CHILDREN'S ONCOLOGY GROUP

The world's childhood cancer experts

COG Supportive Care Endorsed Guidelines

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The Children's Oncology Group (COG) Supportive Care Endorsed Guidelines are comprised of evidence-based guidelines which have been developed by other organizations and endorsed by the COG. The COG guideline endorsement process is available on the COG Supportive Care Guidelines webpage. The endorsed guideline developers' assessment of the strength of each recommendation and the quality of the evidence to support the recommendation is provided whenever possible (see Appendix 1). When the endorsed guideline developers used another method to communicate the strength of each recommendation and the quality of the evidence to support the recommendation, the method is provided in the guideline summary.

To discuss any aspect of the COG Supportive Care Guidelines please contact a member of the COG Supportive Care Guideline Committee.

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1. Guideline for Antibacterial Prophylaxis Administration in Pediatric Cancer and Hematopoietic Stem Cell Transplantation

The "Guideline for Antibacterial Prophylaxis Administration in Pediatric Cancer and Hematopoietic Stem Cell Transplantation" developed by the Pediatric Oncology Group of Ontario was endorsed by the COG Supportive Care Guideline Committee in June 2020.

The source clinical practice guideline is published (Lehrnbecher T, Fisher BT, Phillips B, et al. Guideline for antibacterial prophylaxis administration in pediatric cancer and hematopoietic stem cell transplantation. *Clinical Infectious Diseases* 2020; 71 (1): 226-36.) and is available at: https://doi.org/10.1093/cid/ciz1082.

The purpose of the source clinical practice guideline is to provide recommendations for systemic antibacterial prophylaxis administration in pediatric patients with cancer and recipients of hematopoietic stem cell transplant. These recommendations are presented in the table below.

Summary of Recommendations for Antibacterial Prophylaxis Administration in Pediatric Cancer and Hematopoietic Stem Cell Transplantation

RECOMMENDATIONS	Strength of Recommendation and Quality of Evidence*
Which pediatric patients with cancer and HSCT recipients (if any) should routinely receive systemic antibacterial prophylaxis?	
1. Consider systemic antibacterial prophylaxis administration in children with AML and relapsed ALL receiving intensive chemotherapy expected to result in severe neutropenia (absolute neutrophil count <500/µL) for at least 7 days. *Remarks*: This is a weak recommendation because the benefits of prophylaxis were closely balanced against its known and potential impacts on resistance. The panel valued what is known about efficacy and resistance outcomes of prophylaxis administered within the finite time frame of a clinical trial among enrolled participants but also considered the less certain impacts of a universal prophylaxis strategy at both the patient and institutional level. Limiting prophylaxis to patient populations at highest risk of fever and neutropenia, bacteremia, and infection-related mortality could limit antibiotic utilization to those most likely to benefit from prophylaxis. Careful discussion with patients and families about the potential risks and benefits of prophylaxis is important. Understanding local resistance epidemiology is critical to the decision of whether to implement prophylaxis.	Weak recommendation High-quality evidence

RECOMMENDATIONS	Strength of Recommendation and Quality of Evidence*
2. We suggest that systemic antibacterial prophylaxis not be used routinely for children receiving induction chemotherapy for newly diagnosed ALL. *Remarks:* The panel acknowledged the paucity of direct contemporary randomized data applicable to children living in high-income countries. A recommendation to provide universal systemic prophylaxis to this group could have a substantial impact on institutions, given that ALL is the most common cancer diagnosis in children. There is great variability in duration of neutropenia and risk of bacteremia based on treatment protocol and patient-level characteristics. Further data are required to identify subgroups of pediatric patients with ALL who might particularly benefit from prophylaxis.	Weak recommendation Low-quality evidence
3. Do not use systemic antibacterial prophylaxis for children whose therapy is not expected to result in severe neutropenia (absolute neutrophil count severe neutropenia (absolute neutrophil count <500/µL) for at least 7 days. *Remarks*: This strong recommendation was based on reduced chance of benefit combined with continued risk of harm associated with systemic antibacterial prophylaxis.	Strong recommendation Moderate-quality evidence
4. We suggest that systemic antibacterial prophylaxis not be used routinely for children undergoing autologous HSCT. *Remarks:* This weak recommendation against routine use of antibacterial prophylaxis in autologous HSCT recipients acknowledged the risk reduction of bacteremia among this cohort. However, the panel believed that the lower baseline risk of bacteremia resulted in the impact on resistance (known and potential) outweighing the benefits. The moderate quality of evidence reflected the lack of granular data specifically in autologous HSCT recipients rather than HSCT patients as a group.	Weak recommendation Moderate-quality evidence
5. We suggest that systemic antibacterial prophylaxis not be used routinely for children undergoing allogeneic HSCT. *Remarks*: The panel acknowledged that the granularity of available data did not allow a different recommendation for allogeneic compared with autologous HSCT recipients. However, the panel noted that allogeneic HSCT recipients often have preceding conditions that could be associated with prophylaxis (eg, AML or relapsed ALL) and have prolonged neutropenia during the HSCT process, which could influence the effectiveness and adverse effects associated with prophylaxis.	Weak recommendation Moderate-quality evidence

RECOMMENDATIONS	Strength of Recommendation and Quality of Evidence*
Which agents should be used for systemic antibacterial prophylaxis in children with cancer and HSCT recipients?	
6.Levofloxacin is the preferred agent if systemic antibacterial prophylaxis is planned. *Remarks:* The strong recommendation to use levofloxacin is related to direct contemporary data in children and its microbiological spectrum of activity. If levofloxacin is not available or not able to be used, ciprofloxacin is an alternative, although lack of activity against gram-positive bacteria including viridans group streptococci may reduce the benefits of prophylaxis. Patients and families should be informed about potential short- and long-term fluoroquinolone-related adverse effects. Understanding local resistance epidemiology is critical to the decision of whether to implement fluoroquinolone prophylaxis. If fluoroquinolones are not available or cannot be used, providing no systemic antibacterial prophylaxis is an important option to consider.	Strong recommendation Moderate-quality evidence
When should systemic antibacterial prophylaxis be started and stopped?	
7.If systemic antibacterial prophylaxis is planned, we suggest that administration be restricted to the expected period of severe neutropenia (absolute neutrophil count <500/µL). *Remarks*: This is a weak recommendation based on low-quality evidence because there are no trials that compared different start and stop criteria. In general, trials administered prophylaxis during severe neutropenia and thus this recommendation reflects the available evidence and the panel's desire to minimize duration of prophylaxis administration.	Weak recommendation Low-quality evidence

*see Appendix 1

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2. Clinical Practice Guideline for Systemic Antifungal Prophylaxis in Pediatric Patients with Cancer and Hematopoietic Stem-Cell Transplantation Recipients

The "Clinical Practice Guideline for Systemic Antifungal Prophylaxis in Pediatric Patients with Cancer and Hematopoietic Stem-Cell Transplantation Recipients" developed by the Pediatric Oncology Group of Ontario was endorsed by the COG Supportive Care Guideline Committee in August 2020.

The source clinical practice guideline is published (Lehrnbecher T, Fisher BT, Phillips B, et al. Clinical practice guideline for systemic antifungal prophylaxis in pediatric patients with cancer and hematopoietic stem-cell transplantation recipients. JCO 2020; [ePub May 27, 2020]) and is available at: https://ascopubs.org/doi/full/10.1200/JCO.20.00158

The purpose of the source clinical practice guideline is to provide recommendations for systemic antifungal prophylaxis administration in pediatric patients with cancer and hematopoietic stem cell transplant recipients. These recommendations are presented in the table below.

Summary of Recommendations for Systemic Antifungal Prophylaxis in Pediatric Patients with Cancer and Hematopoietic Stem-Cell Transplantation Recipients

RECOMMENDATIONS	Strength of Recommendation and Quality of Evidence*
Which pediatric patients with cancer and HSCT recipients should routinely receive systemic antifungal prophylaxis?	
Acute myeloid leukemia	
1. Administer systemic antifungal prophylaxis to children and adolescents receiving treatment of acute myeloid leukemia that is expected to result in profound and prolonged neutropenia. *Remarks*: This strong recommendation is based on the increasing benefit of systemic antifungal prophylaxis versus no prophylaxis to reduce proven or probable invasive fungal disease (IFD) as the risk for IFD increases. Although this recommendation advocates for a universal prophylaxis approach, future research should identify patient and treatment factors that may allow tailoring of prophylaxis to those at the highest risk for IFD.	Strong recommendation High-quality evidence

