Current standard-of-care NCCN Guidelines do not adequately address some of issues in COVID-19:

- Limited blood supply
- Possible impact on those with active infection
- Measures that might shorten or prevent hospitalization

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Neutropenia-Related Considerations

1. Expand prophylactic use of G-CSF to minimize risk of febrile neutropenia

- Change threshold for use of G-CSF with regimens from only high risk (>20% risk of febrile neutropenia) to intermediate (10%–20% risk of febrile neutropenia) or high risk.
- Thus not adding to the overwhelming number of cases in emergency rooms (ERs) and hospitals.

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Disease Setting and Chemotherapy Regimens With a High Risk For Febrile Neutropenia (>20%) Based On MGF-1 Part of NCCN 2020 Guideline

Acute Lymphoblastic Leukemia (ALL)
- Select ALL regimens as directed by treatment protocol (See NCCN Guidelines for ALL)

Bladder Cancer
- Dose-dense MVAC (methotrexate, vinblastine, doxorubicin, cisplatin)[1]

Bone Cancer
- VAI (vincristine, doxorubicin or dactinomycin, ifosfamide)[2]
- VDC-IE (vincristine, doxorubicin or dactinomycin, and cyclophosphamide alternating with ifosfamide and etoposide)[3]
- Cisplatin/doxorubicin[4]
- VDC (cyclophosphamide, vincristine, doxorubicin or dactinomycin)[5]
- VIDE (vincristine, ifosfamide, doxorubicin or dactinomycin, etoposide)[6]

Breast Cancer
- Dose-dense AC followed by dose-dense paclitaxel (doxorubicin, cyclophosphamide, paclitaxel)[7]
- TAC (docetaxel, doxorubicin, cyclophosphamide)[8]
- TC[a,b] (docetaxel, cyclophosphamide)[9]
- TCH[a] (docetaxel, carboplatin, trastuzumab)[10]

Colorectal Cancer

FOLFOXIRI (fluorouracil, leucovorin, oxaliplatin, irinotecan)[11]

Head and Neck Squamous Cell Carcinoma
- TPF (docetaxel, cisplatin, 5-fluorouracil)[12-14]

Hodgkin Lymphoma
- Brentuximab vedotin + AVD (doxorubicin, vinblastine, dacarbazine)[15]
- Escalated BEACOPP[c] (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone)[16]

Kidney Cancer
- Doxorubicin/gemcitabine[17]

Non-Hodgkin's Lymphomas
- Dose-adjusted EPOCH[a] (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin)[18]
- ICE (ifosfamide, carboplatin, etoposide)[a,19,20]
- Dose-dense CHOP-14[a] (cyclophosphamide, doxorubicin, vincristine, prednisone)[21,22]
- MINE[a] (mesna, ifosfamide, mitoxantrone, etoposide)[23]
- DHAP[a] (dexamethasone, cisplatin, cytarabine)[24]
- ESHAP[a] (etoposide, methylprednisolone, cisplatin, cytarabine)[25]
- HyperCVAD[a] (cyclophosphamide, vincristine, doxorubicin, dexamethasone)[26,27]

Melanoma
- Dacarbazine-based combination with IL-2, interferon alfa (dacarbazine, cisplatin, vinblastine, IL-2, interferon alfa)[28]

Multiple Myeloma
- DT-PACE (dexamethasone/thalidomide/cisplatin/doxorubicin/cyclophosphamide/etoposide)[29] ± bortezomib (VTD-PACE)[30]

Ovarian Cancer
- Topotecan[a,31]
- Docetaxel[32]

Pancreatic Cancer

FOLFIRINOX[d] (fluorouracil, leucovorin, irinotecan, oxaliplatin)

Soft Tissue Sarcoma
- MAID (mesna, doxorubicin, ifosfamide, dacarbazine)[33]
- Doxorubicin[a,34]
- Ifosfamide/doxorubicin[35]

Small Cell Lung Cancer
- Topotecan[36]

Testicular Cancer
- VeIP (vinblastine, ifosfamide, cisplatin)[37]
- VIP (etoposide, ifosfamide, cisplatin)
- TIP (paclitaxel, ifosfamide, cisplatin)[38]

