CHILDREN'S ONCOLOGY GROUP

The world's childhood cancer experts

COG Supportive Care Endorsed Guidelines

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The COG Supportive Care Endorsed Guidelines are comprised of evidence-based guidelines which have been developed by other organizations and endorsed by the Children's Oncology Group. The COG guideline endorsement process is available on the COG Supportive Care Guidelines webpage (link). 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 using the GRADE method (see Appendix 1, page 21). 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 one of the members of the COG Supportive Care Guideline Committee.

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1. Guideline for Primary Antifungal Prophylaxis for Pediatric Patients with Cancer or Hematopoietic Stem Cell Transplant Recipients

The "Guideline for Primary Antifungal Prophylaxis for Pediatric Patients with Cancer or Hematopoietic Stem Cell Transplant Recipients" was endorsed by the COG Supportive Care Guideline Committee in October 2015. The entire document is available at: http://www.c17.ca/index.php?cID=86

A summary was published (Science M, Robinson P, MacDonald T, Rassekh SR, Dupuis LL, Sung L. Guideline for primary antifungal prophylaxis for pediatric patients with cancer or hematopoietic stem cell transplant recipients. Pediatr Blood Cancer 2014; 61:393-400) and is available at: http://onlinelibrary.wiley.com/doi/10.1002/pbc.24847/epdf

The purpose of this guideline is to provide healthcare professionals with evidence-based recommendations on the use of primary antifungal prophylaxis in children with cancer or undergoing hematopoietic stem cell transplant.

The recommendations of the endorsed guideline are presented below.

I. Summary of Recommendations for Primary Antifungal Prophylaxis for Pediatric Patients with Cancer or Hematopoietic Stem Cell Transplant Recipients

RECOMMENDATIONS	Strength of Recommendation and Quality of Evidence
ALLOGENEIC HSCT	
• For children 1 month to <19 years of age undergoing allogeneic HSCT, administer fluconazole 6–12 mg/kg/day (maximum 400 mg/day) intravenous (IV) or oral (PO) from the start of conditioning until engraftment	Strong recommendation, High quality evidence
• For the above children where fluconazole is contraindicated, administer an echinocandin as an alternative to fluconazole	Strong recommendation, Moderate quality evidence
ALLOGENEIC HSCT WITH ACUTE GRADE II–IV GVHD OR CHRONIC EXTENSIVE GVHD	
• For children 13 years of age or older undergoing allogeneic HSCT with acute Grade II–IV or chronic extensive GVHD, prophylaxis with posaconazole 200 mg PO TID from GVHD diagnosis until resolution of acute Grade II–IV GVHD or chronic extensive GVHD is suggested	Weak recommendation Moderate quality evidence
• For the above children where posaconazole is contraindicated, fluconazole 6–12 mg/kg/day (maximum 400 mg/day) IV/PO is suggested as an alternative to posaconazole	Weak recommendation Low quality evidence
• For children 1 month to <13 years of age undergoing allogeneic HSCT with acute Grade II–IV or chronic extensive GVHD, fluconazole 6–12 mg/kg/day (maximum 400 mg/day) IV/PO from GVHD diagnosis until resolution of acute Grade II–IV GVHD or chronic extensive GVHD is suggested	Weak recommendation Low quality evidence

RECOMMENDATIONS	Strength of Recommendation and Quality of Evidence
AUTOLOGOUS HSCT WITH ANTICIPATED NEUTROPENIA >7 DAYS	
• For children 1 month to <19 years of age undergoing autologous HSCT with anticipated neutropenia for >7 days, administer fluconazole 6–12 mg/kg/day (maximum 400 mg/day) IV/PO from the start of conditioning until engraftment	Strong recommendation Moderate quality evidence
PATIENTS WITH AML/MDS	
• For children 1 month to <19 years of age with AML or MDS, administer fluconazole 6–12 mg/kg/day (maximum 400 mg/day) IV/PO during chemotherapy-associated neutropenia	Strong recommendation Moderate quality evidence
• For children 13 years of age or older with AML or MDS, posaconazole 200 mg PO TID is suggested as an alternative to fluconazole in centers where there is a high local incidence of mold infections or if fluconazole is not available	Weak recommendation Moderate quality evidence
FOR OTHER PATIENTS WITH MALIGNANCY WITH ANTICIPATED NEUTROPENIA >7 DAYS	
• The panel suggests that antifungal prophylaxis not be given routinely to children with malignancy and neutropenia anticipated to persist for >7 days, outside of patients undergoing HSCT or those with AML/MDS	Weak recommendation Moderate quality evidence

HSCT, hematopoietic stem cell transplant; GVHD, graft-versus-host-disease; AML, acute myeloid leukemia; MDS, myelodysplastic syndrome.

2. Antithrombotic Therapy in Neonates and Children: Antithrombotic Therapy and Prevention of Thrombosis

The "Antithrombotic Therapy in Neonates and Children: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-based Clinical Practice Guidelines" were endorsed by the COG Supportive Care Guideline Committee in May 2015. The entire document and is available at: http://chestjournal.chestpubs.org/content/141/2_suppl/e737S.full.html.
Supplementary material provided by the guideline developers is available at:
http://chestjournal.chestpubs.org/content/suppl/2012/02/03/141.2_suppl.

The purpose of this guideline is to provide evidence-based recommendations for antithrombotic therapy in neonates and children with cancer and the perioperative management of antithrombotic therapy.