RECOMMENDATIONS	Strength of Recommendation and Quality of Evidence*
Acute lymphoblastic leukemia	
2. Consider administering systemic antifungal prophylaxis to children and adolescents with newly diagnosed and relapsed acute lymphoblastic leukemia at high risk for IFD. *Remarks:* Children and adolescents with acute lymphoblastic leukemia encompass a group with wide variability in IFD risk that is not solely accounted for by relapse status. Those with relapsed acute lymphoblastic leukemia receiving intensive myelosuppressive chemotherapy are most likely to warrant systemic antifungal prophylaxis, whereas greater uncertainty is present for those with newly diagnosed acute lymphoblastic leukemia. Given the heterogeneity in IFD risk across protocols overall and by phase of treatment, adaptation will be required for each protocol to recommend whether and when systemic antifungal prophylaxis should be administered.	Weak recommendation Low-quality evidence
3. Do not routinely administer systemic antifungal prophylaxis to children and adolescents with acute lymphoblastic leukemia at low risk for IFD. *Remarks*: A low risk for IFD can be inferred based on absence of risk factors such as prolonged neutropenia and corticosteroid administration and observed IFD rates across different protocols. This group includes, for example, pediatric patients receiving maintenance chemotherapy for acute lymphoblastic leukemia.	Strong recommendation Low-quality evidence
Other malignancies including most patients with lymphomas and solid tumors	
4. Do not routinely administer systemic antifungal prophylaxis to children and adolescents with cancer at low risk for IFD, such as most pediatric patients with lymphomas and solid tumors. *Remarks:* In pediatric patients at low risk for IFD, the benefit of systemic antifungal prophylaxis is likely to be small and outweighed by the risk for adverse effects, costs, and inconvenience. Thus, systemic antifungal prophylaxis should not routinely be administered in this setting.	Strong recommendation Moderate-quality evidence

RECOMMENDATIONS	Strength of Recommendation and Quality of Evidence*
HSCT	
5. Administer systemic antifungal prophylaxis to children and adolescents undergoing allogeneic HSCT pre-engraftment and to those receiving systemic immunosuppression for the treatment of graft-versus host disease. *Remarks*: The panel recognized that these two phases of therapy are associated with different epidemiology of IFD. However, the nature of the trials included in the systematic review precluded the ability to make separate recommendations for them. This strong recommendation was influenced by the finding in the systemic prophylaxis versus no systemic prophylaxis stratified analysis that HSCT recipients experienced greater benefit in IFD reduction compared with chemotherapy recipients. In addition, the subgroup analysis showed that among the HSCT stratum, prophylaxis significantly reduced fungal infection–related mortality.	Strong recommendation Moderate-quality evidence
6. We suggest that systemic antifungal prophylaxis not be used routinely in children and adolescents undergoing autologous HSCT. *Remarks*: This weak recommendation was based on the lower risk for IFD associated with autologous HSCT. There is less certainty in the setting of tandem transplantations where the cumulative duration of neutropenia may be longer.	Weak recommendation Low-quality evidence
If systemic antifungal prophylaxis is planned, which agents should be used?	
7. If systemic antifungal prophylaxis is warranted, administer a mold-active agent. *Remarks:* This strong recommendation was based on the comparison of different systemic antifungal prophylaxis agents where mold-active agent versus fluconazole significantly reduced proven or probable IFD, mold infection, and invasive aspergillosis (IA), and reduced fungal infection–related mortality. Direct pediatric data were available, increasing quality of the evidence.	Strong recommendation High-quality evidence
8. In choosing a mold-active agent, administer an echinocandin or a mold-active azole. *Remarks*: The choice of specific mold-active agent is influenced by multiple factors including local epidemiology, adverse effect profile, potential for drug interactions, costs, and jurisdictional availability. For children younger than 13 years of age, an echinocandin, voriconazole, or itraconazole is suggested based on efficacy and adverse effects. In those 13 years of age and older, posaconazole also is an option.	Strong recommendation Moderate-quality evidence

RECOMMENDATIONS	Strength of Recommendation and Quality of Evidence*
9. Do not use amphotericin routinely as systemic antifungal prophylaxis. *Remarks*: This strong recommendation was based on the finding that both conventional and lipid formulations of amphotericin were not more effective than fluconazole in reducing IFD. It is important to note that liposomal amphotericin was not included in studies comparing amphotericin versus fluconazole and, thus, there is less certainty about the benefits and risks of this formulation.	Strong recommendation Low-quality evidence
When should systemic antifungal prophylaxis be started and stopped?	
10. If systemic antifungal prophylaxis is warranted, consider administration during periods of observed or expected severe neutropenia. For allogeneic HSCT recipients, consider administration during systemic immunosuppression for graft-versus-host disease treatment. *Remarks*: There are limited data that inform the decision of when to initiate and discontinue systemic antifungal prophylaxis. This recommendation was based on the criteria used in the included randomized trials and the anticipated highest risk period.	Weak recommendation Low-quality evidence

*see Appendix 1

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3. Atraumatic (pencil-point) versus conventional needles for lumbar puncture: a clinical practice guideline

The "Atraumatic (pencil-point) versus conventional needles for lumbar puncture: a clinical practice guideline" developed by the MAGIC group and The BMJ was endorsed by the COG Supportive Care Guideline Committee in May 2019.

The source guideline is published (Rochwerg B, Almenawer SA, Siemieniuk RAC, Vandvik PO, Agoritsas T, Lytvyn L, et al. BMJ 2018; 361:k1920.) and is available at:
https://www.bmj.com/content/361/bmj.k1920

The purpose of the source clinical practice guideline is to create a recommendation on the type of needle (atraumatic versus conventional) that should be used when performing a lumbar puncture. The recommendation from the endorsed clinical practice guideline is presented in the table below.

Recommendation on atraumatic (pencil-point) versus conventional needles for lumbar puncture

RECOMMENDATION	Strength of Recommendation and Quality of Evidence*
Which needles should be used for lumbar puncture for any indication?	
We recommend the use of atraumatic over conventional needles in lumbar puncture for any indication in all patients (adults and children).	Strong recommendation Moderate to high quality evidence

*see Appendix 1

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4. Guidelines on Chemotherapy-induced Nausea and Vomiting in Pediatric Cancer Patients

This document summarizes four clinical practice guidelines on the topic of chemotherapy-induced nausea and vomiting:
I. The "Classification of the Acute Emetogenicity of Chemotherapy in Pediatric Patients: A Clinical Practice Guideline" (endorsed by the COG Supportive Care Guideline Committee in August 2019).
II. The "Guideline for the Prevention of Acute Nausea and Vomiting due to Antineoplastic Medication in Pediatric Cancer Patients" (endorsed by the COG Supportive Care Guideline Committee in January 2018) and the "Antiemetics: ASCO Guideline Update" (endorsed by the COG Supportive Care Guideline Committee in December 2020) and
III. The "Guideline for the Treatment of Breakthrough and Treatment of Refractory Chemotherapy-induced Nausea and Vomiting in Pediatric Cancer Patients" (endorsed by the COG Supportive Care Guideline Committee in October 2016).

4.1 Classification of Chemotherapy Emetogenicity

The "Classification of the Acute Emetogenicity of Chemotherapy in Pediatric Patients: A Clinical Practice Guideline" developed by the Pediatric Oncology Group of Ontario was endorsed by the COG Supportive Care Guideline Committee in August 2019.

The source guideline is published (Paw Cho Sing E, Robinson PD, Flank J et al. Pediatr Blood Cancer. 2019; 66: e27646.) and is available at https://onlinelibrary.wiley.com/doi/epdf/10.1002/pbc.27646. It is an update of an earlier guideline that was published in 2011.

The purpose of this guideline is to provide evidence-based recommendations regarding the acute emetic potential of chemotherapy in pediatric oncology patients aged 1 month to 18 years. The recommendations of the endorsed guideline are presented below.

Summary of Recommendations for the Classification of Chemotherapy Emetogenicity

RECOMMENDATIONS	Strength of Recommendation and Quality of Evidence*
1. Which chemotherapy regimens are highly emetogenic?	
Single-agent regimens: Asparaginase (*Erwinia*) IV ≥ 20,000 IU/m^2/dose Busulfan IV ≥ 0.8mg/kg/dose Busulfan PO ≥ 1mg/kg/dose Carboplatin IV ≥ 175 mg/m^2/dose Cisplatin IV ≥ 12 mg/m^2/dose Cyclophosphamide IV ≥ 1,200 mg/m^2/dose Cytarabine IV ≥ 3g/m^2/day Dactinomycin IV ≥ 1.35 mg/m^2/dose Doxorubicin IV ≥ 30 mg/m^2/dose Idarubicin PO ≥ 30 mg/m^2/dose Melphalan IV Methotrexate IV ≥ 12 g/m^2/dose	Strong recommendation Very low to high quality of evidence

