic before the fever. This approach is associated with risk reduction of morbidity and mortality. The Infectious Diseases Society of America (IDSA) and American Society of Clinical Oncology (ASCO) have developed a guidelines for the evaluation and management of fever in neutropenic patients with cancer in 2010 and 2018 respectively [2-4]. The recommendations in this review are generally aligned with these guidelines.

There is some disagreement between experts on the precise definition of neutropenia, however, an absolute neutrophil count (ANC) below 1500 or 1000 cells in micro liter (cell/microL) is considered neutropenia. Severe neutropenia is an absolute neutrophil count < 500 cells/microL and higher than 100 cells/microL; profound neutropenia is an ANC < 100 cells/microL [2,5]. The risk of clinically important infection increases with severe neutropenia (less than 500 cells/microL) and with prolonged duration of neutropenia for more than 7 days. Further increase in the risk for bacterial infection was observed with profound neutropenia (ANC < 100 cells/microL). If the ANC is not directly stated, it can be calculated by multiplying the total white blood cell (WBC) count by the percentage of polymorphonuclear cells (PMNs) and band neutrophils.

In this review, we will discuss the last available evidence about the risk of neutropenic fever in patient treated with chemotherapy and the antibacterial agent to prevent the condition. Antifungal and antiviral drugs are not discussed in this review, antibacterial treatment in active neutropenic fever should be dedicated another review.

### Methods

We conducted a thorough search on PubMed search engine (<http://www.ncbi.nlm.nih.gov/>) and Google Scholar search engine (<https://scholar.google.com>) for all studies examining neutropenic febrile syndrome. All relevant available full articles were reviewed and included. The terms used in the search were: neutropenic febrile syndrome; chemotherapy-related neutropenia; risks of neutropenic fever; prevention; antimicrobial agent with chemotherapy.

### Predictors and risk assessment of adults on chemotherapy

Numerous studies have examined the likelihood of neutropenic febrile syndrome in patient with neutropenia due to antineoplastic drugs. The predictor of neutropenic fever could be related to the patient, the disease, and the cytotoxic agent used. The following patient-related predictors increase the risk of neutropenic fever: patient age especially older than 65 [6-9]; female gender [10]; concomitant active comorbidity negatively affecting patient's performance as cardiovascular, renal, endocrine, or pulmonary conditions [10,11]; higher body surface area [12]; bad nutritional status [13].

Regarding the predictors related to the disease, it was found that elevated lactate dehydrogenase (LDH) in patients with lymphoreticular diseases increase the risk of neutropenic fever syndrome [13]. Bone marrow failure due to replacement of hematopoietic tissue by abnormal tissue (myelophthisis) is another predictor [13]. Higher stage of cancer [7,10,14-16] and neutropenia associated with lymphopenia [17,18] are also positive predictor.

Increased intensity and density of high-dose chemotherapy [9,18-21] and neglecting the use of prophylactic hematopoietic growth factor [8,21] are considered the most noted agent-related predictors of the development of neutropenic.

### Antibacterial prophylaxis

Antimicrobial prophylaxis aims to prevent or reduce the risk of neutropenic fever and its complication in cancer patient receiving antineoplastic drugs. In this review we are focusing on antibacterial preventive measures. Fungal and viral cause will not be discussed here.

It is not clear what is the optimal time for initiating and discontinuing antibacterial prophylaxis due to lack of evidence. When indicated, many clinicians start antibacterial prophylaxis either on the first day of administering cytotoxic chemotherapy or on the last day of the cycle of chemotherapy. It is usual to discontinue antibacterial prophylaxis once the neutropenia has been resolved or when an empiric antibacterial regimen is needed for patients who become febrile during neutropenia.

In a 2006 meta-analysis, the benefit of antibiotic prophylaxis was found to be greater for high-risk patients than for low-risk patients [22]. In a meta-analysis of 109 randomized trials published in 2012 on afebrile neutropenic patients with neutropenia duration > 7 days for most cases, antibiotic prophylaxis was associated with lower all-cause mortality compared to placebo or no treatment; the relative risk (RR) was 0.66 [23]. Antibiotic prophylaxis was also associated with substantially reduced incidence of fever, less clinically reported and microbiologically recorded infections, less infections due to gram-positive and gram-negative bacteria, less bacteremia and a lower risk of infection-related death.

