

Prevention of febrile neutropenia

Risk factors predicting febrile neutropenia

As infection in patients with neutropenia is primarily the direct consequence of chemotherapy-induced neutropenia, attempts to prevent febrile neutropenia (FN) episodes during chemotherapy administration requires the evaluation of the risk factors associated with the development of significant neutropenia.

Neutropenia in chemotherapy-treated patients with solid tumors is related to the intensity of the administered chemotherapy and, consequently, most common chemotherapy regimens have been associated with a predictable risk of FN [1]. However, this prediction is far from being highly accurate, as other patient-related risk factors should be taken into account, in addition to the intensity of chemotherapy. Particular consideration should be given to the elevated risk of FN in elderly patients (aged 65 and over). Other adverse risk factors that may influence FN risk include: advanced stage of disease, experience of previous episodes of FN, lack of prophylaxis (granulocyte colony-stimulating factor [G-CSF] use or antibiotic prophylaxis) as well as the use of concomitant immunosuppressive agents or various serious comorbidities, such as diabetes, cirrhosis, and others.

In patients with hematological malignancies, it has been confirmed that an aggressive chemotherapy regimen was the major predictor of FN. Other independent predictors were the underlying disease, the involvement of the bone marrow, a body surface $\leq 2 \text{ m}^2$, and a baseline

monocyte count $<150/\mu\text{l}$ [2]. Many other attempts have been made to predict the occurrence of FN and several predictive factors have been proposed, such as the slope of the myelosuppression-time profile [3] or the type of cancer and renal function tests [4], but further prospective validation is needed.

Based on these different risk factors, models have been proposed to better predict the occurrence of FN in patients treated with chemotherapy, and consequently provide the greatest clinical benefit and cost effective use of prophylaxis [5]. However, so far none of these models have gained wide acceptance and/or have been validated in large prospective trials.

While elderly patients clearly have a higher rate of complications during FN than younger patients treated with similar regimens [6], in children the aggressiveness of chemotherapy and the level of neutropenia at the onset of FN appear to be the strongest risk factors associated with the development of FN [7].

Chemoprophylaxis

Attempts had been made 50 years ago to reduce the occurrence of FN in high-risks patients (ie, those with acute leukemia aggressively treated with chemotherapy) with the implementation of a protective environment (eg, isolation and the use of low-bacterial diet) in combination with orally administered nonabsorbable antibiotics. Overall, these approaches have been disappointing in terms of efficacy and tolerability by the patients. Moreover, recent reviews stressed the essential role of orally administered antibiotics compared to the other components of the protective environment, namely isolation and low-bacterial diet [8]; on the other hand, oral-nonabsorbable antibiotics given to leukemia patients within protective environments have been associated with the emergence of resistant strains [9]. For all these reasons, the protective environment approach has been largely abandoned.

The prophylactic oral administration of absorbable antibiotics has been initially successful with the use of co-trimoxazole. However, the emergence of co-trimoxazole-resistant strains rapidly limited the clinical effectiveness of that approach [10].

More recently, fluoroquinolones have been used for the prevention of FN in patients treated with chemotherapy, with either solid or hematological malignancies. Meta-analyses indicated that such an antimicrobial prophylaxis reduced the frequency of infection and infection-related mortality in neutropenic patients with cancer [11] but led to the emergence of quinolone-resistant strains that could be resistant to a wide spectrum of antibiotics [12]. It should be emphasized that the favorable results of the prophylactic fluoroquinolones has been mainly observed in patients with a high risk of FN (ie, patients treated for acute leukemia and/or receiving hematopoietic stem cell transplantation); for the patients with a low risk for FN, the evidence that antibacterial prophylaxis improves the outcome is less robust. Based on these considerations and because the routine use of antibacterial prophylaxis may increase the spread of resistant strains, recent guidelines from the American Society of Clinical Oncology (ASCO) recommend that clinicians limit the use of antibacterial prophylaxis to patients at high risk for FN [13]. Nonetheless, others recommend the mere avoidance of prophylactic use of fluoroquinolones for the prevention of FN. First, the use of fluoroquinolones for prophylaxis will eventually make that approach useless, as a result of the emergence of resistant strains, just as it has been the case with trimethoprim-sulfamethoxazole. Next, the emergence of fluoroquinolone resistance might be associated with a worse outcome of bacteremia, through the emergence of multiresistance, and that situation would require new paradigms in terms of empirical therapy. Finally, fluoroquinolone prophylaxis makes the empirical therapy of FN based on fluoroquinolones impossible [14], although in patients not previously exposed to quinolones such an approach has been shown to be highly effective [15]. For all these reasons, it would appear sensible to discontinue the prophylactic use of fluoroquinolones in patients with cancer.