RECOMMENDATIONS	Strength of Recommendation and Quality of Evidence*
Multiple-agent regimens: Cyclophosphamide ≥ 600 mg/m^2/dose + dactinomycin ≥ 1 mg/m^2/dose Cyclophosphamide ≥ 400 mg/m^2/dose + doxorubicin ≥ 40 mg/m^2/dose Cytarabine IV ≥ 90 mg/m^2/dose + methotrexate IV ≥ 150 mg/m^2/dose Cytarabine IV + teniposide IV Dacarbazine IV ≥ 250 mg/m^2/dose + doxorubicin IV ≥ 60 mg/m^2/dose Dactinomycin IV ≥ 900 µg/m^2/dose + ifosfamide IV ≥ 3 g/m^2/dose Etoposide IV ≥ 60 mg/m^2/dose + ifosfamide IV ≥ 1.2 g/m^2/dose Etoposide IV ≥ 250 mg/m^2/dose + thiotepa IV ≥ 300 mg/m^2/dose	
2. Which single-agent and multiple-agent chemotherapy regimens are moderately emetogenic?	
Single-agent regimens: Cyclophosphamide IV 1000 mg/m^2/dose Cytarabine IV 75 mg/m^2/dose Dactinomycin IV 10 µg/kg/dose Doxorubicin IV 25 mg/m^2/dose Gemtuzumab IV 3–9mg/m^2/dose Imatinib PO > 260 mg/m^2/day Interferon alpha IV 15–30 million U/m^2/day Ixabepilone IV 3–10 mg/m^2/dose Methotrexate IV 5 g/m^2/dose Methotrexate IT Topotecan PO 0.4–2.3 mg/m^2/day Multiple-agent regimens: Cytarabine IV 100 mg/m^2/dose + daunorubicin IV 45 mg/m^2/dose + etoposide IV 100 mg/m^2/dose + prednisolone PO + thioguanine PO 80mg/m^2/dose Cytarabine 60 or 90 mg/m^2/dose + methotrexate 120 mg/m^2/dose Liposomal doxorubicin IV 20–50 mg/m^2/dose + topotecan PO 0.6mg/m^2/day	Strong recommendation Very low to high quality of evidence

RECOMMENDATIONS	Strength of Recommendation and Quality of Evidence*
3. Which single-agent and multiple-agent chemotherapy regimens are of low emetogenicity?	
Single-agent regimens: Cyclophosphamide IV 500 mg/m^2/dose Cyclophosphamide PO2–3 mg/kg/dose Dasatinib PO 60–120 mg/m^2/dose Erlotinib PO 35–150 mg/m^2/day Everolimus PO 0.8–9mg/m^2/day Gefitinib PO 150–500 mg/m^2/day Imatinib PO 260 mg/m^2/day Mafosfamide IT 1–6.5 mg/dose Melphalan PO 0.2 mg/kg/dose Mercaptopurine PO ≤ 4.2mg/kg/dose Methotrexate 38–83 mg/m^2/dose IV Mitoxantrone IV ≤ 33 mg/m^2/dose Procarbazine PO 50–100 mg/m^2/day Ruxolitinib PO 15–21 mg/m^2/dose Selumetinib PO 20–30 mg/m^2/dose Sorafenib PO 150–325 mg/m^2/dose Temozolomide PO 200 mg/m^2/dose Multiple-agent regimens: Cytarabine IV 60 mg/m^2/dose + methotrexate IV 90 mg/m^2/dose	Strong recommendation Very low to moderate quality of evidence
4. Which single-agent and multiple-agent chemotherapy regimens are minimally emetogenic?	
Single-agent regimens: Asparaginase (*E. coli*) IM ≤ 6000 IU/m^2/dose Asparaginase (*Erwinia*) IM ≤ 25 000 IU/m^2/dose Chlorambucil ≤ 0.2mg/kg/day PO Doxorubicin IV 10 mg/m^2/dose Liposomal doxorubicin IV ≤ 50 mg/m^2/dose Mercaptopurine PO ≤ 4.2mg/kg/dose Methotrexate PO/SC ≤ 10 mg/m^2/dose Pracinostat PO 25–45 mg/m^2/dose Vincristine IV ≤ 1.5mg/m^2/dose Multiple-agent regimens: Cisplatin ≤ 60 mg/m^2/dose intra-arterially + doxorubicin ≤ 30 mg/m^2/dose intra-arterially Cisplatin ≤ 60 mg/m^2/dose intra-arterially + pirarubicin ≤ 30 mg/m^2/dose intra-arterially Mercaptopurine PO ≤ 2.5mg/kg/dose + methotrexate PO ≤ 0.1mg/kg/day	Strong recommendation Very low to low quality of evidence

*see Appendix 1

4.2 **Prevention of Acute Chemotherapy-induced Nausea and Vomiting**

The "Guideline for the Prevention of Acute Nausea and Vomiting due to Antineoplastic Medication in Pediatric Cancer Patients" developed by the Pediatric Oncology Group of Ontario was endorsed by the COG in January 2018. The "Antiemetics: ASCO Update" developed by the American Society of Clinical Oncology was endorsed by the COG in December 2020.

The source guidelines are published Patel P, Robinson PD, Thackray J, et al. Pediatr Blood Cancer. 2017; 2017; 64: e26542. and Hesketh P, Kris MG, Basch E et al. JCO 2020; 38 (24): 2782-97.) and are available at: http://onlinelibrary.wiley.com/doi/10.1002/pbc.26542/epdf and https://ascopubs.org/doi/10.1200/JCO.20.01296

Implementation tools developed by the guideline developer are available at: https://www.pogo.ca/healthcare/practiceguidelines/chemotherapy-induced-nausea-and-vomiting-cinv/

The purpose of this guideline is to provide evidence-based recommendations for the prevention of acute chemotherapy-induced nausea and vomiting in children. The recommendations of the endorsed guideline are presented below.

Summary of Recommendations for the Prevention of Acute Chemotherapy-induced Nausea and Vomiting (CINV)

RECOMMENDATIONS	Strength of Recommendation and Quality of Evidence
1. What pharmacological interventions provide optimal control of acute CINV in children receiving highly emetogenic chemotherapy (HEC)?	
We recommend that: • Children ≥ 6 months old receiving HEC which is *not* known or suspected to interact with aprepitant receive: *granisetron, ondansetron or palonosetron + dexamethasone + aprepitant/fosaprepitant* • Children < 6 months old receiving HEC receive: *granisetron, ondansetron or palonosetron + dexamethasone* • Children ≥ 6 months old receiving HEC which is known or suspected to interact with aprepitant/fosaprepitant receive: *granisetron, ondansetron or palonosetron + dexamethasone* • Children ≥ 6 months old receiving HEC which is *not* known or suspected to interact with aprepitant/fosaprepitant and who cannot receive dexamethasone for CINV prophylaxis receive: *palonosetron + aprepitant/fosaprepitant* (POGO 2017 and ASCO 2020)	Strong recommendation Moderate quality evidence Strong recommendation Moderate quality evidence Strong recommendation Moderate quality evidence Strong recommendation Moderate quality evidence

RECOMMENDATIONS	Strength of Recommendation and Quality of Evidence
We suggest that: • Children < 6 months old receiving HEC and who *cannot* receive dexamethasone for CINV prophylaxis receive: *palonosetron* • Children receiving HEC which is known or suspected to interact with aprepitant/fosaprepitant and who *cannot* receive dexamethasone for CINV prophylaxis receive: *palonosetron* (POGO 2017 and ASCO 2020)	Weak recommendation Moderate quality evidence Weak recommendation Moderate quality evidence
2. What pharmacological interventions provide optimal control of acute CINV in children receiving moderately emetogenic chemotherapy (MEC)?	
We recommend that: • Children receiving MEC receive: *granisetron, ondansetron or palonosetron + dexamethasone* We suggest that: • Children ≥ 6 months old receiving MEC who *cannot* receive dexamethasone for CINV prophylaxis receive: *granisetron, ondansetron or palonosetron + aprepitant/fosaprepitant* • Children < 6 months old receiving MEC who cannot receive dexamethasone for CINV prophylaxis receive: *palonosetron* • Children receiving MEC which is known or suspected to interact with aprepitant/fosaprepitant and who *cannot* receive dexamethasone for CINV prophylaxis receive: *palonosetron* (POGO 2017 and ASCO 2020)	Strong recommendation Moderate quality evidence Weak recommendation Moderate quality evidence Weak recommendation Moderate quality evidence Weak recommendation Moderate quality evidence
3. What doses of aprepitant and palonosetron are known to be effective in children receiving chemotherapy?	
We suggest the following **aprepitant** dose for children ≥ 6 months old: *Day 1: 3 mg/kg/dose (maximum: 125mg) PO x 1;* *Days 2 and 3: 2 mg/kg/dose (maximum: 80mg) PO once daily* (POGO 2017)	Weak recommendation Moderate quality evidence
We suggest the following **palonosetron** dose for children: *1 month to < 17 years: 0.02 mg/kg/dose (maximum 1.5 mg) IV once pre-therapy* *≥ 17 years: 0.5 mg/dose PO once pre-therapy* (POGO 2017)	Weak recommendation Moderate quality evidence

*see Appendix 1

4.3 **Treatment of Breakthrough and Prevention of Refractory Chemotherapy-Induced Nausea and Vomiting**

The "Guideline for the Treatment of Breakthrough and Prevention of Refractory Chemotherapy-induced Nausea and Vomiting in Pediatric Cancer Patients" and the implementation tools provided by the guideline developers are available at: http://www.pogo.ca/healthcare/practiceguidelines/breakthrough-and-refractory-cinv/

A summary of the guideline is published in Pediatric Blood and Cancer 2016;63:1144–1151. http://onlinelibrary.wiley.com/doi/10.1002/pbc.25955/epdf

The purpose of this guideline is to provide evidence-based recommendations to optimize breakthrough and refractory CINV control in children. The recommendations of the endorsed guideline are presented below.

