Clinical Practice Guidelines – Medical Oncology Toxicity Group

Guideline Title:	Therapeutic Use of Myeloid Growth Factors for Chemotherapy-Induced Neutropenia in High Risk and Intermediate Risk Patients.	**Date:**	**(O):** **(R):**	Mar 31, 2012
Tumor Group:	Medical Oncology Toxicity Group	**Page:**		1 of 14
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Adapted From:	National Comprehensive Cancer Network (NCCN) "Myeloid growth factors" guideline, 2012 (60).			

Introduction:

Neutropenia is a common yet potentially serious complication of chemotherapy treatment. Severe neutropenia during chemotherapy for cancer patients can result in dose reduction of chemotherapy drugs, treatment delays or development of febrile neutropenia (FN), all of which can have a negative impact on treatment outcomes (1-7). FN is generally defined as a fever (single oral temperature ≥38.3°C or ≥38.0°C for >1 h) with grade 3/4 neutropenia which is an absolute neutrophil count (ANC) of <1.0 or $<0.5 \times 10^9$/l (8). Prophylaxis with granulocyte colony-stimulating factors (G-CSFs) reduces the severity and duration of chemotherapy-induced neutropenia, and plays an important role in supporting the delivery of myelosuppressive chemotherapy (8-11). Appropriate management of the risk for chemotherapy-induced neutropenia complications continues to be an important aspect of quality care in oncology.

Chemotherapy-induced neutropenia (CIN) is the primary dose limiting toxicity associated with systemic chemotherapy in patients being treated for cancer (12). Dose reduction is a technique commonly used to minimize chemotherapy toxicity however, data suggests that treatment with full dose chemotherapy delivered on time can improve patients survival, therefore oncology caregivers should aim to achieve recommended dose intensity and timely treatments for patients (13,14). Evidence shows that neutropenic events occur less often during the first cycle of chemotherapy, when patients receive full dose chemotherapy with the use of supportive care, such as colony stimulating factors (CSFs) (15).

By developing and implementing clinical practice guidelines for the management of CIN, healthcare professionals provide an evidence-based systematic process to promote tolerance to chemotherapy and potentially improve patient outcomes (60). Severe neutropenia can increase the risk of life threatening infection, hospitalization and need for intravenous antibiotics, and while most patients will recover uneventfully from CIN, it still carries substantial risk of both morbidity and mortality (15). The incidence and associated mortality of neutropenia have shown to be highest in patients with more than one major comorbidity at 21.4% (16).While it may be

difficult to eliminate CIN entirely, through the use of clinical practice guidelines and patient risk identification, the incidence of FN can be greatly reduced (12,60).

Questions:

1. What evidence supports the therapeutic use of myeloid growth factors in the prevention of chemotherapy induced neutropenia?

2. What are the patient selection criteria for the therapeutic use of myeloid growth factors to prevent chemotherapy-induced neutropenia (CIN) within Eastern Health

Target Population:

The recommendations are aimed toward adult patients who are receiving systemic therapy for solid tumors, lymphoma and non-myeloid malignancies, and that are deemed at increased risk for developing febrile neutropenia as a result of myelosuppression.

Supporting Evidence:

Granulocyte-colony stimulating factors (G-CSFs), filgrastim and pegfilgrastim currently have FDA and Health Canada approval for use in prevention of chemotherapy-induced neutropenia. A 2002 literature review found that 25-40% of treatment-naive patient's, develop febrile neutropenia (FN), with common chemotherapy regimens (17). Development of FN has also been shown to increase diagnostic and treatment costs and often leads to longer hospital stays (18). Meta-analyses have confirmed the efficacy of prophylactic G-CSFs in decreasing rates of infection (19,20). Researchers have also shown that correlations exist between changes in neutrophil counts and quality of life as measured by physical functioning, vitality, and mental health (14). Several randomized controlled trials and meta-analyses have confirmed that the myeloid growth factors reduce the risk of neutropenia complications and may facilitate delivered dose intensity in patients receiving cancer chemotherapy (16,19,21). Three major professional oncology organizations and a Canadian consensus recommend prophylactic use of G-CSFs when the risks of developing complications from febrile neutropenia are 20% or higher, as well as for those patients with variables that increase their risk of neutropenic complications (57-60).