These recommendations are supported by recent evidence obtained in the pediatric population (in which the quinolones are usually not used because of their possible interference with bone metabolism). Although ciprofloxacin significantly reduced the occurrence of FN in children with acute lymphoblastic leukemia in the induction phase of chemotherapy, the percentage of *Escherichia coli* and *Klebsiella pneumoniae*

susceptible to ciprofloxacin were significantly lower in the patients having received ciprofloxacin [16].

Besides antibacterial prophylaxis, as indicated in Table 2.1, antiviral and antifungal prophylactic measures need to be considered for patients with prolonged neutropenia and/or severe immunodepression, namely in patients undergoing hematopoietic stem cell transplantation [17]. In those patients, vaccination programs should avoid live vaccines as long as the immunologic recovery as not complete.

The use of granulopoietic colony stimulating

The development of the G-CSFs provided oncologists a much more physiological way to prevent chemotherapy-associated FN, compared with chemoprophylaxis.

Primary prophylaxis

In 2007, Kuderer et al published a comprehensive systematic review and meta-analysis of all reported randomized controlled trials comparing

Antibacterial prophylaxis		
Modality	Patient group	Treatment
Vaccination		Yearly influenza vaccine 5-year pneumococcal vaccine No live vaccines (eg, oral polio, oral typhoid, yellow fever, measles, mumps, rubella, BCG, VZV)
Antibacterial	Patients undergoing intensive chemotherapy and expected to present a prolonged and profound neutropenia (ANC <100 cells/mm ³ for more than 7 days)	Ciprofloxacin Levofloxacin
Antiviral	Patients with recurrent herpes infections undergoing intensive chemotherapy and expected to present a prolonged and profound neutropenia; lymphopenic patients	Acyclovir Valacyclovir
Antifungal	Patients undergoing intensive chemotherapy and expected to present a prolonged and profound neutropenia	Fluconazole Posaconazole Itraconazole

Table 2.1 Antibacterial prophylaxis. ANC, absolute neutrophil count; BCG, Bacillus Calmette–Guérin; VZV, varicella-zoster virus. Reproduced with permission from © Marcel Decker 2013, Bron [17]. All Rights Reserved.

G-CSF with placebo or untreated controls in adults with solid tumors or lymphomas [18]. The most important conclusions were a significant reduction of the infection-related mortality (from 2.8% to 1.5%) and a significant reduction of FN episodes (from 39% to 22%), impacting morbidity and cost of care. Moreover, the relative dose intensity was clearly higher in the patients receiving G-CSF: 90–99% in patients receiving G-CSF versus 71–95% in the control groups, suggesting that dose reductions and delays in the administration of chemotherapy had been reduced.

More recently, another systematic review and meta-analysis reported similar results [19]. Overall, it was found that the relative risk of FN for G-CSF prophylaxis versus no primary prophylaxis was 0.51 in patients with solid tumors and lymphomas.

In patients treated with high-dose chemotherapy followed by stem cell transplantation, another recent meta-analysis showed that G-CSF reduced the risk of documented infections and time to hematologic recovery as well as the duration of hospital stay [20]. However, there was no difference between G-CSF treatment group and placebo group for all-cause mortality.