The recommendations of the endorsed guideline pertaining to children receiving cancer treatment are provided here.

I. Summary of Recommendations for Antithrombotic Therapy in Neonates and Children with Cancer

RECOMMENDATIONS	Strength of Recommendation and Quality of Evidence
GENERAL MANAGEMENT OF PEDIATRIC PATIENTS WITH THROMBOEMBOLISM	
Pediatric patients with thromboembolism	
• Suggest that where possible, pediatric hematologists with experience in thromboembolism manage pediatric patients with thromboembolism	Weak recommendation, low- or very-low-quality evidence
• When this is not possible, suggest a combination of a neonatologist/pediatrician and adult hematologist supported by consultation with an experienced pediatric hematologist	Weak recommendation, low- or very-low-quality evidence
VTE IN CHILDREN	
Children with first VTE (CVAD and non-CVAD related)	
• Recommend acute anticoagulation therapy with either UFH or LMWH	Strong recommendation, moderate-quality evidence
• Recommend initial treatment with UFH or LMWH for at least 5 days	Strong recommendation, moderate-quality evidence
• For ongoing therapy, recommend LMWH	-
Children with secondary VTE (ie VTE that has occurred association with a clinical risk factor) whom the risk factor has resolved	
• Suggest continuing anticoagulant therapy beyond 3 months as compared with no further therapy	Weak recommendation, low- or very-low-quality evidence

RECOMMENDATIONS	Strength of Recommendation and Quality of Evidence
Children who have ongoing but potentially reversible risk factors such as active nephrotic syndrome or ongoing asparaginase therapy:	
• Suggest continuing anticoagulant therapy beyond 3 months in either therapeutic or prophylactic doses until the risk factor has resolved	Weak recommendation, low- or very-low-quality evidence
Children with a CVAD place who have a VTE:	
• If a CVAD is no longer required or is nonfunctioning, recommend it be removed	Strong recommendation, moderate-quality evidence
• Suggest at least 3 to 5 days of anticoagulation therapy prior to its removal rather than no anticoagulation prior to removal	Weak recommendation, low- or very-low-quality evidence
• If CVAD access is required and the CVAD is still functioning, suggest that the CVAD remain in situ and the patient given anticoagulants	Weak recommendation, low- or very-low-quality evidence
Children with first CVAD-related VTE:	
• Suggest initial management as for secondary VTE as previously described	-
Children with CVAD in place who a VTE and in whom the CVAD remains necessary:	
• Suggest, after the initial 3 months of therapy, that prophylactic doses of VKAs (INR range, 1.5-1.9) or LMWH (anti-Xa level range, 0.1-0.3 units/mL) be given until the CVAD is removed	Weak recommendation, low- or very-low-quality evidence
• If recurrent thrombosis occurs while the patient is receiving prophylactic therapy, suggest continuing therapeutic doses until the CVAD is removed and for a minimum of 3 months following the VTE	Weak recommendation, low- or very-low-quality evidence
DVT IN CHILDREN WITH CANCER	
Children with cancer:	
• Suggest that management of VTE follow the general recommendations for management of VTE in children	-
• Suggest the use of LMWH in the treatment of VTE for a minimum of 3 months until the precipitating factor has resolved (eg, use of asparaginase) *Remarks: The presence of cancer, the need for surgery, chemotherapy, or other treatments may modify the risk-benefit ratio for treatment of VTE, and clinicians should consider these factors on an individual basis*	Weak recommendation, low- or very-low-quality evidence
CHILDREN WITH CVADS	
Children with CVADs:	
• Suggest flushing with normal saline or heparin or intermittent recombinant urokinase to maintain patency as compared with no therapy	Weak recommendation, low- or very-low-quality evidence

RECOMMENDATIONS	Strength of Recommendation and Quality of Evidence
Children with blocked CVADs:	
• Suggest tPA or recombinant urokinase to restore patency	Weak recommendation, low- or very-low-quality evidence
• If at least 30 minutes following local thrombolytic instillation CVAD patency is not restored, suggest a second dose be administered	-
• If the CVAD remains blocked following two doses of local thrombolytic agent, suggest radiologic imaging to rule out a CVAD-related thrombosis	Weak recommendation, low- or very-low-quality evidence
Children with short- to medium-term CVADs:	
• Recommend against the use of routine systemic thromboprophylaxis	Strong recommendation, moderate-quality evidence

II. Summary of Recommendations for Perioperative Management of Antithrombotic Therapy

RECOMMENDATIONS	Strength of Recommendation and Quality of Evidence
PERIOPERATIVE USE OF IV UFH	
Patients who are receiving bridging anticoagulation with therapeutic-dose IV UFH:	
• Suggest stopping UFH 4 to 6 h before surgery instead of closer to surgery	Weak recommendation, low- or very-low-quality evidence
PERIOPERATIVE INTERRUPTION OF THERAPEUTIC-DOSE BRIDGING LMWH	
Patients who are receiving bridging anticoagulation with therapeutic-dose SC LMWH:	
• Suggest administering the last preoperative dose of LMWH approximately 24 h before surgery instead of 12 h before surgery	Weak recommendation, low- or very-low-quality evidence
POSTOPERATIVE RESUMPTION OF THERAPEUTIC-DOSE BRIDGING LMWH	
Patients who are receiving bridging anticoagulation with therapeutic-dose SC LMWH and are undergoing high-bleeding-risk surgery:	
• Suggest resuming therapeutic dose LMWH 48 to 72 h after surgery instead of resuming LMWH within 24 h after surgery	Weak recommendation, low- or very-low-quality evidence

3. Clinical Practice Guideline on Central Venous Catheter Care for the Patient with Cancer

The "Clinical Practice Guideline on Central Venous Catheter Care for the Patient with Cancer" was endorsed by the COG Supportive Care Guideline Committee in October 2016.

