CHILDREN'S ONCOLOGY GROUP

The world's childhood cancer experts

Supportive Care Guidelines

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The COG Supportive Care 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 12). 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.

1. 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 February 2014. The entire document and implementation tools provided by the guideline developers are available at: http://www.sickkids.ca/HaematologyOncology/IPFNG/index.html

A summary is published in the Journal of Clinical Oncology 2012; 30:4427-4438. http://jco.ascopubs.org/content/30/35/4427.full.pdf+html

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
1. Initial Presentation of Febrile Neutropenia	
1.1 Risk Stratification	
1.1a Adopt a validated risk stratification strategy and incorporate it into routine clinical management	Strong recommendation Low or very low quality evidence
1.2 Evaluation	
1.2a Obtain blood cultures at onset of febrile neutropenia from all lumens of central venous catheters	Strong recommendation Low or very low quality evidence
1.2b Consider peripheral-blood cultures concurrent with obtaining central venous catheter cultures	Weak recommendation Low or very low quality evidence
1.2c Consider urinalysis and urine culture in patients where clean-catch, midstream specimen is readily available	Weak recommendation Low or very low quality evidence
1.2d Obtain chest radiography only in symptomatic patients	Strong recommendation Moderate quality evidence
1.3 Treatment	
1.3a High-risk Febrile Neutropenia: Use monotherapy with antipseudomonal β-lactam or carbapenem as empiric therapy in pediatric high-risk febrile neutropenia	Strong recommendation High quality evidence
1.3b High-risk Febrile Neutropenia: Reserve addition of second Gram-negative agent or glycopeptides for patients who are clinically unstable, when resistant infection is suspected or for centers with high rate of resistant pathogens.	Strong recommendation Moderate quality evidence
1.3c Low-risk Febrile Neutropenia: In children with 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
1.3d Low-risk Febrile Neutropenia: In children with low-risk Febrile Neutropenia, consider oral antibiotic administration if child is able to tolerate this route of administration reliably.	Weak recommendation Moderate quality evidence

RECOMMENDATIONS	Strength of Recommendation and Quality of Evidence
2. Ongoing Management of Febrile Neutropenia: ≥ 24 to 72 hours after Initiation of Empiric Antibacterial Treatment	
2.1 Modification of Treatment	
2.1a 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
2.1b Do not modify initial empiric antibacterial regimen based solely on persistent fever in children who are clinically stable	Strong recommendation Low or very low quality evidence
2.1c In children with persistent fever who become clinically unstable, escalate initial empiric antibacterial regimen to include coverage for resistant Gram-negative, Gram positive, and anaerobic bacteria	Strong recommendation Low or very low quality evidence
2.2 Cessation of Treatment	
2.2a All patients: Discontinue empiric 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 or very low quality evidence
2.2b Low-risk Febrile Neutropenia: Consider discontinuation of empiric antibiotics at 72 hours in low-risk 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
3. Empiric Antifungal Treatment ≥96 Hours after Initiation of Empiric Antibacterial Treatment	
3.1Risk Stratification	
3.1a Patients at high risk of Invasive Fungal Disease are those with AML or relapsed acute leukemia, those receiving highly myelosuppressive chemotherapy for other malignancies, and those undergoing allogeneic HSCT with persistent fever despite prolonged (≥ 96 hours) broad-spectrum antibiotic therapy and expected prolonged neutropenia (> 10 days); all others should be categorized as Invasive Fungal Disease low risk	Strong recommendation Moderate quality evidence
3.2 Evaluation	
3.2a All patients: Consider galactomannan in brochoalveolar lavage and cerebrospinal fluid to support diagnosis of pulmonary or CNS aspergillosis	Weak recommendation Low or very low quality evidence
3.2b In children, do not use β-D-glucan testing for clinical decisions until further pediatric evidence has accumulated	Strong recommendation Low or very low quality evidence
3.2c Invasive Fungal Disease high risk: Consider prospective monitoring of serum galactomannan twice per week in Invasive Fungal Disease high-risk hospitalized children for early diagnosis of invasive aspergillosis	Weak recommendation Moderate quality evidence
3.2d In Invasive Fungal Disease high-risk children with persistent Febrile Neutropenia beyond 96 hours, perform evaluation for IFD; evaluation should include CT of lungs and targeted imaging of other clinically suspected areas of infection; consider CT imaging of sinuses in children ≥ 2 years of age	Weak recommendation Low or very low quality evidence
3.2e Invasive Fungal Disease low risk: In low-risk patients, do not implement routine galactomannan screening	Strong recommendation Low or very low quality evidence