Gram-negative bacilli especially *Pseudomonas aeruginosa* are among most incriminated pathogens that may cause life-threatening infections and complications in patient receiving chemotherapy. Researchers have frequently examined the clinical benefits of prophylactic antibacterial agents. Most of these studies have been focused on fluoroquinolones and levofloxacin in 500 - 750 mg/day; ciprofloxacin on 1000 - 1500 mg/day. It is suggested that levofloxacin is preferred antibacterial in patients at increased risk for viridian streptococcal infection related to oral mucositis [2]. Additionally, fluoroquinolone prophylaxis reduced the risk for all-cause mortality (RR 0.54) as well as infection-related mortality, fever, and clinically and microbiologically documented infections [23].

The number of patients needed to treat (NNT) to prevent one febrile episode was 5 for leukemia or HCT recipients compared with 23 for solid tumor or lymphoma patients.

On the other hand, the NNT to prevent one documented infection was 6 versus 13 for leukemia or HCT group compared with solid tumor or lymphoma group respectively. The number needed to treat to prevent one death was 43 for leukemia or HCT patients versus 132 for solid tumor or lymphoma patients [24]. Systematic monitoring of the prevalence of fluoroquinolone resistance among gram-negative bacilli should be performed in institutions which use fluoroquinolone agent for prophylaxis. Based on available data, fluoroquinolone prophylaxis is suggested for high-risk neutropenic patients who do not have a contraindication to receive fluoroquinolone [2,25,26]. Ciprofloxacin has greater in vitro activity than levofloxacin against *P. aeruginosa*, but levofloxacin has greater in vitro activity against gram-positive bacteria (e.g. alpha-hemolytic streptococci) and is given only once daily compared with twice daily for ciprofloxacin.

In patients at risk of a prolonged QT interval, fluoroquinolone prophylaxis should be considered with caution, because QT prolongation is a known side effect of fluoroquinolone toxicity. This is especially important in patients who may require additional QT prolonging agents, such as voriconazole. Fluoroquinolone use was also reported to cause tendon rupture. Additionally, doses in patients with renal insufficiency must be decreased.

Another significant factor in determining whether or not to use fluoroquinolone as prophylaxis includes the possibility of increasing resistance of gram-negative and gram-positive bacteria [27]. In institutions and geographic regions where fluoroquinolone resistance rates are significant, the use of these agents for prophylaxis is less likely to be effective [28,29]. There was also concern over the possibility of increasing the risk of *Clostridioides difficile* infections, although this has not been proven in neutropenic patients receiving fluoroquinolone prophylaxis [27]. A large multicenter randomized trial examined the use of levofloxacin as prophylaxis in children patient undergoing chemotherapy for different conditions, the study found no increase in *C. difficile* infection in those who received levofloxacin prophylaxis compared with those who received no prophylaxis [30]. In a subsequent retrospective review, fluoroquinolone prophylaxis was specifically associated with the development of *P. aeruginosa* bacteremia resistant to meropenem [31].

Older trials have examined the role of Trimethoprim-sulfamethoxazole (TMP-SMX) as prophylaxis [23]. However, the drug is no longer used since it has no activity against *P. aeruginosa*. In addition, susceptibility to TMP-SMX among a variety of bacterial species has declined worldwide.

Antibacterial prophylaxis may be given to an additional category of patients defined as “intermediate-risk” patients. The decision on whether to give intermediate-risk patients antibacterial prophylaxis should be taken on individual basis.

### Conclusion

Excessive amounts of chemotherapy needed to treat cancer patients adversely affect myelopoiesis leading to severe and sometimes prolonged neutropenia, which may result in potentially fatal infection. The inflammatory response could be compromised in the magnitude and fever may be the earliest and only sign of infection. Other symptoms and signs are usually minimal or even absent. An absolute neutrophil count (ANC) below 1500 or 1000 cells in micro liter (cell/microL) is considered neutropenia. The risk of clinically important infection increases with severe neutropenia (less than 500 cells/microL) and with prolonged duration of neutropenia for more than 7 days.

The predictor of neutropenic fever could be related to the patient, the disease, and the cytotoxic agent used. Female gender, concomitant active comorbidity negatively affecting patient’s performance as cardiovascular, renal, endocrine, or pulmonary conditions, higher body surface area, and bad nutritional status are associated with higher risk of neutropenic fever and its complication. Antimicrobial prophylaxis aims to prevent or reduce the risk of neutropenic fever and its complication.

It is not clear what is the optimal time for initiating and discontinuing antibacterial prophylaxis due to lack of evidence. Gram-negative bacilli especially *Pseudomonas aeruginosa* are among most incriminated pathogens. Fluoroquinolone prophylaxis reduced the risk for all-cause mortality as well as infection-related mortality, fever, and clinically and microbiologically documented infections.

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