The source guideline is published (Schiffer CA, Mangu PB, Wade JC, et al. JCO 2013: 31:1357-1370. DOI: 10.1200/JCO.2012.45.5733) and is available at:
http://jco.ascopubs.org/content/31/10/1357.full.pdf+html

The purpose of this guideline is to assist in care and decision making for patients with cancer who often have long-term central venous catheters and to identify areas of controversy, promoting future research and clinical trials.

The recommendations of the endorsed guideline are presented below.

Summary of Recommendations for Central Venous Catheter Care for the Patient with Cancer

RECOMMENDATIONS	Strength of Recommendation and Quality of Evidence*
In patients with cancer, does catheter type, insertion site, or placement technique affect complication rates?	
1.1. There is insufficient evidence to recommend one type of CVC routinely for all patients with cancer; the choice of catheter should be influenced by the expected duration of use, chemotherapy regimens, and patient ability to provide care; the minimum number of lumens essential for the management of the patient is recommended; these issues should be discussed with the patient 1.2. There is insufficient evidence to recommend one insertion site or approach (left sided or right sided) for tunneled CVCs for patients with cancer; individual risks and benefits (comfort, security, maintenance of asepsis) of the catheter site should be considered; the Panel recommends that CVC insertion into the femoral vein be avoided because of increased infection risks and concerns about thrombosis, except in certain emergency situations 1.3. Most CVC placement in patients with cancer is performed as an elective procedure; although image-guided insertion (eg, ultrasound guided, fluoroscopy) of CVCs is recommended, well-trained providers who use the landmark method regularly (eg, for subclavian or internal jugular) may have high rate of success and low incidence of acute and/or chronic complications	**No formal grading system used**

RECOMMENDATIONS	Strength of Recommendation and Quality of Evidence*
What is effective prophylaxis for the prevention of catheter related infections?	
2.1. CVC care clinical bundle (including hand hygiene, maximal barrier precautions, chlorhexidine skin antisepsis during catheter insertion, optimal catheter site selection, and assessment of CVC necessity) is recommended for placement and maintenance of all CVCs to prevent infections; there is no evidence that particular dressing types or more frequent IV set and/or dressing changes decrease risk of infection; use of topical antibiotic ointment or cream on insertion sites is not recommended because of potential to promote fungal infections and resistance to antimicrobials; scheduled guidewire exchange of CVC may be associated with greater risk of infection versus catheter replacement at new vascular site; thus, guidewire exchange is not routinely recommended, unless access options are limited 2.2. Use of antimicrobial/antiseptic-impregnated or -coated CVCs (CH-SS or minocycline/rifampin) and/or heparin impregnated catheters is recommended to decrease risk of catheter-related infections for short-term CVCs, particularly in high-risk groups such as bone marrow transplantation recipients or patients with leukemia; however, relative benefit and increased cost must be carefully considered before they are routinely used 2.3. Prophylactic use of systemic antibiotics (IV or oral) before insertion of long-term CVCs is not recommended 2.4. There are conflicting data about the relative value of prophylactic heparin with saline flushes to prevent catheter-associated bloodstream infections or thrombosis; data are not sufficient to recommend for or against routine use of antibiotic-flush/antibiotic-lock therapy	**No formal grading system used**
What are effective treatments for the management of catheter related infections?	
3.1. Cultures of blood from the catheter and when appropriate of soft tissues at entrance-exit sites or tunnel should be obtained before initiation of antibiotic therapy; most exit- or entrance-site infections can be treated successfully with appropriate antimicrobial therapy without the need for catheter removal, although removal is usually needed for clinically apparent tunnel or port-site infections; antimicrobial agents should be optimized once pathogens are identified and antibiotic susceptibilities defined	**No formal grading system used**

RECOMMENDATIONS	Strength of Recommendation and Quality of Evidence*
What is effective prophylaxis for the prevention of catheter related thrombosis?	
4.1. Use of systemic anticoagulation (warfarin, LMWH, UFH) has not been shown to decrease incidence of catheter-associated thrombosis; therefore, routine prophylaxis with anticoagulants is not recommended for patients with cancer with CVCs; routine flushing with saline of the CVC to prevent fibrin buildup is recommended 4.2. Data are insufficient to recommend routine use of urokinase (not available in the United States) and/or other thrombolytics to prevent catheter occlusion	**No formal grading system used**
What are effective treatments for the management of catheter related occlusions?	
5.1. Instillation of 2-mg t-PA is recommended to restore patency and preserve catheter function 5.2. Although it is appropriate to try to clear thrombosis with the CVC in place, if there is radiologically confirmed thrombosis that does not respond to fibrinolytic therapy or if fibrinolytic or anticoagulation therapy is contraindicated, catheter removal is recommended; prolonged retention of unneeded CVCs can lead to significant problems associated with thrombosis and fibrosis; 3 to 6 months of anticoagulant therapy with LMWH or LMWH followed by warfarin (INR, 2.0 to 3.0) is recommended for treatment of symptomatic CVC thrombosis, with duration depending on clinical issues in individual patients	**No formal grading system used**