RECOMMENDATIONS	Strength of Recommendation and Quality of Evidence
3.3 Treatment	
3.3a All patients: Use either caspofungin or liposomal amphotericin B for empiric antifungal therapy	Strong recommendation High quality evidence
3.3b Invasive Fungal Disease high risk: In neutropenic Invasive Fungal Disease high-risk children, initiate empiric antifungal treatment for persistent or recurrent fever of unclear etiology that is unresponsive to prolonged (≥ 96 hours) broad-spectrum antibacterial agents	Strong recommendation Low or very low quality evidence
3.3c Invasive Fungal Disease low risk: In neutropenic Invasive Fungal Disease low-risk children, consider empiric antifungal therapy in setting of persistent Febrile Neutropenia	Weak recommendation Low or very low quality evidence

2. **Guideline for the Prevention of Nausea and Vomiting due to Antineoplastic Medication in Pediatric Cancer Patients**

The "Guideline for the Prevention of Nausea and Vomiting due to Antineoplastic Medication in Pediatric Cancer Patients" was endorsed by the COG Supportive Care Guideline Committee in August 2014.

2.1 **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.

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
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	*Cytarabine 3 g/m^2/dose	*Methotrexate ≥ 12 g/m^2
*Carboplatin	Dacarbazine	Procarbazine (oral)
Carmustine > 250 mg/m^2	*Dactinomycin	Streptozocin
*Cisplatin	Mechlorethamine	*Thiotepa ≥ 300 mg/m^2
*Cyclophosphamide ≥1 g/m^2		
Moderate Level of Emetic Risk (30-90% frequency of emesis in absence of prophylaxis)		
Aldesleukin > 12 to 15 million units/m^2	Cyclophosphamide (oral)	*Intrathecal therapy (methotrexate, hydrocortisone & cytarabine)
Amifostine > 300 mg/m^2	Cytarabine > 200 mg to < 3 g/m^2	Irinotecan
Arsenic trioxide	*Daunorubicin	Lomustine
Azacitidine	*Doxorubicin	Melphalan > 50 mg/m^2
Bendamustine	Epirubicin	Methotrexate ≥ 250 mg to < 12 g/m^2
Busulfan	Etoposide (oral)	Oxaliplatin > 75 mg/m^2
*Carmustine ≤ 250 mg/m^2	Idarubicin	Temozolomide (oral)
*Clofarabine	Ifosfamide	Vinorelbine (oral)
*Cyclophosphamide < 1 g/m^2	Imatinib (oral)	
Low Level of Emetic Risk (10-<30% frequency of emesis in absence of prophylaxis)		
Amifostine ≤ 300 mg/m^2	Etoposide	Nilotinib
Amsacrine	Fludarabine (oral)	Paclitaxel
Bexarotene	5-Fluorouracil	Paclitaxel-albumin
*Busulfan (oral)	Gemcitabine	Pemetrexed
Capecitabine	Ixabepilone	Teniposide
Cytarabine ≤ 200 mg/m^2	Methotrexate > 50 mg to < 250 mg/m^2	Thiotepa < 300 mg/m^2
Docetaxel	Mitomycin	Topotecan
Doxorubicin (liposomal)	Mitoxantrone	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
Decitabine	Methotrexate ≤ 50 mg/m2	Vincristine
Denileukin diftitox	Nelarabine	Vindesine
Dasatinib	Panitumumab	Vinorelbine
Dexrazoxane	Pentostatin	

* 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.

2.2 **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 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

RECOMMENDATIONS	Strength of Recommendation and Quality of 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
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

RECOMMENDATIONS	Strength of Recommendation and Quality of 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*	Weak recommendation Low quality evidence
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
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

RECOMMENDATIONS	Strength of Recommendation and Quality of 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
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 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 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

2.3 **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

3. Fertility Preservation for Patients with Cancer

The "Fertility Preservation for Patients with Cancer" 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**

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.