The National Comprehensive Cancer Network (NCCN) source guideline provides category I evidence that recommends routine CSF use to decrease the risk of FN, the risk of hospitalization, and the use of antibiotics in patients treated with a chemotherapy regimen, associated with a 20% risk of FN (60). This recommendation includes patients receiving curative or adjuvant treatment as well as treatment to prolong survival or improve quality of life. In the case of chemotherapy regimens with FN rates between 10%-20%, the decision to use CSFs should be based on patient related risk factors, such as age, advanced stage of disease or previous neutropenia complications. The importance of assessing individual patient risk factors have been identified by all three oncology groups, and is well documented in retrospective meta-analyses (8,11).

It has been reported that older age and certain co-morbidities significantly increase the risk of febrile neutropenia and its consequences (8,11). One study which looked at myelotoxocity in elderly patients with non-Hodgkin lymphoma (NHL) showed that if older patients are treated with

recommended doses, they can have outcomes equal to those of younger patients (22). Elderly patients have not always been considered candidates for full-dose aggressive chemotherapy, but there is a growing body of evidence to show that, with adequate G-CSF support, delivery of myelosuppressive chemotherapy is reasonable in this population (23-26).

Recently reported data from a national study of oncology practice, has confirmed previous observations that FN is most common in the first cycle of chemotherapy, and this underlines the need to start G-CSF from the first cycle in appropriate patients (27,28). A prospective cohort study of 3760 patients identified variables that have been reported to increase the risk of FN such as older age, the presence of co-morbidities, low baseline white blood cells, neutrophils and hemoglobin levels, as well as the intensity of the specific chemotherapy regimen (29). As age ≥65 years has consistently been shown to be linked with increased FN risk, G-CSF prophylaxis should be considered to support chemotherapy delivery in all elderly patients receiving myelotoxic chemotherapy (27,30).

There is now sufficient data to suggest that reduced chemotherapy dose intensity due to delays and dose reductions, can potentially compromise survival outcomes in patients receiving curative treatment (2,4-7,27). Even moderate reductions can negatively impact survival as seen in a study looking at NHL patients treated with CHOP (cyclophosphamide, vincristine, procarbazine and prednisone) -like chemotherapy (2). Data from 17 clinical trials encompassing 3,493 patients was analyzed by the University of Rochester Medical Centre in Rochester, New York (31). The results confirmed that the use of G-CSF decreased the risk of FN, regardless of the type of cancer patients had, or the type of CSF they received. It was also reported that fewer patients died while receiving chemotherapy, and on average patients treated with G-CSF received more than 90% of the total amount of chemotherapy planned versus those in the control groups. The studies suggested that chemotherapy is more likely to cure the disease, if the patient receives a higher percentage of the planned dose. Though, in this study, it was unclear whether patients treated with the G-CSF lived longer or remained cancer free longer than those not receiving G-CSF.

The proactive use of G-CSFs under current guidelines, have shown a decrease in the duration and severity of CIN and subsequently the incidence of FN (19,21). However, it is important that G-CSFs are used according to recommendations, in order to gain the maximum therapeutic benefit. Data from clinical trials indicates that in the case of filgrastim, this requires 9-14 injections per chemotherapy cycle (9,32).

Selection Criteria: The clinical trial and meta-analysis data surrounding the therapeutic use of G-CSF is evident in all four chosen source guidelines (19,57-60). The consensus of the Medical Oncology Toxicity group was to accept the criteria for high risk and intermediate risk patients and offer primary prophylactic G-CSF, where appropriate. Patients are divided into three groups based on the percentage of risk of developing FN.