4. Guidelines for the Prevention and Treatment of Nausea and Vomiting due to Antineoplastic Medication in Pediatric Cancer Patients

This document summarizes four clinical practice guidelines on the topic of chemotherapy-induced nausea and vomiting:
4.1 The "Guideline for Classification of the Acute Emetogenic Potential of Antineoplastic Medication in Pediatric Cancer Patients" (endorsed by the COG Supportive Care Guideline Committee in August 2014).
4.2 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 August 2014).
4.3 The "Guideline for the Prevention and Treatment of Anticipatory Nausea and Vomiting due to Chemotherapy in Pediatric Cancer Patients" (endorsed by the COG Supportive Care Guideline Committee in August 2014) and
4.4 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 "Guideline for Classification of the Acute Emetogenic Potential of Antineoplastic Medication in Pediatric Cancer Patients" and implementation tools provided by the guideline developers can be found at: http://www.pogo.ca/healthcare/practiceguidelines/pogoemetogenicitycla/

A summary of the guideline is published in Pediatric Blood and Cancer 2011; 2011; 57:191-8. http://onlinelibrary.wiley.com/doi/10.1002/pbc.23114/pdf)

The purpose of this guideline is to provide an evidence-based approach to the assessment of the emetogenic potential of antineoplastic regimens in children. 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. What risk of acute phase CINV do antineoplastic therapies present to children with cancer?	
The single antineoplastic agents provided in Table 1 have high, moderate, low or minimal emetogenic potential in children.	Strong recommendation Very low to low quality of evidence
2. Is the risk of CINV with multi-agent, single day antineoplastic therapy different than that of the most emetogenic antineoplastic given?	
With the exceptions noted in Table 2 below, the emetogenicity of multiple agent antineoplastic therapy given to children is classified based on the emetogenic potential of the most highly emetogenic agent in the combination to be given.	Strong recommendation Very low to low quality of evidence

RECOMMENDATIONS	Strength of Recommendation and Quality of Evidence
3. Is the risk of CINV with multiple day antineoplastic therapy regimens different than that of the most emetogenic antineoplastic therapy given on any individual day?	
The emetogenicity of multiple day antineoplastic therapy is classified in children based on the emetogenic potential of the most highly emetogenic agent on each day of therapy.	Weak recommendation Very low quality of evidence

Table 1: Classification of the Acute Emetogenic Potential of Antineoplastic Medication in Pediatric Cancer Patients Given as Single Agents

High Level of Emetic Risk (> 90% frequency of emesis in absence of prophylaxis)		
Altretamine *Carboplatin Carmustine > 250 mg/m^2 *Cisplatin *Cyclophosphamide ≥1 g/m^2	*Cytarabine 3 g/m^2/dose Dacarbazine *Dactinomycin Mechlorethamine	*Methotrexate ≥ 12 g/m^2 Procarbazine (oral) Streptozocin *Thiotepa ≥ 300 mg/m^2
Moderate Level of Emetic Risk (30-90% frequency of emesis in absence of prophylaxis)		
Aldesleukin > 12 to 15 million units/m^2 Amifostine > 300 mg/m^2 Arsenic trioxide Azacitidine Bendamustine Busulfan *Carmustine ≤ 250 mg/m^2 *Clofarabine *Cyclophosphamide < 1 g/m^2	Cyclophosphamide (oral) Cytarabine > 200 mg to < 3 g/m^2 *Daunorubicin *Doxorubicin Epirubicin Etoposide (oral) Idarubicin Ifosfamide Imatinib (oral)	*Intrathecal therapy (methotrexate, hydrocortisone & cytarabine) Irinotecan Lomustine Melphalan > 50 mg/m^2 Methotrexate ≥ 250 mg to < 12 g/m^2 Oxaliplatin > 75 mg/m^2 Temozolomide (oral) Vinorelbine (oral)
Low Level of Emetic Risk (10-<30% frequency of emesis in absence of prophylaxis)		
Amifostine ≤ 300 mg/m^2 Amsacrine Bexarotene *Busulfan (oral) Capecitabine Cytarabine ≤ 200 mg/m^2 Docetaxel Doxorubicin (liposomal)	Etoposide Fludarabine (oral) 5-Fluorouracil Gemcitabine Ixabepilone Methotrexate > 50 mg to < 250 mg/m^2 Mitomycin Mitoxantrone	Nilotinib Paclitaxel Paclitaxel-albumin Pemetrexed Teniposide Thiotepa < 300 mg/m^2 Topotecan Vorinostat

Minimal (<10% frequency of emesis in absence of prophylaxis)		
Alemtuzumab	Erlotinib	Rituximab
Alpha interferon	Fludarabine	Sorafenib
Asparaginase (IM or IV)	Gefitinib	Sunitinib
Bevacizumab	Gemtuzumab ozogamicin	Temsirolimus
Bleomycin	Hydroxyurea (oral)	Thalidomide
Bortezomib	Lapatinib	Thioguanine (oral)
Cetuximab	Lenalidomide	Trastuzumab
Chlorambucil (oral)	Melphalan (oral low-dose)	Valrubicin
Cladribine (2-chlorodeoxyadenosine)	Mercaptopurine (oral)	Vinblastine
	Methotrexate ≤ 50 mg/m^2	Vincristine
Decitabine	Nelarabine	Vindesine
Denileukin diftitox	Panitumumab	Vinorelbine
Dasatinib	Pentostatin	
Dexrazoxane		

* Pediatric evidence available. Note: All agents given intravenously (IV) unless stated otherwise.