Based on these data G-CSF primary prophylaxis significantly reduces the morbidity resulting from FN, improves the quality of life of the patients, possibly makes chemotherapy more efficacious, and the overall management of the patients less expensive. The effect on FN and mortality has been extensively discussed in the literature, as indicated in Figure 2.1 [21].

Secondary prophylaxis

Secondary prophylaxis is the administration of G-CSF to patients who already experienced an episode of FN during a previous cycle of chemotherapy; it has been less studied than primary prophylaxis.

The initial G-CSF registration study in patients with small cell lung cancer receiving intensive chemotherapy allowed patients in the placebo group to receive open-label G-CSF in subsequent cycles of chemotherapy after an FN episode during the first cycle. The secondary prophylaxis in those patients, all of whom had experienced FN during the first cycle,

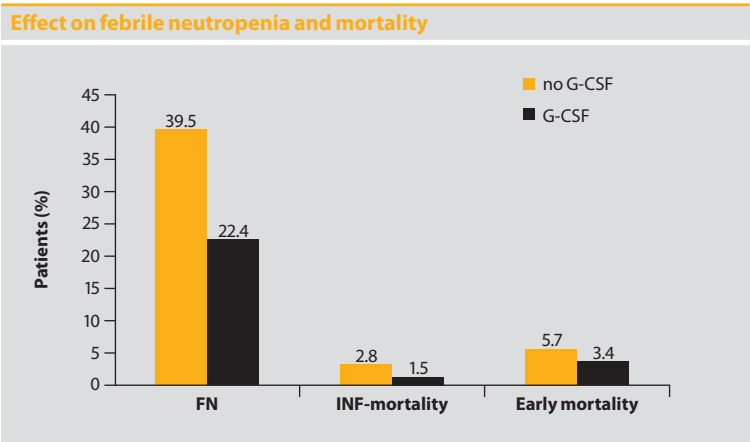


Figure 2.1 Effect on febrile neutropenia and mortality. Efficacy of primary prophylactic G-CSF (pegfilgrastim, filgrastim, or lenograstim) versus placebo or no treatment in preventing febrile neutropenia, INF-related mortality, and early mortality (all-cause, during chemotherapy) in 3493 patients treated with chemotherapy for solid tumors or lymphoma. Results of a meta-analysis of 17 studies. FN, febrile neutropenia; G-CSF, granulocyte colony-stimulating factor; INF, infection. Reproduced with permission from © Springer-Verlag 2013, Aapro et al [21]. All Rights Reserved.

was associated with FN in only 23% [22]. Similar results were presented in a more recent investigation in 48 patients with different tumors and therapies and who all developed an FN episode during the first cycle of chemotherapy. These patients received G-CSF during the subsequent course of the same chemotherapy without any reduction of the dose intensity; with secondary prophylaxis the frequency of FN was 2% (one patient out of 48) [23]. The level of the reduction of the risk of FN with secondary prophylaxis is probably influenced by factors, such as the type of tumor and chemotherapy; it might be greater with less aggressive regimens. Those two studies showed a dramatic reduction of FN with secondary prophylaxis; however, it should be recognized that the risk of FN has been found greatest during the initial treatment cycle [24].

Another study [25] reported the results of a randomized trial comparing adjuvant docetaxel, doxorubicin, cyclophosphamide (TAC) and fluorouracil, doxorubicin, cyclophosphamide (FAC) for high-risk cancer patients; the study indicated that secondary prophylaxis was effective but also suggested that with regimens associated with a high risk of

FN (TAC), primary prophylaxis should be the rule as the frequency of FN was still 24% with secondary prophylaxis while only 6% with the primary approach.