- **High Risk* -** patients receiving chemotherapy regimens with a 20% risk of febrile neutropenia or higher; the use of G-CSF is required and recommended;

* *Examples of high-risk chemotherapy regimens can be found in Appendix.*

- **Intermediate Risk* -** patients receiving chemotherapy regimens with a 10-20% risk of febrile neutropenia; the use of G-CSF should be considered based on the presence of variables that may increase individual risk of neutropenic complications, such as age, previous neutropenic complication or co morbidities;
- **Low Risk –** patients are considered low risk when the risk of febrile neutropenia is less than 10%; no indication for G-CSF use unless a specific patient is at significant risk of serious consequences of FN and that patient is being treated with curative or adjuvant intent.

Granulocyte-Colony Stimulating Factor (G-CSF): G-CSF is a protein produced by the body that stimulates the bone marrow to produce more white blood cells and release them into the blood stream. G-CSF is also available as a pharmaceutical. Treatment with a G-CSF is a form of biological therapy. There are currently two forms of G-CSFs that are indicated for the therapeutic use in prevention of CIN and approved for use in Canada.

1. **Pegfilgrastim (Neulasta®)** is available in a single 6mg fixed dose suitable for patients between 46kg and 132kg. Pegfilgrastim should be stored in a refrigerator and protected from light. It should be administered s/c once no sooner than 24hrs post chemotherapy and no later than 14 days prior to next chemotherapy cycle**. Once used it should be continued with all subsequent cycles unless contraindicated. Pegfilgrastim is present throughout the neutropenic nadir and is eliminated from circulation as the neutrophils recover.

   Phase II studies in NHL, Hodgkin's disease, breast, lung, colorectal and germ cell tumors, have evaluated the safety and efficacy of pegfilgrastim in 14 day intervals or less. These studies show that because of its neutrophil-mediated clearance, pegfilgrastim concentrations appear to reach sub-therapeutic levels prior to the next administration of chemotherapy (33-39). Therefore, pegfilgrastim can be both safe and effective when given with Q2 weekly chemotherapies such as FOLFOX, CHOP-R and AC for women with early breast cancer, and is now supported and recommended by the 2012 version of the NCCN guideline (60).

   **Note: ****Pegfilgrastim (Neulasta®) should not be used in chemotherapy regimens that are given less than every 2 weeks.

2. **Filgrastim (Neupogen®)** should be administered subcutaneously as a single daily injection 5mcg/kg/day s/c x 7-14 days, until the ANC has surpassed 10×10^9/l following the expected CIN nadir. Filgrastim should be stored in a refrigerator but not allowed to freeze. It should be administered s/c daily at a dose suitable for patient's weight. For patients <75kg, filgrastim 300mcg s/c should be administered daily. For patient's ≥75kg, filgrastim 480mcg s/c should be administered daily. Filgrastim should be administered 24 hours post-chemotherapy.

   Filgrastim (Neupogen®) should be given daily, until ANC returns to the normal range; data from clinical trials indicate that this requires approximately 9–14 injections per chemotherapy cycle (9, 32). However, it is common practice to administer fewer doses than this and/or to start treatment relatively late after chemotherapy (40-42). Several analyses have shown that, when used in this manner, filgrastim may provide suboptimal protection against FN (41, 42).

** Examples of intermediate risk chemotherapy regimens can be found in Appendix.*

Bloodwork: The current drug monograph for filgrastim recommends a complete blood count (CBC) including differential and platelet count, prior to starting chemotherapy and then repeated 2 times/week during therapy. However, this is not the current practice of the Cancer Care Program, Eastern Health, or the practice of oncology agencies across the country, as neither high nor low ANC values, prior to a patient recovering from their nadir, would require a change in supportive care. In a randomized, double blind multicenter, phase III study comparing single administration of pegfilgrastim vs. daily filgrastim, the safety profiles were noted to be similar when assessed for adverse events, antibody formation and lab values (43). Transient neutropenia was observed, with the overall hematological profiles reflective of the characteristics of patients receiving myelosuppressive chemotherapy. Leukocytosis has been observed in 2% of patients receiving filgrastim, and occurred at doses above 5mcg/kg/day.