Table 2: Classification of the Acute Emetogenic Potential of Specific Antineoplastic Medication in Pediatric Cancer Patients Given in Combination

High Level of Emetic Risk (> 90% frequency of emesis in absence of prophylaxis)	
Cyclophosphamide + anthracycline	*Cytarabine 300 mg/m^2 + etoposide
*Cyclophosphamide + doxorubicin	*Cytarabine 300 mg/m^2 + teniposide
*Cyclophosphamide + epirubicin	*Doxorubicin + ifosfamide
*Cyclophosphamide + etoposide	Doxorubicin + methotrexate 5 g/m^2
*Cytarabine 150-200 mg/m^2 + daunorubicin	*Etoposide + ifosfamide

* Pediatric evidence available
Note: All agents given intravenously (IV) unless stated otherwise.

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" and the implementation tools provided by the guideline developers are available at: http://www.pogo.ca/healthcare/practiceguidelines/acuteainvguideline/

A summary of the guideline is published in Pediatric Blood and Cancer 2013; 60: 1073-82. http://onlinelibrary.wiley.com/doi/10.1002/pbc.24508/pdf

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. How is optimal control of acute CINV defined?	
We recommend that optimal control of acute CINV be defined as no vomiting, no retching, no nausea, no use of antiemetic agents other than those given for CINV prevention and no nausea-related change in the child's usual appetite and diet. This level of CINV control is to be achieved on each day that antineoplastic therapy is administered and for 24 hours after administration of the last antineoplastic agent of the antineoplastic therapy block	Strong recommendation Very low quality evidence
2a. What pharmacological interventions provide optimal control of acute CINV in children receiving antineoplastic agents of high emetic risk?	
We recommend that: • Children ≥ 12 years old and receiving anti-neoplastic agents of high emetic risk which are not known or suspected to interact with aprepitant receive: *ondansetron or granisetron + dexamethasone + aprepitant* • Children ≥ 12 years old and receiving anti-neoplastic agents of high emetic risk which are known or suspected to interact with aprepitant receive: *ondansetron or granisetron + dexamethasone* • Children < 12 years old and receiving antineoplastic agents of high emetic risk receive: *ondansetron or granisetron + dexamethasone*	Strong recommendation Very low quality evidence Strong recommendation Moderate quality evidence Strong recommendation Moderate quality evidence
2b. What pharmacological interventions provide optimal control of acute CINV in children receiving antineoplastic agents of moderate emetic risk?	
We recommend that children receiving antineoplastic agents of moderate emetogenicity receive: *ondansetron or granisetron + dexamethasone*	Strong recommendation Moderate quality evidence
2c. What pharmacological interventions provide optimal control of acute CINV in children receiving antineoplastic agents of low emetic risk?	
We recommend that children receiving antineoplastic agents of low emetic risk receive: *ondansetron or granisetron*	Strong recommendation Moderate quality evidence
2d. What pharmacological interventions provide optimal control of acute CINV in children receiving antineoplastic agents of minimal emetic risk?	
We recommend that children receiving antineoplastic agents of low emetic risk receive: *no routine prophylaxis*	Strong recommendation Very low quality evidence

RECOMMENDATIONS	Strength of Recommendation and Quality of Evidence
3. What adjunctive non-pharmacological interventions provide control of acute CINV in children receiving antineoplastic agents of any emetic risk?	
We suggest that acupuncture, acupressure, guided imagery, music therapy, progressive muscle relaxation and psycho-educational support and information may be effective in children receiving antineoplastic agents. Virtual reality may convey benefit. We suggest that the following dietary interventions may be effective: • eat smaller, more frequent meals; • reduce food aromas and other stimuli with strong odours; • avoid foods that are spicy, fatty or highly salty; • take antiemetics prior to meals so that the effect is present during and after meals; and • measures and foods (e.g. "comfort foods") that helped to minimize nausea in the past	Weak recommendation Very low quality evidence
4. What is the role of aprepitant in children receiving antineoplastic therapy?	
We recommend that the use of aprepitant be restricted to children 12 years of age and older who are about to receive highly emetogenic antineoplastic therapy which is not known or suspected to interact with aprepitant. There is no evidence to support the safe and effective use of aprepitant in younger children.	Strong recommendation Very low quality evidence
5. What pharmacological interventions provide optimal control of acute CINV in children receiving highly or moderately emetogenic agents in whom corticosteroids are contra-indicated?	
We suggest that children receiving highly emetogenic antineoplastic therapy who cannot receive corticosteroids receive: *ondansetron or granisetron* *+* *chlorpromazine or nabilone* We suggest that children receiving moderately emetogenic antineoplastic therapy who cannot receive corticosteroids receive: *ondansetron or granisetron* *+* *chlorpromazine or metoclopramide or nabilone*	Weak recommendation Low quality evidence Weak recommendation Low quality evidence