The choice of granulocyte colony-stimulating factor for primary prophylaxis

At the present time, there are two preparations of G-CSF available for clinical use. Filgrastim is eliminated by the renal route as well as inactivation by the rising number of neutrophils, and requires a daily administration until neutrophil recovery. The other is a long-acting preparation, obtained by pegylation: pegfilgrastim is inactivated by the stimulated neutrophils a few days after its administration, and thus only needs a single administration.

There have been numerous studies comparing these two preparations and the optimal ways for their administration [26]. Recent reviews suggest that pegfilgrastim might be associated with a lower risk of FN-related hospitalization of patients with solid tumors than filgrastim prophylaxis [27]. In patients treated with intensive chemotherapy and autologous peripheral stem cell transplantation, recent reports state that both drugs are at least equally effective [28]. There are no indications that one of these preparations is safer than the other; both can be associated with some bone pain but serious complications are extremely rare.

The choice between the use of pegfilgrastim or filgrastim may take into account the convenience of administration of pegfilgrastim (a single injection) and the lower cost of filgrastim, especially if reduced schedules of administration and the use of less expensive biosimilars are taken into consideration.

Guidelines for selecting patients for granulocyte colony-stimulating factor prophylaxis

All of the published guidelines about the use of G-CSF for the prophylaxis of FN estimate risk for developing FN based on the type of chemotherapy used. Although there are lists of chemotherapy regimens with an estimation of the risk of FN associated, respectively [1], there is no validated tool for categorizing chemotherapy regimens according to their toxicity

on the neutrophils. Moreover, various comorbidities might significantly increase the risk of FN, for a given regimen, namely age.

All published guidelines use a three-step classification with three categories: high risk of developing FN (ie, >20%), intermediate risk (10–20%), and low risk (<10%). The underlying drive is cost effectiveness, a delicate balance between the savings resulting from effective prevention of FN and the cost of G-CSF.

All guidelines recommend using G-CSF if the risk of FN is greater than 20% (the high-risk group) but diverge as far as the other groups are concerned; however, there might be a consensus for not giving prophylaxis with G-CSF to patients with a lower than 10% risk of developing FN.

The recommendations made by European Organisation for Research and Treatment of Cancer (EORTC) in 2010 [1] represent a pragmatic approach and are summarized in Figure 2.2 [1]. Although these guidelines adopt the three-step approach, common to all published recommendations so far, they provide a significant space for the role of various comorbidities in the decision planning. This is a very important step towards a more precisely tailored approach of the indications for the use of G-CSF, taking into account not only the aggressiveness of the chemotherapy but also the characteristics of the patients.

Few trials have been conducted so far to elaborate clinical models using the patient's characteristics for predicting the risk of FN. However, such predictive factors exist and might more or less significantly influence the level of risk for FN. Patient-related predictive factors for FN that might be significant are indicated in Table 2.2 [29].

In a recent study in patients with hematological malignancies, an attempt has been made to incorporate some of these factors into a predictive model, namely the underlying disease, the involvement of the bone marrow, a body surface less than 2 m², a baseline monocyte lower than 150 μ l, and the baseline hemoglobin level [2]. A rule of prediction of FN was computed with a sensitivity 78.6%, specificity 62.3%, positive predictive value 42.7%, and negative predictive value 89.1%.

A systematic review of the literature confirmed that age, performance status, and nutritional status are associated with a higher risk of FN [30] and various comorbid conditions, such as renal and liver function

Algorithm to decide primary prophylactic granulocyte colony-stimulating factor usage, adapted from European Organisation for Research and Treatment of Cancer guidelines