Therefore, the recommendation of the Medical Oncology Toxicity Group around the monitoring of bloodwork is as follows:

- CBC, including differential and platelet count, should be obtained prior to each chemotherapy administration. Hematocrit value, white blood cells and platelet count should be assessed with all blood work, while a patient is receiving G-CSF for supportive care. More frequent blood work may be ordered if the patient experiences fever, exhibits signs and symptoms of infection, or at the discretion of the treating physician.

Contraindications:

- G-CSFs are currently **not** recommended for use when a patient is receiving radiation therapy.
- It should be noted that long term data on the use of G-CSFs in patients with leukemia, demonstrated no adverse effect on disease status or patient safety (44).
- Avoid use in patients with known hypersensitivity to *E.coli* derived products or to any constituent of the product.

Cautions:

- Splenic rupture, including fatal cases has been reported following filgrastim administration. Patients who report left upper abdominal pain &/or shoulder tip pain should be evaluated for an enlarged spleen or splenic rupture;
- For patients on lithium treatment; lithium may cause more neutrophils than normal to enter the blood stream;
- Increased hematopoietic activity of the bone marrow in response to growth factor therapy has been associated with transient positive bone imaging changes. This should be considered when interpreting bone-imaging results;
- Patients who have a history of gout or malignancies that are known to be associated with increased uric acid levels should be monitored regularly;
- A recent meta-analysis found that intensified chemotherapy with G-CSF support slightly increased the risk of second malignancies when compared with standard chemotherapy without G-CSF, however this was more than offset by the survival benefits (45). Thus, the overall risk/benefit ratio continues to favor G-CSF use (46), as it facilitates chemotherapy delivery and prevents life-threatening FN;

- There may be an increased risk for pulmonary toxicity, when using G-CSF for Hodgkin's lymphoma patients receiving bleomycin-containing therapy. One retrospective review reported this to be true, especially for the systemic therapy regimen of doxorubicin, bleomycin, vinblastine and dacarbazine (ABVD) but it remains unclear whether the pulmonary toxicity is brought about by the addition of G-CSF or by the combination of chemotherapy agents itself (47,48).

Side effects: Patients using G-CSFs have reported such symptoms as injection site reactions; headaches; hepatomegaly; arthralgia (bony pain); osteoporosis; rash; alopecia; hematuria and proteinuria. One third of patients reported bone or musculoskeletal pain, which was generally mild to moderate and managed with non-narcotic analgesics (49-51). Another reported side effect listed as uncommon, was the exacerbation of existing psoriasis.

A proportion of patients may experience leukocytosis (white blood cell count $>100 \times 10^9$/l), which has been observed in approximately 2% of patients receiving filgrastim at doses above 5mcg/kg/day (43, 52). At ANC recovery, pegfilgrastim clearance increases, resulting in a rapid decrease in serum concentrations. This results in less "overshoot" of ANC post-nadir compared with daily filgrastim (27, 53). Pegfilgrastim concentrations are negligible by day 12 and therefore unlikely to over-stimulate neutrophil production (54).

Primary Prophylaxis: G-CSF is recommended for the prevention of CIN in patients who have a high risk of FN. Oncologists and treating physicians should also consider the individual patient risk factors that can predispose a patient to increased complications from prolonged neutropenia. Risk factors can include age ≥65; poor performance status; previous episode of FN; extensive prior treatment including large radiation ports; bone marrow involvement; poor nutritional status; open wounds or active infections and co morbidities such as COPD, diabetes, uncontrolled hypertension, heart disease and kidney or liver disease. Patients should be assessed prior to beginning chemotherapy and prior to each cycle and should be supported with G-CSF where appropriate. For dose-dense chemotherapy regimens, G-CSF is required and recommended.