RECOMMENDATIONS	Strength of Recommendation and Quality of Evidence
6. What doses of antiemetic agents are known to be effective in children receiving antineoplastic agents?	
We recommend the following **aprepitant** dose for children 12 years of age and older: *Day 1: 125mg PO x 1; Days 2 and 3: 80mg PO once daily*	Strong recommendation Moderate quality evidence
We recommend the following **chlorpromazine** dose: *0.5mg/kg/dose IV q6h*	Strong recommendation Low quality evidence
We suggest the following **dexamethasone** for children receiving highly emetogenic antineoplastic therapy: *6 mg/m^2/dose IV/PO q6h* If given concurrently with aprepitant, reduce dexamethasone dose by half.	Weak recommendation Low quality evidence
We recommend the following **dexamethasone** for children receiving moderately emetogenic antineoplastic therapy: *≤ 0.6m^2: 2mg/dose IV/PO q12h* *> 0.6m^2: 4mg/dose IV/PO q12h* If given concurrently with aprepitant, reduce dexamethasone dose by half	Strong recommendation Low quality evidence
We recommend the following IV **granisetron** dose for children receiving highly emetogenic antineoplastic therapy: *40 mcg/kg/dose IV as a single daily dose*	Strong recommendation Low quality evidence
We recommend the following IV **granisetron** dose for children receiving moderately emetogenic antineoplastic therapy: *40 mcg/kg/dose IV as a single daily dose*	Strong recommendation Moderate quality evidence
We suggest the following oral **granisetron** dose for children receiving moderately emetogenic antineoplastic therapy: *40 mcg/kg/dose PO q12h*	Weak recommendation Low quality evidence
We recommend the following IV **granisetron** dose for children receiving antineoplastic therapy of low emetogenicity: *40 mcg/kg/dose IV as a single daily dose*	Strong recommendation Low quality evidence
We suggest the following oral **granisetron** dose for children receiving antineoplastic therapy of low emetogenicity: *40 mcg/kg/dose PO q12h*	Weak recommendation Low quality evidence
We recommend the following **metoclopramide** dose for children receiving moderately emetogenic antineoplastic therapy: *1 mg/kg/dose IV pre-therapy x 1 then* *0.0375 mg/kg/dose PO q6h* Give diphenhydramine or benztropine concurrently.	Strong recommendation Low quality evidence

RECOMMENDATIONS	Strength of Recommendation and Quality of Evidence
We suggest the following **nabilone** dose: *< 18 kg: 0.5 mg/dose PO twice daily* *18 to 30 kg: 1 mg/dose PO twice daily* *> 30 kg: 1 mg/dose PO three times daily* *Maximum: 0.06 mg/kg/day*	Weak recommendation Low quality evidence
We recommend the following ondansetron dose for children receiving highly emetogenic antineoplastic therapy: *5 mg/m^2/dose (0.15 mg/kg/dose) IV/PO pre-therapy x 1 and then q8h*	Strong recommendation Moderate quality evidence
We recommend the following ondansetron dose for children receiving moderately emetogenic antineoplastic therapy: *5 mg/m^2/dose (0.15 mg/kg/dose; maximum 8 mg/dose) IV/PO pre-therapy x 1 and then q12h*	Strong recommendation Moderate quality evidence
We recommend the following ondansetron dose for children receiving therapy of low emetogenicity: *10 mg/m^2/dose (0.3 mg/kg/dose; maximum 16 mg/dose IV or 24 mg/dose PO) pre-therapy x 1*	Strong recommendation Low quality evidence

4.3 **Prevention and Treatment of Anticipatory Chemotherapy-Induced Nausea and Vomiting**

The "Guideline for the Prevention and Treatment of Anticipatory Nausea and Vomiting due to Chemotherapy in Pediatric Cancer Patients" and the implementation tools provided by the guideline developers are available at: http://www.pogo.ca/healthcare/practiceguidelines/anticipatorycinv/

A summary of the guideline is published in Pediatric Blood and Cancer 2014; 61: 1506-12. http://onlinelibrary.wiley.com/doi/10.1002/pbc.25063/pdf

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

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

RECOMMENDATIONS	Strength of Recommendation and Quality of Evidence
1. What approaches are recommended to prevent the development of anticipatory chemotherapy induced nausea and vomiting (CINV) in children?	
Control of acute and delayed CINV should be optimized for each child in order to minimize the risk of the child developing anticipatory CINV.	Strong recommendation Low quality evidence
2. What interventions are recommended to control anticipatory CINV in children who develop it?	
We suggest that psychological interventions such as hypnosis or systematic desensitization may be offered to children with anticipatory CINV.	Weak recommendation Moderate quality evidence
We suggest that lorazepam in a dose of 0.04 to 0.08 mg/kg/dose (maximum: 2 mg/dose) once at bedtime the night before chemotherapy and once the next day prior to administration of chemotherapy may be used to prevent or treat anticipatory CINV in children.	Weak recommendation Low quality evidence

4.4 **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

5. Fertility Preservation for Patients with Cancer

The "Fertility Preservation for Patients with Cancer" guideline was endorsed by the COG Supportive Care Guideline Committee in December 2014. The entire document and implementation tools provided by the guideline developers are available at:
http://www.instituteforquality.org/fertility-preservation-patients-cancer-american-society-clinical-oncology-guideline-update

A summary is published in the Journal of Clinical Oncology 2013; 31:2500-2510. http://jco.ascopubs.org/content/31/19/2500

The purpose of this guideline is to address four questions: (1) Are patients with cancer interested in interventions to preserve fertility? (2) What is the quality of evidence supporting current and forthcoming options for preservation of fertility in males? (3) What is the quality of evidence supporting current and forthcoming options for preservation of fertility in females? (4) What is the role of the oncologist in advising patients about fertility preservation options? Special fertility preservation considerations for children and adolescents with cancer are also provided.