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Children's Oncology Group

Supportive Care Guidelines

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Supportive Care Guidelines

The following guidelines are provided for institutional consideration. Investigator discretion should be used and institutional considerations made for specific patient situations. Study Chairs should be notified of any Serious Adverse Events, an investigator's decision to deviate in a major way from protocol-directed therapy, or a patient taken off study. All such actions should be documented in the medical record and the case report forms.

Aggressive supportive care improves outcome, particularly in high-risk patient populations. The following guidelines are intended to give general direction for optimal patient care and to encourage uniformity in the treatment of patients on COG studies. Additional supportive care guidance may also be found in:

Altman, AJ, ed. *Supportive Care of Children with Cancer*. 3rd ed. Baltimore, MD: The Johns Hopkins University Press; 2004.

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Blood components and transfusion support

Blood products should be irradiated following the current FDA guidelines found at: http://www.fda.gov/cber/gdlns/gamma.htm.

In Canada, blood and blood components are regulated by the Biologics and Genetics Therapies Directorate of Health Canada and are governed by the Food and Drugs Act, the Food and Drug Regulations, and the CSA standards for Blood and Blood Components CAN/CSA-Z902-04 (March 2004).

Red Blood Cells

Transfusion with red blood cells (RBCs) is indicated to correct severe or symptomatic anemia or acute blood loss.

Platelets

Transfusion with platelets is indicated to correct bleeding manifestations and may be indicated for severe thrombocytopenia without bleeding particularly in the setting of an invasive procedure.

Transfusion Support

Leukoreduced blood products are recommended for immune compromised hosts. Red blood cells (RBCs) and platelets should be irradiated (recommended dose 2500 cGy) to optimize inactivation of T-lymphocyte production. Additionally, leucofiltration is done to decrease the frequency of platelet alloimmunization, febrile nonhemolytic transfusion reactions, infections, graft versus host disease (GVHD), and transfusion-related acute lung injury (TRALI). Filtration is best accomplished at the time of blood collection by the blood bank.

Cytomegalovirus (CMV)-negative products are typically limited to those patients who are seronegative or are anticipated to need a solid organ transplant such as the liver for non-resectable hepatoblastoma, and potential bone marrow transplant recipients.

Diarrhea

Diarrhea may be a result of damage to the cellular lining of the GI tract secondary to the administration of antineoplastic agents. Anti-metabolites, especially fluorouracil, and agents such as irinotecan, hematopoietic stem cell transplant, and abdominal or pelvic irradiation are most commonly associated with diarrhea.[2] Uncontrolled diarrhea can lead to serious fluid and electrolyte imbalances, contribute to the child's nutritional deficits and feelings of fatigue, and cause perianal skin breakdown.

General measures:

Avoid fatty, greasy foods, and limit intake of dairy products or consider the use of lactase or low-lactose milk products. Consume easy to digest carbohydrates such as rice, white bread and potatoes. Drink fluids frequently between meals to avoid dehydration (Gatorade®, bouillon, apple juice, gelatin, and grape juice). Avoid caffeinated drinks including soft drinks.

To prevent perianal skin breakdown clean the perianal area with mild soap and warm water after each loose bowel movement. Dry skin thoroughly and allow exposure to air as much as possible. Apply barrier cream such as A&D ointment or a zinc oxide containing ointments to dried area.

Diarrhea associated with Hematopoietic Stem Cell Transplant:
Apply general measures above and consider evaluation for infection (e.g.: clostridium difficile, CMV, cryptosporidium, etc.) and GI GVHD.

Diarrhea Secondary to Irinotecan
Patients who have the onset of diarrhea during the irinotecan infusion or in the several hours following completion of the irinotecan infusion should receive a dose of atropine (suggested dose 0.01 mg/kg IV, maximum dose 0.4 mg). Each family should be instructed to have antidiarrheal medication available and begin treatment at the first episode of poorly formed or loose stools or the earliest onset of bowel movements more frequent than normally expected for the patient. Patients should also be instructed to contact their physician if any diarrhea occurs.

Loperamide dosing recommendations for late diarrhea which occurs 8 hours after irinotecan (based on body weight):

Under 13 kg: Take 0.5 mg after the first loose bowel movement, followed by 0.5 mg every 3 hours. During the night, the patient may take 0.5 mg every 4 hours. Do not exceed 4 mg per day.