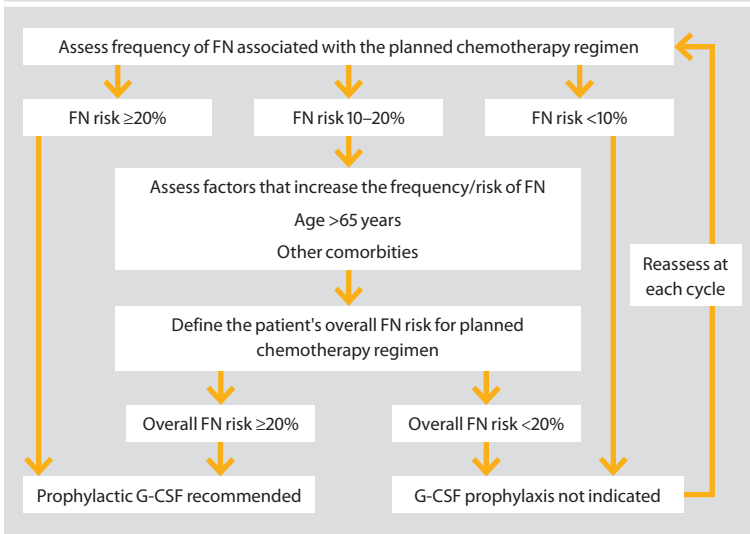


Figure 2.2 Algorithm to decide primary prophylactic granulocyte colony-stimulating factor usage, adapted from European Organisation for Research and Treatment of Cancer guidelines. FN, febrile neutropenia; G-CSF, granulocyte colony-stimulating factor. Reproduced with permission from © Pergamon 2013, Aapro et al [1]. All Rights Reserved.

impairment, heart disease, and hypertension as well as obstructive lung disease, are associated with more frequent complications during FN [1].

Although the aggressiveness of chemotherapy currently remains the main predictive factor for the risk of chemotherapy-associated FN (and thus for deciding whether or not primary prophylaxis with G-CSF is indicated), it is nonetheless clear that many other factors, namely age and major comorbidities, must influence the clinician's decision. Until reliable predictive tools are developed, the decision should be made on the basis of presently available clinical evidence and medical expertise.

Should the indications for primary prophylaxis with granulocyte colony-stimulating factor be extended?

There are actually several reasons that militate for the extension of the indications for primary prophylaxis with G-CSF (Table 2.3).

Factors potentially associated with an increased risk for developing febrile neutropenia during chemotherapy

1. Older age
2. Advanced disease/metastases
3. No antibiotic prophylaxis
4. Prior febrile neutropenia
5. No granulocyte colony-stimulating factor use
6. Female sex
7. Anemia
8. Cardiovascular disease
9. Abnormal liver tests
10. High-dose intensity chemotherapy
11. Poor performance status
12. Poor nutrition
13. More than one comorbidity
14. Lymphoma histology
15. Asian origin
16. Body surface less than 2 m²
17. Pretreatment neutrophils less than 1.5
18. Albumin less than 3.5 g/dl

Table 2.2 Factors potentially associated with an increased risk for developing febrile neutropenia during chemotherapy. Reproduced with permission from © Lippincott Williams & Wilkins 2013, Lyman, Shayne [29]. All Rights Reserved.

The prediction of the risk of FN based solely on the type of chemotherapy administered is not entirely reliable; in addition, elderly patients and those with various comorbidities have an increased risk of FN with a given chemotherapy regimen and present more frequently with complications if FN occurs.

Many regimens used for the treatment of patients with solid tumors have a risk of FN lower than 20%. On the other hand, when FN occurs in such patients, the morbidity and mortality that are associated with it are in the same range as what is observed in patients with a high risk of development of FN [31]. We have observed that FN, in patients with a <10% and <20% risk of developing FN, has a frequency of complications of 9% and 10% and a mortality of 4% and 6%, respectively. Moreover, it has been reported that in patients with a moderate risk of FN (<20%), impaired chemotherapy delivery (timing and dose) was

Reasons for extending the indications for primary prophylaxis with granulocyte colony-stimulating factor to patients with a <20% risk of febrile neutropenia