Summary of Recommendations for the Treatment of Breakthrough and the Prevention of Refractory Chemotherapy-induced Nausea and Vomiting

RECOMMENDATIONS	Strength of Recommendation and Quality of Evidence
1. What interventions are recommended to treat breakthrough CINV in children? *Breakthrough CINV is defined as* nausea and/or vomiting presumed to be attributable to antineoplastic chemotherapy and with no other pathological cause that occurs during the acute or delayed phase despite CINV prophylaxis.	
For children receiving acute CINV prophylaxis recommended for minimally, low, or moderately emetogenic chemotherapy, clinicians should upgrade or escalate the acute CINV prophylaxis provided to that recommended for chemotherapy of the next higher level of emetogenic risk.	Strong recommendation Low quality evidence
For children receiving acute CINV prophylaxis recommended for highly emetogenic chemotherapy, we suggest that olanzapine be added to guideline-consistent CINV prophylaxis.	Weak recommendation Low quality evidence
For children receiving acute CINV prophylaxis recommended for highly emetogenic chemotherapy and who cannot receive olanzapine, we suggest that one of the following antiemetic agents be added to guideline-consistent CINV prophylaxis: • methotrimeprazine (also known as levomepromazine) or • metoclopramide (in children older than 1 year) Given the possibility of extrapyramidal reactions with these agents, the risks and benefits of their use should be weighed carefully and co-administration of prophylaxis aimed at preventing extrapyramidal symptoms (EPS) should be considered. Patients and families should also be educated about the possible occurrence of EPS.	Weak recommendation Very low quality evidence

RECOMMENDATIONS	Strength of Recommendation and Quality of Evidence
2. What interventions are recommended to prevent CINV in children who have refractory CINV? *Refractory CINV is defined as* nausea and/or vomiting presumed to be attributable to antineoplastic chemotherapy and with no other pathological cause which occurs during the acute or delayed phase despite CINV prophylaxis in patients who have experienced breakthrough CINV in a previous chemotherapy block.	
For children receiving acute CINV prophylaxis recommended for minimally, low, or moderately emetogenic chemotherapy, clinicians should upgrade or escalate the acute CINV prophylaxis provided to that recommended for chemotherapy of the next higher level of emetogenic risk.	Strong recommendation Very low quality evidence
For children receiving acute CINV prophylaxis recommended for highly emetogenic chemotherapy, we suggest that the 5-HT3 antagonist given for CINV prophylaxis be changed from ondansetron or granisetron to palonosetron. In jurisdictions where palonosetron is not available, we suggest that granisetron be substituted for ondansetron.	Weak recommendation Very low quality evidence
For children experiencing refractory CINV despite initiation of previous recommendations and who have not previously received aprepitant because it is known or suspected to interact with the chemotherapeutic agent(s) being given, we suggest that the addition of aprepitant to acute CINV prophylaxis be considered.	Weak recommendation Low quality evidence
For children experiencing refractory CINV despite initiation of the previous recommendations, we suggest that one of the following interventions be added to the CINV prophylaxis provided: • interventions that were employed successfully for the treatment of breakthrough CINV in previous treatment blocks (olanzapine, methotrimeprazine or metoclopramide); or	Weak recommendation Very low quality evidence
• stimulation of Nei Gaun (P6) by means of acupressure or electroacupuncture.	Weak recommendation Very low quality evidence

*see Appendix 1

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5. Prevention of cisplatin-induced ototoxicity in children and adolescents with cancer: a clinical practice guideline

The clinical practice guideline "Prevention of cisplatin-induced ototoxicity in children and adolescents with cancer" developed by the Pediatric Oncology Group of Ontario were endorsed by the COG Supportive Care Guideline Committee in August 2020.

The source clinical practice guideline is published (Freyer DR, Brock PR, Chang KW, et al. Prevention of cisplatin-induced ototoxicity in children and adolescents with cancer: a clinical practice guideline. Lancet Child Adolescent Health 2020; 4(2): 141-50.) and is available open access at: https://www.thelancet.com/journals/lanchi/article/PIIS2352-4642(19)30336-0/fulltext.

The purpose of the source clinical practice guideline is to address the clinical question: what adjuvant interventions should be offered in conjunction with cisplatin to prevent ototoxicity in children and adolescents with cancer?

Summary of Recommendations for Prevention of Cisplatin-induced Ototoxicity in Children and Adolescents with Cancer

RECOMMENDATIONS	Strength of Recommendation and Quality of Evidence*
1. Do not use amifostine for the prevention of cisplatin-induced ototoxicity in children and adolescents with cancer	Strong recommendation High quality evidence
2. Do not use sodium diethyldithiocarbamate for the prevention of cisplatin-induced ototoxicity in children and adolescents with cancer	Strong recommendation Low quality evidence
3. Use sodium thiosulfate for the prevention of cisplatin-induced ototoxicity in children and adolescents with non-metastatic hepatoblastoma	Strong recommendation High quality evidence
4. Consider sodium thiosulfate for the prevention of cisplatin-induced ototoxicity in children and adolescents with non-metastatic cancers other than hepatoblastoma	Weak recommendation Low quality evidence
5. We suggest sodium thiosulfate not be used routinely for the prevention of cisplatin-induced ototoxicity for children and adolescents with metastatic cancers	Weak recommendation Low quality evidence
6. Do not use intratympanic middle ear therapy for the prevention of cisplatin-induced ototoxicity in children and adolescents with cancer	Strong recommendation Low quality evidence
7. Do not alter cisplatin infusion duration, as a means in itself, to reduce ototoxicity in children and adolescents with cancer	Strong recommendation Low quality evidence

*see Appendix 1

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6. Management of *Clostridium Difficile* Infection in Children and Adolescents with Cancer and Pediatric Hematopoietic Stem-Cell Transplantation Recipients

The "Guideline for the Management of *Clostridium Difficile* Infection in Children and Adolescents with Cancer and Pediatric Hematopoietic Stem-Cell Transplantation Recipients" developed by the Pediatric Oncology Group of Ontario (POGO) was endorsed by the COG Supportive Care Guideline Committee in February 2019.

The source guideline is published (Diorio C, Robinson PD, Ammann R, et al. Guideline for the management of *Clostridium difficile* infection in children and adolescents with cancer and pediatric hematopoietic stem cell transplantation recipients. J Clin Oncol 2018; 36:31, 3162-3171.) and is available at: https://doi.org/10.1200/JCO.18.00407

The purpose of the source guideline is to create a clinical practice guideline for the prevention and treatment of *Clostridium difficile* in children and adolescents with cancer and pediatric HSCT patients. Recommendations from the endorsed clinical practice guideline are presented in the table below.

Summary of Recommendations for the Management of *Clostridium Difficile* Infection in Children and Adolescents with Cancer and Pediatric HSCT Recipients

RECOMMENDATIONS	Strength of Recommendation and Quality of Evidence*
What interventions should be used for the prevention of *Clostridium difficile* infection (CDI) in children and adolescents with cancer and pediatric HSCT patients?	
1. We suggest that probiotics not be used routinely for the prevention of CDI in children and adolescents with cancer and pediatric HSCT patients	Weak recommendation Low quality evidence
What interventions should be used for the treatment of CDI in children and adolescents with cancer and pediatric HSCT patients?	
2. Use either oral metronidazole or oral vancomycin for the treatment of nonsevere CDI in children and adolescents with cancer and pediatric HSCT patients	Strong recommendation Low quality evidence
3. Use oral vancomycin for the treatment of severe CDI in children and adolescents with cancer and pediatric HSCT patients	Strong recommendation Low quality evidence
4. Consider fidaxomicin for the treatment of recurrent CDI in children and adolescents with cancer and pediatric HSCT patients	Weak recommendation Low quality evidence
5. Do not use fecal microbiota transplantation routinely for the treatment of CDI in children and adolescents with cancer and pediatric HSCT patients	Strong recommendation Low quality evidence
6. We suggest that monoclonal antibodies not be used routinely for the treatment of CDI in children and adolescents with cancer and pediatric HSCT patients	Weak recommendation Low quality evidence
7. We suggest that probiotics not be used routinely for the treatment of CDI in children and adolescents with cancer and pediatric HSCT patients.	Weak recommendation Low quality evidence

*see Appendix 1

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7. Management of Fatigue in Children and Adolescents with Cancer and in Pediatric Recipients of Hematopoietic Stem Cell Transplants

The "Management of Fatigue in Children and Adolescents with Cancer and in Paediatric Recipients of Haematopoietic stem-cell Transplants: a Clinical Practice Guideline" was endorsed by the COG Supportive Care Guideline Committee in September 2018.