See Disease Settings and Chemotherapy Regimens with an Intermediate Risk for Febrile Neutropenia, MGF-A (2 of 5)

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Disease Setting and Chemotherapy Regimens With a Intermediate For Febrile Neutropenia (10-20%) Based On MGF-1 Part of NCCN 2020 Guideline

Occult Primary- Adenocarcinoma
- Gemcitabine/docetaxel[41]

Breast Cancer
- Docetaxel[a,42,43]
- AC (doxorubicin, cyclophosphamide) + sequential docetaxel (taxane portion only)[a,44]
- Paclitaxel every 21 days[a,45]

Cervical Cancer
- Cisplatin/topotecan[46-48]
- Paclitaxel/cisplatin[a,48]
- Topotecan[49]
- Irinotecan[50]

Colorectal Cancer
FOLFOX[a] (fluorouracil, leucovorin, oxaliplatin)[e,51]

Esophageal and Gastric Cancers
- Irinotecan/cisplatin[a,52]
- Epirubicin/cisplatin/5-fluorouracil[53]
- Epirubicin/cisplatin/capecitabine[53]

Non-Hodgkin's Lymphomas
- GDP (gemcitabine, dexamethasone, cisplatin/carboplatin)[a,54]
- CHOP[a] (cyclophosphamide, doxorubicin, vincristine, prednisone)[55,56] including regimens with pegylated liposomal doxorubicin[57,58]
- CHP (cyclophosphamide, doxorubicin, prednisone) + brentuximab vedotin
- Bendamustine[a]

Non-Small Cell Lung Cancer
- Cisplatin/paclitaxel[59]
- Cisplatin/vinorelbine[60]
- Cisplatin/docetaxel[59,61]
- Cisplatin/etoposide[62]
- Carboplatin/paclitaxel[a,f,63]
- Docetaxel[61]

Ovarian Cancer
- Carboplatin/docetaxel[64]

Prostate Cancer
- Cabazitaxel[g,65]

Small Cell Lung Cancer
- Etoposide/carboplatin[66]

Testicular Cancer
- BEP[h] (bleomycin, etoposide, cisplatin)[67-69]
- Etoposide/cisplatin[70]

Uterine Sarcoma
- Docetaxel[71]

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Neutropenia-Related Considerations

2. Expand therapeutic use if patients previously not on G-CSF develop febrile neutropenia

- To include all patients, not just those with a risk factor for complication. The primary goal would be to minimize days of hospitalization.