1. Type of chemotherapy does not accurately predict the risk of FN
2. Older age and various comorbidities increase the risk of FN for a given chemotherapy regimen and increase the risk of complications resulting from FN
3. Many common chemotherapy regimens are associated with <20% risk of FN; these patients are denied prophylaxis with G-CSF
4. The frequency of complications and mortality associated with FN are the same regardless of the initial risk for FN
5. Patients with a low risk of FN benefit from primary prophylaxis in terms of a reduced incidence of FN
6. Cost effectiveness in patients with a low risk of developing FN during chemotherapy might be dealt with through reduced dosage of G-CSF and use of biosimilars

Table 2.3 Reasons for extending the indications for primary prophylaxis with granulocyte colony-stimulating factor to patients with a <20% risk of febrile neutropenia. FN, febrile neutropenia; G-CSF, granulocyte colony-stimulating factor.

observed in 40% of the patients developing FN [32]. Additionally, there is evidence that these patients, with a low or moderate risk of developing FN during chemotherapy administration, significantly benefit from primary prophylaxis with G-CSF [31,32].

Conversely, it was found that a lower baseline risk for FN might be associated with a greater reduction in the relative risk by G-CSF [18]. This can explain why noncontinuous G-CSF therapy may be safe in patients at a relatively low risk of FN, as suggested by Papaldo et al [33]; these investigators evaluated different G-CSF schedules in patients with breast cancer and an overall risk rate for FN of 7%; they found that 300 µg/day of filgrastim on days 8 and 12 were just as efficacious as more standard regimens (eg, days 8–14) or higher doses of G-CSF. These retrospective investigations are supported by more recent prospective studies [34], suggesting that shorter G-CSF schedules (eg, on days 5, 7, 9, 11) were more active than standard filgrastim or pegfilgrastim in patients with breast cancer receiving adjuvant dose-dense chemotherapy, with a 6% risk of FN (historical controls).

At the present time, these observations suggest that a large proportion of the patients receiving chemotherapy is left without protection against FN, just for economic reasons. As will be discussed later, the cost effectiveness of primary prophylaxis with G-CSF may improve by the

rational use of reduced doses of G-CSF and utilization of less expensive biosimilars, leading to other paradigms for prophylaxis than those proposed today (Figure 2.3), although these proposals need prospective controlled validation.

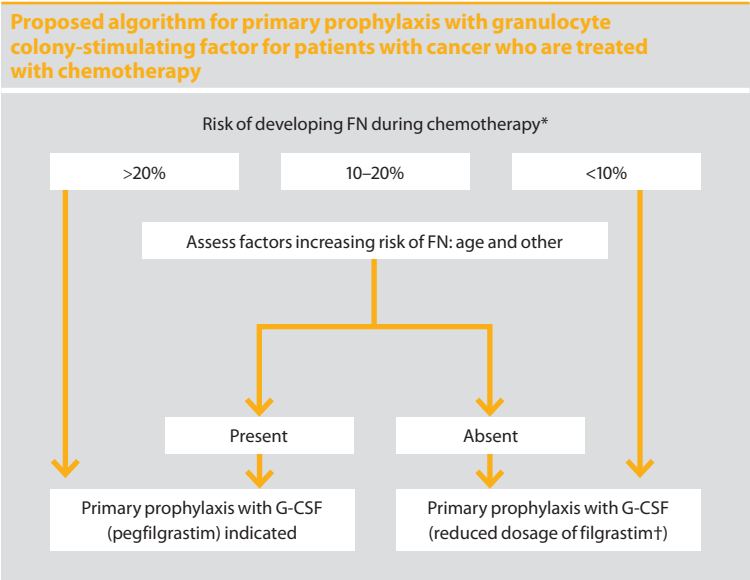


Figure 2.3 Proposed algorithm for primary prophylaxis with granulocyte colony-stimulating factor for patients with cancer who are treated with chemotherapy.
*Based on the aggressiveness of the regimen; †Use biosimilars if available. FN, febrile neutropenia; G-CSF, granulocyte colony-stimulating factor.

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