The source guideline is published (Robinson PD, Oberoi S, Tomlinson D, et al. Guideline for the management of fatigue in children and adolescents with cancer and pediatric hematopoietic stem cell transplantation recipients. The Lancet Child and Adolescent Health 2018; 2: 371-8.) and is available at: http://dx.doi.org/10.1016/S2352-4642(18)30059-2

The purpose of this guideline is to provide guidance for management of fatigue in children and adolescents with cancer and paediatric recipients of hematopoietic stem cell transplantation recipients.

The recommendations of the endorsed guideline are presented below.

Summary of Recommendations for the Management of Fatigue in Children and Adolescents with Cancer and Paediatric Recipients of Hematopoietic Stem Cell Transplantation

RECOMMENDATIONS	Strength of Recommendation and Quality of Evidence*
What are effective interventions for the management of fatigue in children and adolescents with cancer or paediatric HSCT recipients?	
• Use physical activity interventions to manage fatigue in children and adolescents with cancer or paediatric HSCT recipients	Strong recommendation, Moderate quality evidence
• Do not routinely use pharmacological approaches to manage fatigue in children and adolescents with cancer or paediatric HSCT recipients	Strong recommendation, Moderate quality evidence
• Use relaxation or mindfulness, or both, for children and adolescents with cancer or pediatric HSCT recipients who can participate in these approaches to manage fatigue	Strong recommendation, Moderate quality evidence
• In settings where other recommended approaches are not feasible or were not successful, cognitive or cognitive behavioural therapies may be offered to children and adolescents with cancer or paediatric HSCT recipients who can participate in these approaches	Weak recommendation, Moderate quality evidence

*see Appendix 1

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8. Fertility Preservation for Patients with Cancer

The "Fertility Preservation for Patients with Cancer: ASCO Clinical Practice Guideline Update" guideline was endorsed by the COG Supportive Care Guideline Committee in November 2018. It is an update to the 2014 clinical practice guideline that was also endorsed by the COG and is now archived. The 2018 document and implementation tools provided by the guideline developers are available at: https://www.asco.org/practice-guidelines/quality-guidelines/guidelines/patient-and-survivor-care#/9661

A summary is published in the Journal of Clinical Oncology 2018 36:19, 1994-2001. http://ascopubs.org/doi/pdf/10.1200/JCO.2018.78.1914

The goal of this guideline is to provide oncologists, other health care providers and caregivers with recommendations regarding fertility preservation for adults, adolescents and children with cancer. The recommendations of the source clinical practice guideline are presented below. Note that recommendations 1, 4 and 5 are most pertinent to pediatric oncology.

Summary of Recommendations for Fertility Preservation for Patients with Cancer

RECOMMENDATIONS	Strength of Recommendation and Quality of Evidence
1.1 People with cancer are interested in discussing fertility preservation. Health care providers caring for adult and pediatric patients with cancer (including medical oncologists, radiation oncologists, gynecologic oncologists, urologists, hematologists, pediatric oncologists, surgeons, and others) should address the possibility of infertility as early as possible before treatment starts.	**No formal grading system used**
1.2 Health care providers should refer patients who express an interest in fertility preservation (and those who are ambivalent) to reproductive specialists.	**No formal grading system used**
1.3 To preserve the full range of options, fertility preservation approaches should be discussed as early as possible, before treatment starts. The discussion can ultimately reduce distress and improve quality of life. Another discussion and/or referral may be necessary when the patient returns for follow up after completion of therapy and/or if pregnancy is being considered. The discussions should be documented in the medical record.	**No formal grading system used**
Adult Males	
2.1 Sperm cryopreservation: Sperm cryopreservation is effective, and health care providers should discuss sperm banking with postpubertal males receiving cancer treatment.	**No formal grading system used**
2.2 Hormonal gonadoprotection: Hormonal therapy in men is not successful in preserving fertility. It is not recommended.	**No formal grading system used**

RECOMMENDATIONS	Strength of Recommendation and Quality of Evidence
2.3 Other methods to preserve male fertility: Other methods, such as testicular tissue cryopreservation and reimplantation or grafting of human testicular tissue, should be performed only as part of clinical trials or approved experimental protocols.	**No formal grading system used**
2.4 Postchemotherapy: Men should be advised of a potentially higher risk of genetic damage in sperm collected after initiation of therapy. It is strongly recommended that sperm be collected before initiation of treatment because the quality of the sample and sperm DNA integrity may be compromised after a single treatment. Although sperm counts and quality of sperm may be diminished even before initiation of therapy, and even if there may be a need to initiate chemotherapy quickly such that there may be limited time to obtain optimal numbers of ejaculate specimens, these concerns should not dissuade patients from banking sperm. Intracytoplasmic sperm injection allows the future use of a very limited amount of sperm; thus, even in these compromised scenarios, fertility may still be preserved.	**No formal grading system used**
Adult Women	
3.1 Embryo cryopreservation: Embryo cryopreservation is an established fertility preservation method, and it has routinely been used for storing surplus embryos after in vitro fertilization.	**No formal grading system used**
3.2 Cryopreservation of unfertilized oocytes: Cryopreservation of unfertilized oocytes is an option, and may be especially well suited to women who do not have a male partner, do not wish to use donor sperm, or have religious or ethical objections to embryo freezing. Oocyte cryopreservation should be performed in centers with the necessary expertise. As of October 2012, the American Society for Reproductive Medicine no longer deems this procedure experimental. *Qualifying statement*: More flexible ovarian stimulation protocols for oocyte collection are now available. Timing of this procedure no longer depends on the menstrual cycle in most cases, and stimulation can be initiated with less delay compared with old protocols. Thus, oocyte harvesting for the purpose of oocyte or embryo cryo-preservation is now possible on a cycle day–independent schedule. Of special concern in estrogen-sensitive breast and gynecologic malignancies is the possibility that these fertility preservation interventions (eg, ovarian stimulation regimens that increase estrogen levels) and/or subsequent pregnancy may increase the risk of cancer recurrence. Aromatase inhibitor–based stimulation	**No formal grading system used**

RECOMMENDATIONS	Strength of Recommendation and Quality of Evidence
protocols are now well established and may ameliorate this concern. Studies do not indicate increased cancer recurrence risk as a result of aromatase inhibitor–supplemented ovarian stimulation and subsequent pregnancy.	
3.3 Ovarian transposition: Ovarian transposition (oophoropexy) can be offered when pelvic irradiation is performed as cancer treatment. However, because of radiation scatter, ovaries are not always protected, and patients should be aware that this technique is not always successful. Because of the risk of remigration of the ovaries, this procedure should be performed as close to the time of radiation treatment as possible.	**No formal grading system used**
3.4 Conservative gynecologic surgery: It has been suggested that radical trachelectomy (surgical removal of the uterine cervix) should be restricted to stage IA2 to IB cervical cancer with diameter < 2 cm and invasion < 10 mm. In the treatment of other gynecologic malignancies, interventions to spare fertility have generally centered on doing less radical surgery, with the intent of sparing the reproductive organs as much as possible. Ovarian cystectomy can be performed for early-stage ovarian cancer.	**No formal grading system used**
3.5 Ovarian suppression: There is conflicting evidence to recommend GnRHa and other means of ovarian suppression for fertility preservation. The Panel recognizes that, when proven fertility preservation methods such as oocyte, embryo, or ovarian tissue cryopreservation are not feasible, and in the setting of young women with breast cancer, GnRHa may be offered to patients in the hope of reducing the likelihood of chemotherapy-induced ovarian insufficiency. However, GnRHa should not be used in place of proven fertility preservation methods.	**No formal grading system used**
3.6 Ovarian tissue cryopreservation and transplantation: Ovarian tissue cryopreservation for the purpose of future transplantation does not require ovarian stimulation and can be performed immediately. In addition, it does not require sexual maturity and hence may be the only method available in children. Finally, this method may also restore global ovarian function. However, it should be noted further investigation is needed to confirm whether it is safe in patients with leukemias. *Qualifying statement*: As of the time of this publication, ovarian tissue cryopreservation remains experimental. However, emerging data may prompt reconsideration of this designation in the future (this technique is already considered nonexperimental in some countries, and its experimental status is undergoing evaluation in the United States).	**No formal grading system used**

RECOMMENDATIONS	Strength of Recommendation and Quality of Evidence
Role of Health Care Providers	
4.1 All oncologic health care providers should be prepared to discuss infertility as a potential risk of therapy. This discussion should take place as soon as possible once a cancer diagnosis is made and can occur simultaneously with staging and the formulation of a treatment plan. There are benefits for patients in discussing fertility information with providers at every step of the cancer journey.	**No formal grading system used**
4.2 Encourage patients to participate in registries and clinical studies, as available, to define further the safety and efficacy of these interventions and strategies.	**No formal grading system used**
4.3 Refer patients who express an interest in fertility, as well as those who are ambivalent or uncertain, to reproductive specialists as soon as possible.	**No formal grading system used**
4.4 Refer patients to psychosocial providers when they are distressed about potential infertility.	**No formal grading system used**
Special Considerations: Children	
5.1 Suggest established methods of fertility preservation (eg, semen or oocyte cryopreservation) for postpubertal children, with patient assent and parent or guardian consent. For prepubertal children, the only fertility preservation options are ovarian and testicular cryopreservation, which are investigational.	**No formal grading system used**

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9. Management of Fever and Neutropenia in Children with Cancer and/or Undergoing Hematopoietic Stem-Cell Transplantation

The "Guideline for the Management of Fever and Neutropenia in Children with Cancer and/or Undergoing Hematopoietic Stem-Cell Transplantation" was endorsed by the COG Supportive Care Guideline Committee in September 2017.