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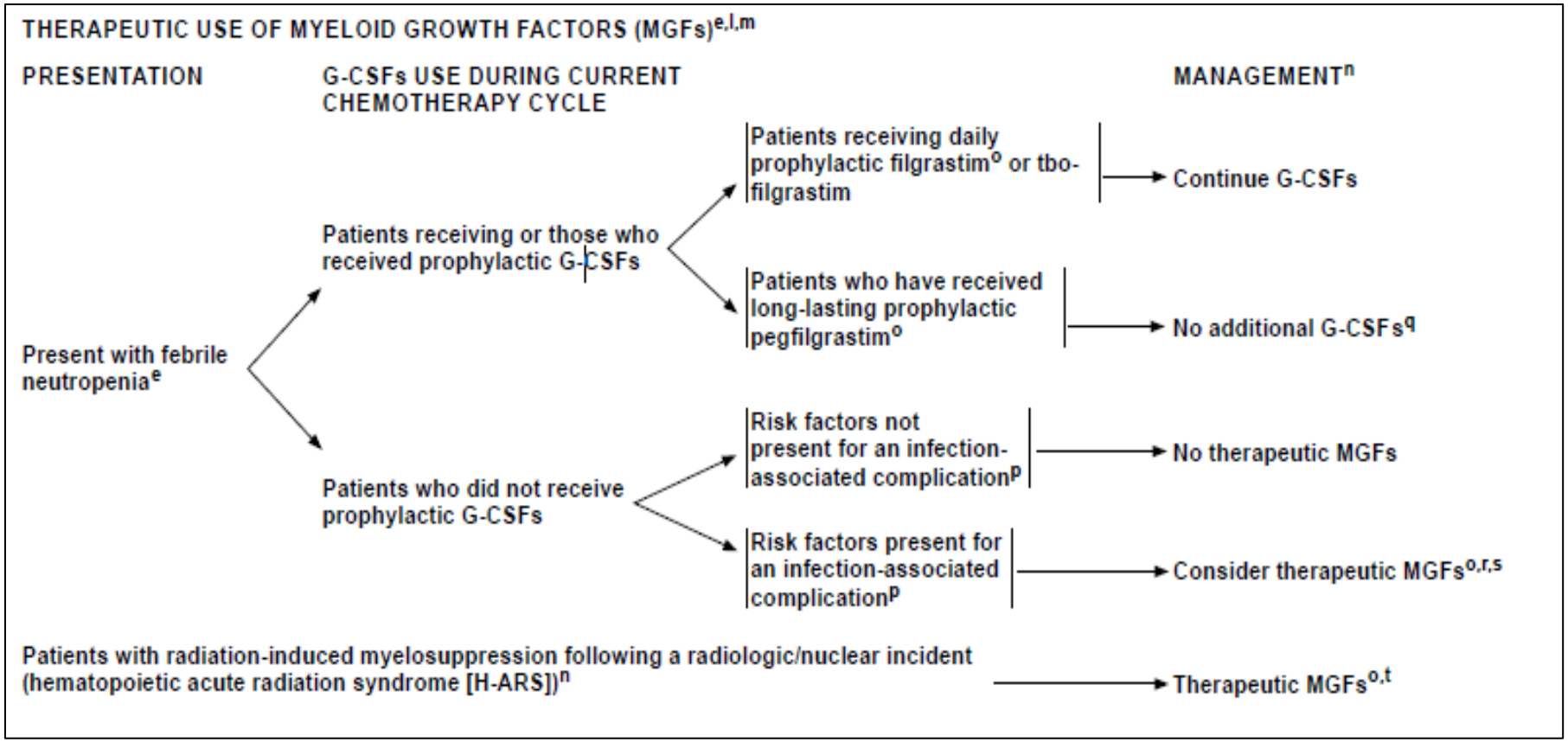
Therapeutic Use of Myeloid Growth Factors Based On MGF-4 Part of NCCN 2020 Guideline



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Neutropenia-Related Considerations

3. Consider use of G-CSF to accelerate post-hematopoietic cell transplant recovery of absolute neutrophil count (ANC)

- To minimize days of hospitalization

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Myeloid Growth Factors In Mobilization and Post Hematopoietic Cell Transplant Based On MGF-C Part of NCCN 2020 Guideline

MYELOID GROWTH FACTORS IN MOBILIZATION AND POST HEMATOPOIETIC CELL TRANSPLANT

Effective mobilization regimens include growth factor alone, chemotherapy and growth factor combined, and incorporation of plerixafor with either approach.

Mobilization of Hematopoietic Progenitor Cells in Autologous Setting

- Single-agent growth factor:[1-3]
  - Filgrastim[a] or tbo-filgrastim
    - Dose: 10–32 mcg/kg per day by subcutaneous injection, in daily or twice-daily dosing. Begin apheresis on day 4 or 5 and continue until leukapheresis.
- Combination chemotherapy followed by filgrastim[a] or tbo-filgrastim with the goal of mobilization during count recovery[4-6] that may result in higher collection yields with fewer days of apheresis but increased rate of hospitalizations for neutropenic fever.[7] This approach may also reduce burden of residual tumor.
  - Filgrastim[a] or tbo-filgrastim is started about 24 hours after completion of chemotherapy.
- Concurrent filgrastim[a] + sargramostim (category 2B)
  - Filgrastim[a] 7.5 mcg/kg each morning, sargramostim 7.5 mcg/kg each evening, and leukapheresis beginning on day 5.[8]
- Filgrastim[a] or tbo-filgrastim + plerixafor[9-14]
  - Plerixafor is FDA approved in combination with G-CSFs for the purpose of mobilizing autologous hematopoietic stem cells to the peripheral blood in patients with non-Hodgkin's lymphoma and multiple myeloma.
  - Existing literature suggests that a preemptive "just in time" strategy of adding plerixafor for patients who do not mount a sufficient CD34+ cell count is highly successful.[15-17]
  - There are limited data on parameters for predicting poor mobilization and which patients may benefit from upfront use of plerixafor. Risk factors that have been associated with poor mobilization include older age, extensive prior therapy, prior radiation to marrow-containing regions, or multiple cycles of certain agents such as fludarabine or lenalidomide. See Discussion.
  - Dosing for MGF and plerixafor: See MGF-C (2 of 4)