From 13 kg to less than 20 kg: Take 1 mg after the first loose bowel movement, followed by 1 mg every 4 hours. Do not exceed 6 mg per day.

From 20 kg to less than 30 kg: Take 2 mg after the first loose bowel movement, followed by 1 mg every 3 hours. During the night, the patient may take 2 mg every 4 hours. Do not exceed 8 mg per day.

From 30 kg to less than 43 kg: Take 2 mg after the first loose bowel movement, followed by 1 mg every 2 hours. During the night, the patient may take 2 mg every 4 hours. Do not exceed 12 mg per day.

->12 years old and adults: Take 4 mg after the first loose bowel movement, followed by 2 mg after each loose stool. Do not exceed 16 mg per day.

High dose loperamide (adults) 2mg every 2 hours

Failure of loperamide to control diarrhea within 24 hours of onset:
Begin subcutaneously or intravenously administered octreotide (Sandostatin®), 1-2 mcg/kg/dose every 12 hours. If needed, the dose may be titrated up to 10 mcg/kg/dose (maximum dose: 500 mcg) every 8 hours.

Antibiotics for GI Toxicities

For patients who develop Grade 3 or 4 gastrointestinal (GI) toxicity (see table below for the indications for antibiotic use) following irinotecan therapy, administration guidelines are provided for cefpodoxime (Vantin®) and cefixime (Suprax®).

Cefpodoxime: 10 mg/kg/day, divided in 2 oral doses; maximum daily dose 400 mg for children < 12 years and maximum daily dose 800 mg for those ≥ 12 years)

or

Cefixime: (8 mg/kg/dose as a single daily oral dose or divided BID; maximum daily dose 400 mg).

The antibiotic should be started 5 days prior to the start of irinotecan therapy only if the patient experienced Grade 3 or 4 colitis, dehydration, diarrhea, abdominal pain, weight loss or vomiting during prior therapy with irinotecan. If it is not feasible to start cefpodoxime or cefixime 5 days prior to therapy with irinotecan, give at least 1 full day of cefpodoxime or cefixime prior to the start of irinotecan course. Refer to institutional guidelines for administration.

Indications for Antibiotic Use (Cefpodoxime or Cefixime) for GI Toxicities Due to Irinotecan

Toxicity	Defined as
Abdominal Pain	Severe pain, pain or analgesics severely interfering with activities of daily living, disabling.
Colitis (Grade 3 or 4)	Abdominal pain, fever, change in bowel habits with ileus or peritoneal signs, and radiographic or biopsy documentation of perforation or requiring surgery or toxic megacolon.
Dehydration	Requiring IV fluid replacement (sustained), physiologic consequences requiring intensive care, hemodynamic collapse.
Diarrhea	Increase of $\geq$ 7 stools/day or incontinence; or need for parenteral support for dehydration, severe increase in loose stool, physiologic consequences requiring intensive care, hemodynamic collapse, or watery stool output compared with pretreatment, interfering with normal activity, physiologic consequences requiring intensive care, hemodynamic collapse.
Vomiting	$\geq$ 6 episodes in 24 hours over pretreatment, or need for IV fluids requiring parenteral nutrition, or physiologic consequences requiring intensive care, hemodynamic collapse.
Weight Loss	> 20%

Adapted from[7] Perry MC et al., ed. *Companion Handbook to Chemotherapy Source Book.* 2nd ed. Baltimore, MD: Lippinkott, Williams and Wilkins; 2004.

Eye Care

Conjunctivitis Prophylaxis

Administer steroid eye drops (0.1% dexamethasone or 1% prednisolone ophthalmic solution), 2 drops each eye q 6 hours beginning immediately before the first dose of high dose cytarabine ($\geq$ 1000 mg/m²/dose) and continuing 24 hours after the last dose. If the patient does not tolerate steroid eye drops, the physician may administer artificial tears on a q 2 to 4 hour schedule to prevent conjunctival and corneal pain.

Growth Factors

Growth Factors with Leukemia

Prophylactic use of hematopoietic growth factors is not recommended for patients with leukemia. Treatment with filgrastim (G-CSF, 5mcg/kg/day) or sargramostim (GM-CSF, 250 mcg/m^2/day) is recommended for patients who have documented or suspected fungal infections or bacterial sepsis, and should be continued until the ANC recovers.