Secondary Prophylaxis: G-CSF is recommended for patients who have experienced a neutropenic complication from a prior cycle of chemotherapy, in which a dose reduction may compromise disease free survival or treatment outcomes. The Medical Oncology Toxicity Group recognizes that in some clinical situations, dose reductions or chemotherapy delays may be an appropriate and reasonable alternative.

Recommendations:

- All patients, with a diagnosis of cancer and receiving chemotherapy, who are deemed at risk for the development of CIN, and have no contraindications, should be offered prophylactic granulocyte-colony stimulating factor (G-CSF).
- Once a patient is supported with a G-CSF, treatment should be continued with each consecutive cycle unless otherwise contraindicated.
- For chemotherapy cycles ≥ 14 days, the options are: pegfilgrastim 6mg s/c once **OR** filgrastim s/c daily, at a dose suitable for the patient's weight, administered 24 hours post chemotherapy for 9-14 days.

- Filgrastim s/c daily for 7-10 days can be used for treatments equal to 14 days.
- For chemotherapy cycles < 14 days, filgrastim s/c should be administered at a dose suitable for the patient's weight. For patients < 75kg, filgrastim 300mcg s/c should be administered 24hrs post chemotherapy, and continued daily for 7-10 days. For patient's ≥ 75kg, filgrastim 480mcg s/c should be administered 24 hours post chemotherapy, and continued daily for 7-10 days. Pegfilgrastim should **not** be used in chemotherapy regimens that are given less than every 2 weeks.
- A complete blood count should be performed prior to each chemotherapy administration. Additional blood work may be ordered if clinically indicated, or at the discretion of the treating physician.
- The use of G-CSFs is currently **not** recommended for patients receiving Radiation Therapy.

Search Strategy:

Literature searches were conducted in Pubmed, Embase, CINAHL, and the Cochrane Library and using keywords "neutropenia" AND "growth factors" AND "chemotherapy", and also "GCSF support". Guideline searches were also carried out on the websites of North America's most highly respected cancer organizations and agencies. All selected literature articles and source guidelines were in English and dated after the year 2000 (unless the selection was an earlier landmark study) up to March 2012. The inclusion/exclusion process consisted of selecting guidelines from reputable cancer organizations, with preference given to those from Canadian sources, where possible. Six source guidelines were identified and conformed to our search criteria, from which four were selected due to currency, quality of content and/or were Canadian in origin (55-60).

The four identified source guidelines/recommendations (57-60) were put through the ADAPTE process (61) with an AGREE II assessment (62), and the NCCN "Myeloid Growth Factors" guideline was chosen to be adapted for use in our guideline (60). The NCCN guideline was selected as the optimal choice due to its applicability, quality and currency of content.

There has been much debate but no consensus on the 'grading of evidence' in Canada. Presently, Canadian experts in the field of guideline development are involved in an ongoing in-depth analysis of the functionality of grading. Until such time as a report is released of their findings, and a consensus reached on whether to assign a grade of recommendation to a guideline, this group has decided to forgo the use of grading.

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Disclaimer:

These guidelines are a statement of consensus of the Medical Oncology Toxicity Group regarding their views of currently accepted approaches to diagnosis and treatment. Any clinician seeking to apply or consult the guidelines is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient's care or treatment.

Contact Information:

For more information on this guideline, please contact Dr. Jehan Siddiqui MD FRCPC, Dr. H. Bliss Murphy Cancer Center, St. John's, NL; Telephone 709-777-7593. For the complete guideline on this topic or for access to any of our guidelines, please visit our Cancer Care Program website at www.easternhealth.ca

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Appendix

Examples of Chemotherapy Regimens with a High Risk of Febrile Neutropenia (>20%)*

Bladder Cancer
·*MVAC* (methotrexate, vinblastine, doxorubicin, cisplatin) (neoadjuvant, adjuvant, metastatic)