The recommendations pertaining to questions 2 and 3 and pediatric considerations are provided here. Please refer to the source document for recommendations pertaining to questions 1 and 4.

Summary of Recommendations for Fertility Preservation for Patients with Cancer

RECOMMENDATIONS	Strength of Recommendation and Quality of Evidence
2. What is the quality of evidence supporting current and forthcoming options for preservation of fertility in males?	
2.1 Sperm cryopreservation: Sperm cryopreservation is effective, and health care providers should discuss sperm banking with post-pubertal males receiving cancer treatment.	No formal grading system used
2.2 Hormonal gonado-protection: Hormonal therapy in men is not successful in preserving fertility. It is not recommended.	No formal grading system used
2.3 Other methods to preserve male fertility: Other methods, such as testicular tissue cryopreservation and re-implantation 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 Post-chemotherapy: 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 session. 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. Intra-cytoplasmic 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

RECOMMENDATIONS	Strength of Recommendation and Quality of Evidence
3. What is the quality of evidence supporting current and forthcoming options for preservation of fertility in females?	
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, particularly for patients 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. 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 cryopreservation is now possible on a cycle day–independent schedule.	No formal grading system used
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 < 10mm. 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

RECOMMENDATIONS	Strength of Recommendation and Quality of Evidence
3.5 Ovarian suppression: Currently, there is insufficient evidence regarding the effectiveness of GnRHa and other means of ovarian suppression in fertility preservation. GnRHa should not be relied upon as a fertility preservation method. However, GnRHa may have other medical benefits such as a reduction of vaginal bleeding when patients have low platelet counts as a result of chemotherapy. This benefit must be weighed against other possible risks such as bone loss, hot flashes, and potential interference with response to chemotherapy in estrogen-sensitive cancers. Women interested in this method should participate in clinical trials, because current data do not support it. In a true emergency or rare or extreme circumstances where proven options are not available, providers may consider GnRHa an option, preferably as part of a clinical trial.	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 or sexual maturity and hence may be the only method available in children. It is considered experimental and should be performed only in centers with the necessary expertise, under IRB-approved protocols that include follow-up for recurrent cancer. A theoretic concern with re-implanting ovarian tissue is the potential for reintroducing cancer cells depending on the type and stage of cancer, although so far there have been no reports of cancer recurrence.	No formal grading system used
3.7 Other considerations: Of special concern in estrogen-sensitive breast and gynecologic malignancies is the possibility that fertility preservation interventions (eg, ovarian stimulation regimens that increase estrogen levels) and/or subsequent pregnancy may increase the risk of cancer recurrence. Ovarian stimulation protocols using the aromatase inhibitor letrozole have been developed and may ameliorate this concern. Studies do not indicate increased cancer recurrence risk as a result of subsequent pregnancy.	No formal grading system used
5. Special fertility preservation considerations for children and adolescents with cancer:	
5.1 Suggest established methods of fertility preservation (eg, semen or oocyte cryopreservation) for postpubertal minor children, with patient assent and parent or guardian consent. For prepubertal minor children, the only fertility preservation options are ovarian and testicular cryopreservation, which are investigational.	No formal grading system used

6. Guideline for the 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

7. Guideline for the Prevention of Oral and Oropharyngeal Mucositis in Children receiving Treatment for Cancer or undergoing Hematopoietic Stem Cell Transplantation

The "Guideline for the prevention of oral and oropharyngeal mucositis in children receiving treatment for cancer or undergoing haematopoietic stem cell transplantation" was endorsed by the COG Supportive Care Guideline Committee in February 2016.

The source guideline is published (Sung L, Robinson P, Treister N, et al. BMJ Supportive & Palliative Care Published Online First: 24/03/2016 doi:10.1136/bmjspcare-2014-000804) and is available at: http://dx.doi.org/10.1136/bmjspcare-2014-000804

The purpose of this guideline is to to develop an evidence-based clinical practice guideline for the prevention of oral mucositis in children (0–18 years) receiving treatment for cancer or undergoing hematopoietic stem cell transplant.

The recommendations of the endorsed guideline are presented below.

Summary of Recommendations for the Prevention of Oral and Oropharyngeal Mucositis in Children receiving Treatment for Cancer or undergoing Hematopoietic Stem Cell Transplantation

RECOMMENDATIONS	Strength of Recommendation and Quality of Evidence
What prophylactic interventions are effective at preventing or reducing the severity of oral and oropharyngeal mucositis in children (0–18 years) receiving treatment for cancer or undergoing haematopoietic stem cell transplantation?	
• We suggest that cryotherapy may be offered to cooperative children receiving chemotherapy or hematopoietic stem cell transplant conditioning with regimens associated with a high rate of mucositis	Weak recommendation, Moderate quality evidence
• We suggest that low-level light therapy may be offered to cooperative children receiving chemotherapy or hematopoietic stem cell transplant conditioning with regimens associated with a high rate of mucositis	Weak recommendation, High quality evidence
• We suggest that keratinocyte growth factor may be offered to children receiving hematopoietic stem cell transplant conditioning with regimens associated with a high rate of severe mucositis	Weak recommendation High quality evidence

8. Guidance for Platelet Transfusion for Patients with Hypoproliferative Thrombocytopenia

The "Guidance for Platelet Transfusion for Patients with Hypoproliferative Thrombocytopenia" was endorsed by the COG Supportive Care Guideline Committee in April 2016.