The source guideline is published in the Journal of Clinical Oncology 2017; 35: 2082-94: http://ascopubs.org/doi/abs/10.1200/JCO.2016.71.7017

The purpose of this guideline is to provide evidence-based recommendations for the empiric management of pediatric febrile neutropenia. The recommendations of the endorsed guideline are presented below.

Summary of Recommendations for the Empiric Management of Febrile Neutropenia

RECOMMENDATIONS	Strength of Recommendation and Quality of Evidence*
A. Initial Management of Febrile Neutropenia	
Risk Stratification	
A1. Adopt a validated risk stratification strategy and incorporate it into routine clinical management	Strong recommendation Low quality evidence
Evaluation	
A2. Obtain blood cultures at onset of febrile neutropenia from all lumens of central venous catheters	Strong recommendation Low quality evidence
A3. Consider obtaining peripheral-blood cultures concurrent with central venous catheter cultures	Weak recommendation Moderate quality evidence
A4. Consider urinalysis and urine culture in patients in whom a clean-catch, midstream specimen is readily available	Weak recommendation Low quality evidence
A5. Obtain chest radiography only in patients with respiratory signs or symptoms	Strong recommendation Moderate quality evidence
Treatment	
A6a. In high-risk febrile neutropenia: Use monotherapy with an antipseudomonal β-lactam, fourth generation cephalosporin, or a carbapenem as empirical therapy in pediatric high-risk febrile neutropenia	Strong recommendation High quality evidence
A6b. In high-risk febrile neutropenia: Reserve addition of second gram-negative agent or a glycopeptide for patients who are clinically unstable, when a resistant infection is suspected or for centers with a high rate of resistant pathogens.	Strong recommendation Moderate quality evidence
A7a. In low-risk febrile neutropenia: Consider initial or step-down outpatient management if infrastructure is in place to ensure careful monitoring and follow-up.	Weak recommendation Moderate quality evidence
A7b. In low-risk febrile neutropenia: Consider oral antibiotic administration if the child is able to tolerate this route of administration reliably.	Weak recommendation Moderate quality evidence

RECOMMENDATIONS	Strength of Recommendation and Quality of Evidence
B. Ongoing Management of Febrile Neutropenia	
Modification of Treatment	
B1. In patients who are responding to initial empiric antibiotic therapy, discontinue double coverage for gram-negative infection or empiric glycopeptide (if initiated) after 24 to 72 hours if there is no specific microbiologic indication to continue combination therapy	Strong recommendation Moderate quality evidence
B2. Do not modify initial empirical antibacterial regimen based solely on persistent fever in children who are clinically stable	Strong recommendation Low quality evidence
B3. In children with persistent fever who become clinically unstable, escalate the initial empirical antibacterial regimen to include coverage for resistant gram-negative, gram-positive, and anaerobic bacteria	Strong recommendation Very low quality evidence
Cessation of Treatment	
B4. In all patients, discontinue empirical antibiotics in patients who have negative blood cultures at 48 hours, who have been afebrile for at least 24 hours, and who have evidence of marrow recovery	Strong recommendation Low quality evidence
B5. In patients with low-risk febrile neutropenia, consider discontinuation of empirical antibiotics at 72 hours in patients who have negative blood cultures and who have been afebrile for at least 24 hours, irrespective of marrow recovery status, as long as careful follow-up is ensured	Weak recommendation Moderate quality evidence
C. Empiric Antifungal Treatment ≥96 Hours after Initiation of Empiric Antibacterial Treatment	
Risk Stratification	
C1. Patients at high risk of invasive fungal disease are those with AML, high-risk ALL, or relapsed acute leukemia and children undergoing allogeneic HSCT. Children with prolonged neutropenia and children receiving high-dose corticosteroids are also at high risk of invasive fungal disease. All others should be categorized as Invasive Fungal Disease low risk.	Strong recommendation Low quality evidence
Evaluation	
C2a. In terms of biomarkers to guide empirical antifungal management for prolonged (≥ 96 hours) febrile neutropenia in invasive fungal disease high-risk patients: Consider not using serum galactomannan	Weak recommendation Moderate quality evidence
C2b. In terms of biomarkers to guide empirical antifungal management for prolonged (≥ 96 hours) febrile neutropenia in invasive fungal disease high-risk patients: Do not use β-D-glucan.	Strong recommendation Low quality evidence
C2c. In terms of biomarkers to guide empirical antifungal management for prolonged (≥ 96 hours) febrile neutropenia in invasive fungal disease high-risk patients: Do not use fungal PCR testing in blood	Strong recommendation Moderate quality evidence

RECOMMENDATIONS	Strength of Recommendation and Quality of Evidence
C3a. In terms of imaging for the evaluation of prolonged (≥ 96 hours) febrile neutropenia in invasive fungal disease high-risk patients: Perform CT of the lungs.	Strong recommendation Low quality evidence
C3b. In terms of imaging for the evaluation of prolonged (≥ 96 hours) febrile neutropenia in invasive fungal disease high-risk patients: Consider imaging of abdomen in patients without localizing signs or symptoms.	Weak recommendation Low quality evidence
C3c. In terms of imaging for the evaluation of prolonged (≥ 96 hours) febrile neutropenia in invasive fungal disease high-risk patients: Consider not routinely performing CT of sinuses in patients without localizing signs or symptoms.	Weak recommendation Low quality evidence
Treatment	
C4. In invasive fungal disease patients with prolonged (≥ 96 hours) febrile neutropenia unresponsive to broad-spectrum antibacterial agents, initiate caspofungin or liposomal amphotericin B for empirical antifungal therapy.	Strong recommendation High quality evidence
C5. In invasive fungal disease low risk patients with prolonged (≥ 96 hours) febrile neutropenia, consider withholding empirical antifungal therapy.	Weak recommendation Low quality evidence

*see Appendix 1

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10. Platelet Transfusion for Patients with Cancer

The evidence-based recommendations included in the "Platelet Transfusion for Patients with Cancer: American Society of Clinical Oncology (ASCO) Clinical Practice Guideline Update" were endorsed by the COG Supportive Care Guideline Committee in October, 2018.

The source guideline is published Schiffer CA, Bohlke K, Delaney M, et al. J Clin Oncol. 2018;36(3):283-299. doi:10.1200/JCO.2017.76.1734) and is available at: http://ascopubs.org/doi/pdf/10.1200/JCO.2017.76.1734

The purpose of the source guideline is to provide evidence-based recommendations regarding the use of platelet transfusion in people with cancer. They are limited to people aged 4 months and older.

Recommendations from the endorsed clinical practice guideline are presented in the table below. Recommendations deemed not to be generalizable to pediatric patients by the source clinical practice guideline panel have been omitted.

Summary of Recommendations for Platelet Transfusion for Patients with Cancer

RECOMMENDATIONS	Strength of Recommendation and Quality of Evidence*
How should platelets for transfusion be prepared?	
• Platelets for transfusion can be prepared either by separation of units of platelet concentrates (PCs) from whole blood using either the buffy coat (BC) or the platelet-rich plasma (PRP) method, which can be pooled before administration, or by apheresis from single donors. Comparative studies have shown that the post-transfusion increments, hemostatic benefit, and adverse effects are similar with any of these platelet products. Thus, in routine circumstances, they can be used interchangeably. In most centers, pooled PCs are less costly. Single-donor platelets from selected donors are necessary when histocompatible platelet transfusions are needed. (ASCO Q1)	Evidence quality: High Strength of recommendation: Strong
Should platelet transfusions be given prophylactically or therapeutically?	
• Prophylactic platelet transfusion should be administered to patients with thrombocytopenia resulting from impaired bone marrow function to reduce the risk of hemorrhage when the platelet count falls below a predefined threshold level. This threshold level for transfusion varies according to the patient's diagnosis, clinical condition, and treatment modality. (ASCO Q4)	Evidence quality: High Strength of recommendation: Strong