Breast Cancer
·docetaxel + trastuzumab (metastatic or relapsed)
·*AC » T* (doxorubicin, cyclophosphamide, paclitaxel) (adjuvant)
·*AT* (doxorubicin, paclitaxel)
·*AT* (doxorubicin, docetaxel)
·*TAC* (docetaxel, doxorubicin, cyclophosphamide) (adjuvant)
·*TC* (docetaxel, cyclophosphomide) (62)
·*FEC-100* (5-fluorouracil or 5-FU, epirubicin, cyclophosphamide) (63)
·*FEC-D* (5-FU, epirubicin, cyclophosphamide, docetaxel) (63)

Esophageal and Gastric Cancer
·docetaxel + cisplatin + fluorouracil

Non-Hodgkin's Lymphoma
·*HyperCVAD* (cyclophosphamide, vincristine, doxorubicin, dexamethasone) + retuximab
·*RICE* (rituximab, ifosfamide, carboplatin, etoposide)
·*CHOP-14* (cyclophosphamide, vincristine, procarbazine, prednisone)

Ovarian Cancer
·topotecan
·paclitaxel
·docetaxel

Pancreatic Cancer
·gemcitabine/docetaxel

Sarcoma
·doxorubicin
·*MAID* (mesna, doxorubicin, ifosfamide, dacarbazine)

Small Cell Lung Cancer
·topotecan

Kidney Cancer
·doxorubicin, gemcitabine

Testicular Cancer
·*VIP* (etoposide, ifosfamide, cisplatin)
·*BEP* (bleomycin, etoposide, cisplatin)
·*TIP* (paclitaxel, ifosfamide, cisplatin)

Bladder Cancer
·*MVAC* (methotrexate, vinblastine, doxorubicin, cisplatin)

** In general, dose dense regimens require growth factor support for chemotherapy administration. This list is not comprehensive; there are other agents/regimens that have high risk for the development of FN.*

Examples of Chemotherapy Regimens with an Intermediate Risk of Febrile Neutropenia (10-20%)*

Breast
·docetaxel Q21 days (100mg/m²)
·paclitaxel Q21 days
·epirubicin (adjuvant)
·*CMF* (cyclophosphamide, methotrexate, 5FU)
·*AC* (doxorubicin, cyclophosphamide) + sequential docetaxel (adjuvant taxane portion only)
·epirubicin + cyclophospamide + methotrexate + 5FU
·*AC* + docetaxel + trastuzumab (adjuvant)
·docetaxel (advanced/mets)
·vinblastine (recurrent/mets)

NSCLC
·cisplatin + paclitaxel
·cisplatin + vinorelbine
·cisplatin + docetaxel
·cisplatin + irinotecan
·cisplatin + etoposide
·carboplatin + paclitaxel
·docetaxel (advanced/metastatic)

SCLC
·etoposide + carboplatin

Cervix
·cisplatin + topotecan (recurrent or metastatic)
·topotecan (recurrent or metastatic)
·irinotecan (recurrent or metastatic)

Ovarian
·carboplatin + docetaxel

Uterine
·Taxotere (uterine sarcoma)

Testicular
·etoposide + cisplatin

Hodgkin Lymphoma
·*ABVD* (doxorubicin,bleomycin, vinblastine, dacarbazine)