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Myeloid Growth Factors In Mobilization and Post Hematopoietic Cell Transplant Based On MGF-C Part of NCCN 2020 Guideline

MYELOID GROWTH FACTORS IN MOBILIZATION AND POST HEMATOPOIETIC CELL TRANSPLANT

- Dosing for MGF and plerixafor:
  - Filgrastim or tbo-filgrastim dose: 10 mcg/kg per day x 4 days.
  - On the evening of day 4 of growth factors, start plerixafor by subcutaneous injection 11 hours prior to initiation of apheresis (day 5 collection the next morning).
  - Repeat plerixafor dose up to 4 consecutive days.
  - Recommended plerixafor dose:[d]

Estimated Creatinine Clearance	Dose	
	Body weight ≤83 kg	Body weight >83 kg and <160 kg
>50 (mL/min)	20 mg or 0.24 mg/kg once daily	0.24 mg/kg once daily (not to exceed 40 mg/day)
≤50 (mL/min)	13 mg or 0.16 mg/kg once daily	0.16 mg/kg once daily (not to exceed 27 mg/day)

Mobilization of Allogeneic Donors

- Allogeneic hematopoietic cell donors:[18-21]
  - Filgrastim[a] or tbo-filgrastim (category 2B)
    - Dose: 10–16 mcg/kg per day by subcutaneous injection, start collection on day 4 or 5.[22-24]
  - Plerixafor (category 2B): Use in normal donors is under study.[25-27]
- For granulocyte transfusion:
  - Filgrastim[a] or tbo-filgrastim (category 2B)
    - Single dose: 5 mcg/kg subcutaneously with dexamethasone 10 mg PO 8–24 hours prior to collection.[28]

Supportive Care Options

- Filgrastim[a,b,29] or tbo-filgrastim
  - Post-autologous hematopoietic cell transplant, haploidentical transplant, or cord blood transplant
  - 5 mcg/kg per day. Begin day 5–7 post transplant until recovery of ANC (eg, >1.5 x 10^9/L x 2 days).[c]
- Pegfilgrastim[a,30-36]- Post-autologous hematopoietic cell transplant

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Neutropenia-Related Considerations

4. Consider self-administration of daily filgrastim or use of long-acting pegfilgrastim (1–3 days post chemotherapy)

- Consider self-administration of daily filgrastim or use of long-acting pegfilgrastim (1–3 days post chemotherapy).

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Cautionary statement

Physicians may wish to avoid use of or discontinue G-CSF in case of:

- Respiratory infection, respiratory symptoms, or confirmed or suspected COVID-19 to avoid increase in pulmonary inflammation or hypothetical risk of increasing inflammatory cytokines associated with adverse outcome.

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Anemia and ESA–Related Issues Given Regional Limited Blood Supply With the COVID-19 Pandemic

1. In the short term, broadening the use of ESA therapy +/- IV iron supplementation to manage anemia in patients with malignancy requiring blood transfusion support.

- Response to ESAs is improved with parenteral iron supplementation.
- Timing of administration of ESAs or iron could coincide with usual blood draws or visits.