The source guideline is published (Nahirniak S, Slichter SJ, Tanael S, et al. Transfusion Medicine Reviews 2015: 29; 3-13. doi.org/10.1016/j.tmrv.2014.11.004) and is available at: http://www.tmreviews.com/article/S0887-7963(14)00095-9/pdf

The purpose of this guideline is to to develop an evidence-based clinical practice guideline to assist hematologists, oncologists, and transfusion medicine specialists in optimizing platelet transfusion therapy for patients with hypoproliferative thrombocytopenia.

The recommendations of the endorsed guideline are presented below.

Summary of Recommendations for Platelet Transfusion for Patients with Hypoproliferative Thrombocytopenia

RECOMMENDATIONS	Strength of Recommendation and Quality of Evidence*
Should patients with hypoproliferative thrombocytopenia receive prophylactic platelet transfusions?	
• Prophylactic platelet transfusion should be given to patients with hypoproliferative thrombocytopenia.	Strong recommendation, Moderate level evidence
What platelet transfusion threshold should be used?	
• A threshold of less than or equal to 10×10^9/L should be used for prophylactic platelet transfusion for patients with hypoproliferative thrombocytopenia.	Strong recommendation, Weak level evidence
• Patients with hypoproliferative thrombocytopenia with clinically significant bleeding attributed to thrombocytopenia should probably receive platelet transfusions even if the platelet count is above 10×10^9/L.	Weak recommendation, Very weak level of evidence
What platelet dose should be used?	
• Low- or standard-dose platelet transfusion (i.e., $1.1 \times 10^{11}/m^2$ or $2.2 \times 10^{11}/m^2$, respectively), as opposed to high-dose platelet transfusion ($4.4 \times 10^{11}/m^2$), should be given to hospitalized patients with hypoproliferative thrombocytopenia who require prophylactic platelet transfusion. Conversion to platelet units can be performed using estimates of 50×10^9 per unit of whole blood derived, random-donor platelet products or 300×10^9 per unit apheresis or buffy coat pooled products.	Strong recommendation, High level of evidence

RECOMMENDATIONS	Strength of Recommendation and Quality of Evidence*
Implementation tips from the COG Supportive Care Guideline Committee: 1) In general, platelets that are collected via apheresis have a higher concentration (plt/mL) than pooled units collected as the platelet portion from whole blood donation. However, there is significant variability in platelet concentration within each type of platelet product (whole blood donation vs. apheresis collection) and between centers. **The platelet doses recommended above can be converted to approximate platelet dose volumes after consultation with local transfusion medicine specialists.** 2) For larger children or adolescents who require prophylactic platelet transfusion, the dose of transfused platelets should not exceed the usual adult dose.	
Should patients receive ABO-matched platelets?	
• Platelet concentrates that are ABO identical should probably be used in patients with hypoproliferative thrombocytopenia, if available.	Weak recommendation, Weak level of evidence
Do patients who are negative for the RhD antigen require Rh immunoglobulin if they receive RhD-positive platelets?	
• Female children and females of child-bearing age/potential, with hypoproliferative thrombocytopenia, who are RhD negative should probably receive Rh immunoglobulin before, immediately after, or within 72 hours of receiving an RhD-positive platelet component (unless antibody testing demonstrates the persistence of anti-D from a previous dose of Rh immunoglobulin)	Weak recommendation, Very weak level of evidence
• Males and females who are not of child-bearing age/potential, with hypoproliferative thrombocytopenia, who are RhD negative and are transfused with RhD-positive platelet components probably do not require Rh immunoglobulin.	Weak recommendation, Very weak level of evidence
Should patients receive HLA/HPA-selected or crossmatch-selected platelets?	
• Patients with hypoproliferative thrombocytopenia who are refractory to platelet transfusions and have class I HLA antibodies should probably receive class I HLA-selected or crossmatch-selected platelet transfusion to increase the platelet count.	Weak recommendation, Weak level of evidence
• Patients with hypoproliferative thrombocytopenia who are refractory to platelet transfusions and have HPA antibodies should probably receive HPA-selected or crossmatch-selected platelet transfusion to increase the platelet count.	Weak recommendation, Very weak level of evidence
• Patients with hypoproliferative thrombocytopenia who are refractory to platelet transfusions solely due to nonimmune factors should probably not receive HLA-selected or crossmatch-selected platelets.	Weak recommendation, Weak level of evidence

RECOMMENDATIONS	Strength of Recommendation and Quality of Evidence*
• Patients with hypoproliferative thrombocytopenia who are not refractory to platelet transfusion should probably not receive HLA-selected, HPA-selected, or crossmatch-selected platelets.	HLA and crossmatch selection: Weak recommendation, Weak level of evidence HPA-selection: Weak recommendation, Very weak level of evidence
Should patients receive apheresis-derived platelets instead of whole blood–derived platelets?	
• When leuko-reduced platelet products are available, WBD platelets (from buffy coat or PRP methods) should be used as equivalent products to apheresis platelets.	Strong recommendation, Moderate level of evidence

*as applied to recommendations for pediatric patients

Appendix 1: GRADE

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 Recommendation	Weak 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

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