RECOMMENDATIONS	Strength of Recommendation and Quality of Evidence*
What platelet transfusion threshold should be used?	
• **Patients with Hematologic Malignancies**: The Panel recommends a threshold of <10 x 10^9/L for prophylactic platelet transfusion in patients receiving therapy for hematologic malignancies. Transfusion at higher levels may be advisable in patients with signs of hemorrhage, high fever, hyperleukocytosis, rapid fall of platelet count, or coagulation abnormalities (eg, acute promyelocytic leukemia) and in those undergoing invasive procedures or in circumstances in which platelet transfusions may not be readily available in case of emergencies, as might be the case for outpatients who live at a distance from the treatment center. (ASCO Q5)	Evidence quality: High Strength of recommendation: Strong
• **Patients in the Setting of Hematopoietic Stem Cell Transplant:** The Panel recommends a threshold of < 10 x 10^9/L for prophylactic platelet transfusion in adult and pediatric patients undergoing allogeneic HSCT. Prophylactic platelet transfusion may be administered at higher counts based on clinician judgment. (ASCO Q6)	Evidence quality: High Strength of recommendation: Moderate
• **Platelet Count at which Surgical or Invasive Procedures may be Performed**: The Panel recommends a threshold of 40 x 10^9/L to 50 x 10^9/L for performing major invasive procedures in the absence of associated coagulation abnormalities. Certain procedures, such as bone marrow aspirations and biopsies, and removal of central venous catheters, can be performed safely at counts < 20 x 10^9/L. There are sparse data, and no randomized trials, addressing the safety of other invasive procedures at much lower count levels. If platelet transfusions are administered before a procedure, it is critical that a post-transfusion platelet count be obtained to prove that the desired platelet count level has been reached. Platelet transfusions should also be available on short notice, in case intraoperative or postoperative bleeding occurs. For alloimmunized patients, histocompatible platelets must be available in these circumstances. (ASCO Q9)	Evidence quality: Low Strength of recommendation: Weak

RECOMMENDATIONS	Strength of Recommendation and Quality of Evidence*
In what circumstances should providers take steps to prevent Rh alloimmunization resulting from platelet transfusion?	
• Prevention of RhD alloimmunization resulting from platelet transfusions to RhD-negative recipients can be achieved either through the exclusive use of platelet products collected from RhD-negative donors or via anti-D immune prophylaxis. These approaches may be used for female children and female adults of child-bearing potential being treated with curative intent. However, because of the low rate of RhD alloimmunization in patients with cancer, these approaches need not be applied universally. (ASCO Q2)	Evidence quality: Intermediate Strength of recommendation: Moderate
How should refractoriness to platelet transfusion be managed?	
Implementation tip from the COG Supportive Care Guideline Committee: The recommendation below applies to platelet refractoriness due to alloimmunization. Other causes of platelet refractoriness should be excluded.	
• Alloimmunization is usually due to antibody against HLA antigens and only rarely to platelet-specific antigens. Patients with alloimmune-refractory thrombocytopenia, as defined previously,† are best managed with platelet transfusions from histocompatible donors matched for HLA-A and HLA-B antigens. Many blood suppliers have access to computerized lists of such donors. For patients (1) whose HLA type cannot be determined, (2) who have uncommon HLA types for whom suitable donors cannot be identified, or (3) who do not respond to HLA-matched platelets, histocompatible platelet donors can often be identified using platelet cross-matching techniques. In many patients, these two techniques are complementary. (ASCO Q11) †A diagnosis of refractoriness to platelet transfusion should be made only when at least two transfusions of ABO-compatible units, stored for < 72 hours, result in poor increments. See: Schiffer CA, et al. J Clin Oncol. 2018; 36(3):283-99.	Evidence quality: High Strength of recommendation: Strong

RECOMMENDATIONS	Strength of Recommendation and Quality of Evidence*
In what circumstances should providers use leukoreduced blood products to prevent alloimmunization?	
• The incidence of alloantibody-mediated refractoriness to platelet transfusion can be decreased in patients with acute myeloid leukemia (AML) receiving induction chemotherapy when both platelet and RBC products are leukoreduced before transfusion. It is therefore appropriate to provide leukoreduced blood products to patients with AML from the time of diagnosis to ameliorate this important clinical problem. Although randomized trials have not been conducted in other patient groups, it is likely that alloimmunization can also be decreased in patients with other types of leukemia and in other patients with cancer who are receiving chemotherapy. There are fewer data in patients who are not receiving chemotherapy in the same time periods that the transfusions are being administered (eg, aplastic anemia, myelodysplasia), although the consensus would favor its use in these patients as well. In the United States and in several other countries, the overwhelming majority of blood products are now leukoreduced at the time of blood collection and component preparation. Other advantages of prestorage leukoreduction include a substantial reduction in transfusion reactions and in transmission of cytomegalovirus infection. (ASCO Q3)	Evidence quality: High Strength of recommendation: Strong

*see Appendix 1

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11. Treatment of Pediatric Venous Thromboembolism

The "Guidelines for Management of Venous Thromboembolism: Treatment of Pediatric Venous Thromboembolism" developed by the American Society of Hematology were endorsed by the COG Supportive Care Guideline Committee in May 2019.

The source clinical practice guideline is published (Monagle P, Cuello CA, Augustine C, Bonduel M, Brandao LR, Capman T et al. American Society of Hematology 2018 Guidelines for management of venous thromboembolism: treatment of pediatric venous thromboembolism. Blood Advances 2018; 2 (22): 3293-3316.) and is available at: http://www.bloodadvances.org/content/2/22/3292. Implementation resources provided by the source clinical practice guideline developers may be found at: https://hematology.org/vte/

The purpose of the source clinical practice guideline is to support patients, clinicians, and other health care professionals in their decisions about management of pediatric venous thromboembolism. Recommendations from the endorsed clinical practice guideline are presented in the table below.

Summary of Recommendations for Treatment of Pediatric Venous Thromboembolism

RECOMMENDATIONS	Strength of Recommendation and Certainty in Evidence*
Anticoagulation in symptomatic and asymptomatic deep vein thrombosis (DVT) or pulmonary embolism (PE)	
Should anticoagulation vs no anticoagulation be used in pediatric patients with symptomatic DVT or PE?	
1. The American Society of Hematology (ASH) guideline panel recommends using anticoagulation rather than no anticoagulation in pediatric patients with symptomatic deep vein thrombosis (DVT) or pulmonary embolism (PE)	Strong recommendation Very low certainty in evidence
Should anticoagulation vs no anticoagulation be used in pediatric patients with asymptomatic DVT or PE?	
2. The ASH guideline panel suggests either using anticoagulation or no anticoagulation in pediatric patients with asymptomatic DVT or PE	Conditional recommendation Very low certainty in evidence
Thrombolysis, thrombectomy, and inferior vena cava filters	
Should thrombolysis followed by anticoagulation vs anticoagulation alone be used in pediatric patients with DVT?	
3. The ASH guideline panel suggests against using thrombolysis followed by anticoagulation; rather, anticoagulation alone should be used in pediatric patients with DVT	Conditional recommendation Very low certainty in evidence
Should thrombolysis followed by anticoagulation vs anticoagulation alone be used in pediatric patients with submassive PE?	
4. The ASH guideline panel suggests against using thrombolysis followed by anticoagulation; rather, anticoagulation alone should be used in pediatric patients with submassive PE	Conditional recommendation Very low certainty in evidence

RECOMMENDATIONS	Strength of Recommendation and Certainty in Evidence*
Should thrombolysis followed by anticoagulation vs anticoagulation alone be used in pediatric patients with PE with hemodynamic compromise?	
5. The ASH guideline panel suggests using thrombolysis followed by anticoagulation, rather than anticoagulation alone, in pediatric patients with PE with hemodynamic compromise	Conditional recommendation Very low certainty in evidence
Should thrombectomy followed by anticoagulation vs anticoagulation alone be used in pediatric patients with symptomatic DVT or PE?	
6. The ASH guideline panel suggests against using thrombectomy followed by anticoagulation; rather, anticoagulation alone should be used in pediatric patients with symptomatic DVT or PE	Conditional recommendation Very low certainty in evidence
Should IVC filter vs anticoagulation be used in pediatric patients with symptomatic DVT or PE?	
7. The ASH guideline panel suggests against using inferior vena cava (IVC) filter; rather anticoagulation alone should be used in pediatric patients with symptomatic DVT or PE	Conditional recommendation Very low certainty in evidence
Thrombolysis, thrombectomy, and inferior vena cava filters	
Should antithrombin (AT) replacement in addition to standard anticoagulation vs standard anticoagulation alone be used in pediatric patients with DVT or cerebral sino venous thrombosis (CSVT) or PE?	
8a. The ASH guideline panel suggests against using AT-replacement therapy in addition to standard anticoagulation; rather, standard anticoagulation alone should be used in pediatric patients with DVT/CSVT/PE	Conditional recommendation Very low certainty in evidence
8b. The ASH guideline panel suggests using AT-replacement therapy in addition to standard anticoagulation rather than standard anti-coagulation alone in pediatric patients with DVT/CSVT/PE who have failed to respond clinically to standard anticoagulation treatment and in whom subsequent measurement of AT concentrations reveals low AT levels based on age appropriate reference ranges	Conditional recommendation Very low certainty in evidence
Central venous access device (CVAD)-related thrombosis	
Should removal of a functioning CVAD vs no removal be used in pediatric patients with symptomatic CVAD-related thrombosis who continue to require access?	
9. The ASH guideline panel suggests no removal, rather than removal, of a functioning CVAD in pediatric patients with symptomatic CVAD-related thrombosis who continue to require venous access	Conditional recommendation Very low certainty in evidence
Should removal of a nonfunctioning or unneeded CVADs vs no removal be used in pediatric patients with symptomatic CVAD-related thrombosis?	
10. The ASH guideline panel recommends removal, rather than no removal, of a nonfunctioning or unneeded CVAD in pediatric patients with symptomatic CVAD-related thrombosis	Strong recommendation Very low certainty in evidence