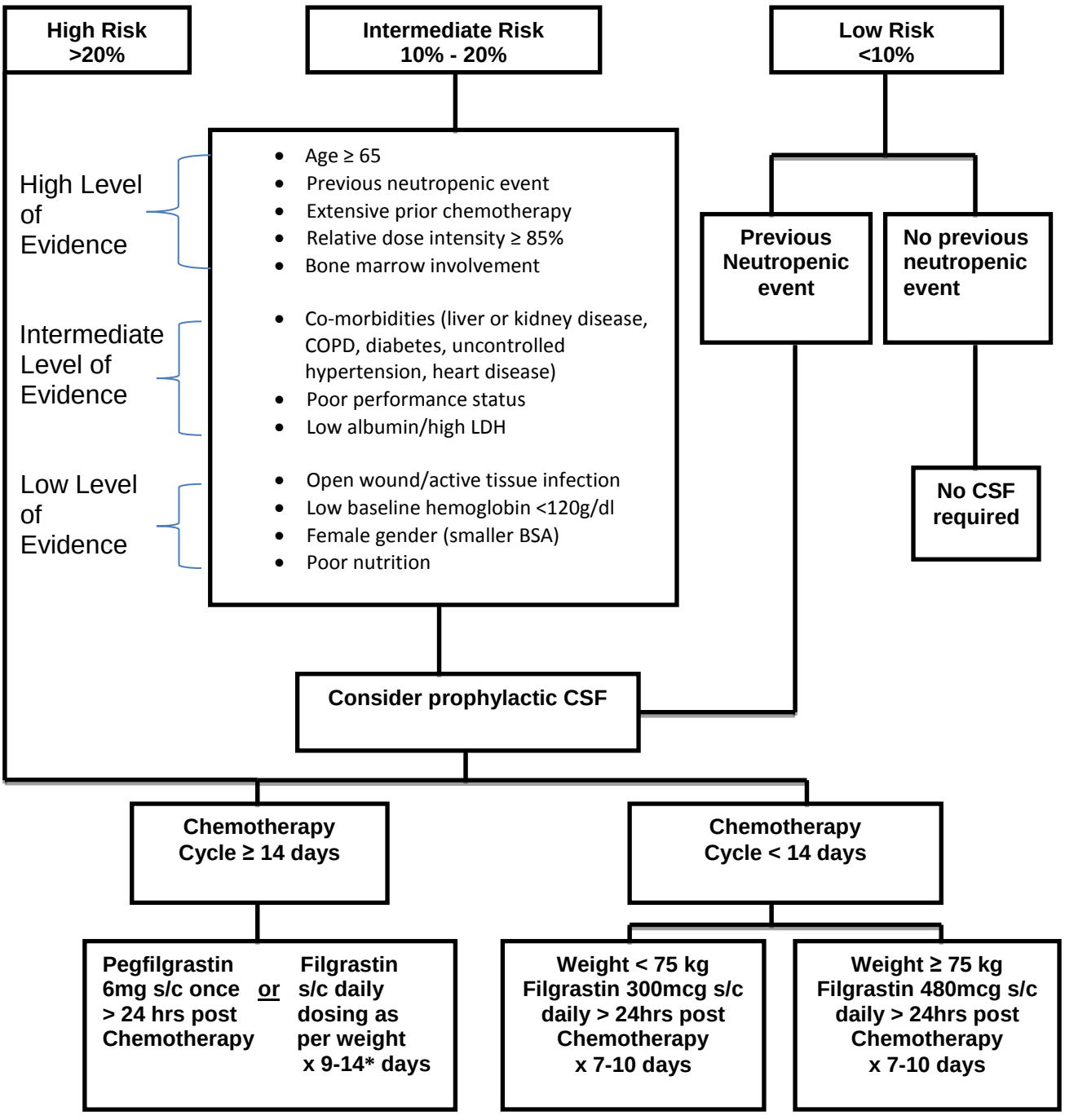
Non Hodgkin's Lymphoma
·*CHOP* + rituximab
·*GDP* (gemcitabine, dexamethasone, cisplatin) +/- rituximab

Esophageal & Gastric
·irinotecan + cisplatin
·epirubicin+ cisplatin+ 5FU

Colorectal
·*FOLFOX* (5-FU, leucovorin, oxaliplatin)

** This list is not comprehensive has there are other agents/regimens that have intermediate risk for the development of FN.*

Neutropenia Risk Assessment Tool*



NOTE: *For treatments equal to 14 days, filgrastin s/c daily x 7-10 days may be used. Once initiated-CSF treatment should be continued with each cycle.*
**Adapted from the 2010 EORTC guideline (59).*