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Parenteral Iron Preparations Recommendations For Administering Parenteral Iron Products Based On ANEM-B Part of NCCN 2020 Guideline

PARENTERAL IRON PREPARATIONS[1-6,a]

RECOMMENDATIONS FOR ADMINISTERING PARENTERAL IRON PRODUCTS

	Low-Molecular-Weight Iron Dextran[8,b]	Ferric Gluconate[11,b]	Iron Sucrose[14,b]	Ferric Carboxymaltose[16,17,18,b] (in select cases)	Ferumoxytol[19,20,21,b,c] (in select cases)
Test dose[d]	Test dose required: 25 mg slow IV push over 1–2 min. If tolerated, follow with 75 mg IV bolus for total dose of 100 mg.	Test dose at MD discretion based on risk for reaction	Test dose at MD discretion based on risk for reaction	Test dose at MD discretion based on risk for reaction	Test dose at MD discretion based on risk for reaction
Dosage[7,e]	100 mg IV over 5 min[3] • Repeated dosing once weekly for 10 doses to total of 1000 mg or • Total dose infusion given over several hours[9,f] ‣ Calculated total iron dextran dose in 500 mL of 0.9% NaCl solution administered at 175 mL/h[10]	125 mg IV over 60 min[2,4,5,12] • Repeated dosing given once weekly for 8 doses • Individual doses above 125 mg are not recommended based on published trial results[12] • Total treatment course = 1000 mg	200 mg IV over 60 min[6] (repeated every 2–3 wks) or 200 mg IV over 2–5 min, 5 times within 14 days • Individual doses over 300 mg are not recommended[15] • Total treatment course = 1000 mg	750 mg IV for patients weighing ≥50 kg (110 lbs) • Repeat dose once at least 7 days later • Total treatment course = 1500 mg or 15 mg/kg body weight IV for patients <50 kg (110 lbs) • Repeat dose once at least 7 days later • Total treatment course not to exceed 1500 mg	510 mg IV dose over 15 min • Repeat 510 mg dose 3–8 days later • Total treatment course = 1020 mg
Routes	IV; IM (not recommended)	IV	IV	IV	IV

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Anemia and ESA–Related Issues Given Regional Limited Blood Supply With the COVID-19 Pandemic

2. Consider for alternatives during severely limited blood supply; broaden use of guidelines for those "who refuse blood transfusions" to include when transfusion support is not available

- Limited blood draws (reduce frequency, reduce volume).
- Utility of iron infusions in improving response to ESAs with transferrin saturation <50%, ferritin <800 (concept of "functional" iron deficiency).
- Assessment of baseline values for B12 and folate and consider nutritional supplements: B12 500–1000 mcg PO daily and folate 1 mg PO daily.

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Management of Cancer And Chemotherapy-Induced Anemia For Patients Who Refuse Blood Transfusions Based On ANEM-C Part of NCCN 2020 Guideline

MANAGEMENT OF CANCER- AND CHEMOTHERAPY-INDUCED ANEMIA FOR PATIENTS WHO REFUSE BLOOD TRANSFUSIONS[1-8]

- There are limited available data on the best management of cancer- and chemotherapy-induced anemia for patients who refuse blood transfusions.
- In extreme cases of severe, life-threatening anemia, pure oxygen (400 mm Hg, SaO2 = 1.0) by mechanical ventilation has been used to increase blood oxygenation.
- To reduce blood loss, minimize phlebotomy, use pediatric tubes, return discard in closed system, and batch test.
- Prior to initiation of myelosuppressive chemotherapy:
  - Consider anemia risk when making treatment decisions
  - Consider daily folic acid and B_{12} supplementation
  - Evaluate and correct baseline coagulation abnormalities
  - In patients with high clinical suspicion of folate and vitamin B_{12} deficiency, nutritional deficiency should be ruled out and iron deficiency should be corrected using intravenous (IV) iron.
- Consider use of ESAs for select patients by FDA dosing/dosing adjustments, given there is no option for transfusion.
  - ESAs are NOT recommended for:
    - Patients with cancer not receiving chemotherapy
    - Patients receiving non-myelosuppressive therapy
  - Therefore, if ESAs are prescribed off-label for the indications listed immediately above, patients should be made aware of the potential increased risks of thrombosis and tumor progression, and should know that under these circumstances the ESAs are being used off-label.
- Blood substitutes
  - A clinician may obtain access to investigational blood substitute products for a single patient by submitting an Expanded Access - Investigational New Drug Application (IND) through the FDA.[4]

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Cautionary statement

Use the lowest dose of ESA sufficient to avoid transfusion

- An increased risk of thrombosis has been observed with ESAs. Therefore, use the lowest dose of ESA sufficient to avoid transfusion. For example, hold ESA for Hgb ≥10.

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