RECOMMENDATIONS	Strength of Recommendation and Certainty in Evidence*
Should immediate removal of a nonfunctioning or unneeded CVAD vs delayed removal be used in pediatric patients with symptomatic CVAD-related thrombosis?	
11. The ASH guideline panel suggests delayed removal of a CVAD until after initiation of anticoagulation (days), rather than immediate removal in pediatric patients with symptomatic central venous line–related thrombosis who no longer require venous access or in whom the CVAD is nonfunctioning	Conditional recommendation Very low certainty in evidence
Should removal of a functioning CVAD vs no removal be used in pediatric patients with symptomatic CVAD-related thrombosis with worsening signs or symptoms, despite anticoagulation, who continue to require access?	
12. The ASH guideline panel suggests either removal or no removal of a functioning CVAD in pediatric patients who have symptomatic CVAD-related thrombosis with worsening signs or symptoms, despite anticoagulation, and who continue to require venous access	Conditional recommendation Very low certainty in evidence
Low-molecular-weight heparin vs vitamin K antagonists	
Should low-molecular-weight heparin vs vitamin K antagonists be used in pediatric patients with symptomatic DVT or PE as maintenance therapy after the first few days?	
13. The ASH guideline panel suggests using either low-molecular weight heparin or vitamin K antagonists in pediatric patients with symptomatic DVT or PE	Conditional recommendation Very low certainty in evidence
Provoked DVT or PE	
Should anticoagulation for > 3 months vs anticoagulation for up to 3 months be used in pediatric patients with provoked DVT or PE?	
14. The ASH guideline panel suggests using anticoagulation for ≤ 3 months rather than anticoagulation for > 3 months in pediatric patients with provoked DVT or PE	Conditional recommendation Very low certainty in evidence
Unprovoked DVT or PE	
Should anticoagulation for > 6 to 12 months vs anticoagulation for 6 to 12 months be used in pediatric patients with unprovoked DVT or PE?	
15. The ASH guideline panel suggests using anticoagulation for 6 to 12 months rather than anticoagulation for > 6 to 12 months in pediatric patients with unprovoked DVT or PE	Conditional recommendation Very low certainty in evidence
CVAD-related superficial vein thrombosis	
Should anticoagulation vs no anticoagulation be used in pediatric patients with CVAD-related superficial vein thrombosis?	
16. The ASH guideline panel suggests using either anticoagulation or no anticoagulation in pediatric patients with CVAD-related superficial vein thrombosis	Conditional recommendation Very low certainty in evidence

RECOMMENDATIONS	Strength of Recommendation and Certainty in Evidence*
Right atrial thrombosis	
Should anticoagulation vs no anticoagulation be used in neonates and pediatric patients with right atrial thrombosis?	
17. The ASH guideline panel suggests using anticoagulation, rather than no anticoagulation, in pediatric patients with right atrial thrombosis	Conditional recommendation Very low certainty in evidence
Should thrombolysis or surgical thrombectomy followed by standard anticoagulation vs anticoagulation alone be used in neonates and pediatric patients with right atrial thrombosis?	
18. The ASH guideline panel suggests against using thrombolysis or surgical thrombectomy, followed by standard anticoagulation; rather, anticoagulation alone should be used in pediatric patients with right atrial thrombosis	Conditional recommendation Very low certainty in evidence
Portal vein thrombosis (PVT)	
Should anticoagulation vs no anticoagulation be used in pediatric patients with PVT?	
21a. The ASH guideline panel suggests using anticoagulation, rather than no anticoagulation, in pediatric patients with PVT with occlusive thrombus, postliver transplant, and idiopathic PVT	Conditional recommendation Very low certainty in evidence
21b. The ASH guideline panel suggests using no anticoagulation, rather than anticoagulation, in pediatric patients with PVT with nonocclusive thrombus or portal hypertension	Conditional recommendation Very low certainty in evidence
Cerebral sino venous thrombosis (CSVT)	
Should anticoagulation vs no anticoagulation be used in pediatric patients with CSVT?	
22a. The ASH guideline panel recommends using anticoagulation, rather than no anticoagulation, in pediatric patients with CSVT without hemorrhage	Strong recommendation Very low certainty in evidence
22b. The ASH guideline panel suggests using anticoagulation, rather than no anticoagulation, in pediatric patients with CSVT with hemorrhage	Conditional recommendation Very low certainty in evidence
Should thrombolysis followed by standard anticoagulation vs anticoagulation alone be used in pediatric patients with CSVT?	
23. The ASH guideline panel suggests against using thrombolysis followed by standard anticoagulation; rather, anticoagulation alone should be used in pediatric patients with CSVT	Conditional recommendation Very low certainty in evidence

*see Appendix 1

Appendix 1: Systems for Classifying Recommendations and Evidence used by the Source Clinical Practice Guidelines

I. GRADE: used by Nahirniak S, Slichter SJ, Tanael S, et al. Transfusion Medicine Reviews 2015: 29; 3-13.

Strength of Recommendations:

Strong Recommendation	When using GRADE, panels make strong recommendations when they are confident that the desirable effects of adherence to a recommendation outweigh the undesirable effects.
Weak or Conditional Recommendation	Weak or conditional recommendations indicate that the desirable effects of adherence to a recommendation probably outweigh the undesirable effects, but the panel is less confident.

Strength of Recommendations Determinants:

Factor	Comment
Balance between desirable and undesirable effects	The larger the difference between the desirable and undesirable effects, the higher the likelihood that a strong recommendation is warranted. The narrower the gradient, the higher the likelihood that a weak recommendation is warranted
Quality of evidence	The higher the quality of evidence, the higher the likelihood that a strong recommendation is warranted
Values and preferences	The more values and preferences vary, or the greater the uncertainty in values and preferences, the higher the likelihood that a weak recommendation is warranted
Costs (resource allocation)	The higher the costs of an intervention—that is, the greater the resources consumed—the lower the likelihood that a strong recommendation is warranted

Quality of Evidence or Certainty in Evidence

High Quality/Certainty	Further research is very unlikely to change our confidence in the estimate of effect
Moderate Quality/Certainty	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate
Low Quality/Certainty	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate
Very Low Quality/Certainty	Any estimate of effect is very uncertain

Guyatt, G.H., et al., *GRADE: an emerging consensus on rating quality of evidence and strength of recommendations.* BMJ, 2008; 336: 924-926.
Guyatt, G.H., et al., *GRADE: going from evidence to recommendations.* BMJ, 2008; 336: 1049-1051.

II. American Society of Clinical Oncology: used by: Schiffer CA, Bohlke K, Delaney M, et al. Platelet Transfusion for Patients With Cancer: American Society of Clinical Oncology Clinical Practice Guideline Update. JCO 2018 36:3, 283-299.

Guide for Strength of Recommendations

Rating for Strength of Recommendation	Definition
Strong	There is high confidence that the recommendation reflects best practice. This is based on (1) strong evidence for a true net effect (eg, benefits exceed harms); (2) consistent results, with no or minor exceptions; (3) minor or no concerns about study quality; and/or (4) the extent of Expert Panelists' agreement. Other compelling considerations (discussed in the guideline's literature review and analyses) may also warrant a strong recommendation.
Moderate	There is moderate confidence that the recommendation reflects best practice. This is based on (1) good evidence for a true net effect (eg, benefits exceed harms); (2) consistent results, with minor and/or few exceptions; (3) minor and/or few concerns about study quality; and/or (4) the extent of Expert Panelists' agreement. Other compelling considerations (discussed in the guideline's literature review and analyses) may also warrant a moderate recommendation.
Weak	There is some confidence that the recommendation offers the best current guidance for practice. This is based on (1) limited evidence for a true net effect (eg, benefits exceed harms); (2) consistent results, but with important exceptions; (3) concerns about study quality; and/or (4) the extent of Expert Panelists' agreement. Other considerations (discussed in the guideline's literature review and analyses) may also warrant a weak recommendation.

Guide for Quality of Evidence

Rating for Strength of Evidence	Definition
High	High confidence that the available evidence reflects the true magnitude and direction of the net effect (i.e., balance of benefits *v* harms) and that further research is very unlikely to change either the magnitude or direction of this net effect.
Intermediate	Moderate confidence that the available evidence reflects the true magnitude and direction of the net effect. Further research is unlikely to alter the direction of the net effect; however, it might alter the magnitude of the net effect.
Low	Low confidence that the available evidence reflects the true magnitude and direction of the net effect. Further research may change either the magnitude and/or direction this net effect.
Insufficient	Evidence is insufficient to discern the true magnitude and direction of the net effect. Further research may better inform the topic. The use of the consensus opinion of experts is reasonable to inform outcomes related to the topic.