Growth Factors with Solid Tumors

The standard dose of filgrastim (G-CSF) is 5 mcg/kg/day (IV or SubQ) (SubQ preferred) for patients with solid tumors. Growth factor treatment, if used, should begin 24 hours after chemotherapy, continue beyond the expected nadir and be stopped at least 24 hours before the next chemotherapy cycle. The proper utilization of growth factors may be regulated by study primary or secondary aims (see individual protocol).

Erythropoietin
At the current time, the FDA is evaluating data on the use of recombinant human erythropoietin and potential significant side effects. Recommendations for continued use in pediatric patients will await the FDA consensus.

Oprelvekin/Neumega®
A safe and effective dose of oprelvekin in children has not been established. Oprelvekin should not be administered to pediatric patients, particularly those under the age of 12 years. Pediatric subjects experienced higher incidences of tachycardia (84%), conjunctival injection (57%), radiographic and echocardiographic evidence of cardiomegaly (21%) and periosteal changes (11%).[10]

Infection

Pneumocystis Prophylaxis[11]
Prophylaxis against pneumocystis *carinii* pneumonia (PCP) (also called *Pneumocystis jiroveci pneumonia*) should begin as soon as possible after the initiation of chemotherapy and continue for at least 3 months following discontinuation of chemotherapy.

All patients should receive trimethoprim/sulfamethoxazole (TMP/SMX) at a dose of TMP 2.5 mg/kg/dose (75mg/m^2/dose) twice daily, maximum dose 160 mg/dose, PO on 3 sequential days per week.

For patients between 1-2 months of age, allergic to, with G-6PD deficiency, or experiencing excessive myelosuppression with TMP/SMX, alternative prophylaxis with dapsone (2 mg/kg/day PO, maximum dose 100 mg/day), aerosolized pentamidine for children old enough to cooperate with administration (≥ 5 years should receive 300 mg inhaled monthly, < 5 years should receive 8mg/kg), or atovaquone PO (1-3 month: 30 mg/kg/day; 4-24 month: 45 mg/kg/day; >24 months: 30mg/kg/day) (may be considered. For children in whom TMP/SMX, dapsone, atovaquone, and inhaled pentamidine cannot be administered, IV pentamidine (4 mg/kg/dose IV every 2 to 4 weeks[12]) should be given. For infants under the age of 2 months, dapsone prophylaxis may be preferred to TMP/SMX due to liver immaturity in these younger infants and the risk of methemoglobinemia with TMP/SMX treatment.

TMP/SMX should be held 24 hours prior to high-dose methotrexate (MTX) infusions and restarted when MTX level < 0.1µM and at least 4 days after high dose MTX. Sulfonamides can displace MTX from plasma binding sites and increase free MTX and/or decrease the renal excretion of MTX. TMP can interfere with the microbiological DHFR assay for MTX; no interference occurs with the RIA. In addition, both agents have similar toxicities, and the administration of TMP/SMX increases the risk of high-dose MTX toxicity.

There have been multiple episodes of PCP reported in patients receiving temozolomide, particularly when taking corticosteroids. For this reason, patients should receive PCP prophylaxis during treatment. However, there have been 3 reports of prolonged myelosuppression and death in older adults receiving chemoradiotherapy with temozolomide at low-dose along with TMP/SMX prophylaxis. For this reason, TMP/SMX should <u>not</u> be utilized as PCP prophylaxis during chemoradiotherapy. Monthly inhaled or IV pentamidine or an appropriate alternative must be administered during chemoradiotherapy. TMP/SMX may be used as PCP prophylaxis during Maintenance chemotherapy.

Bone Marrow transplant patients should discontinue TMP/SMX 2 days before transplantation and then restart when ANC > 500/µL.

Intravenous Immunoglobulin
If clinically indicated, immunoglobulin (IgG) levels may be monitored throughout treatment. If the IgG level falls below institutional normal levels, IV IgG (IVIG) at 400 mg/kg may be administered at the discretion of the investigator. In particular, this should be considered with infants, children with AML and children with Down Syndrome.

Prevention of Herpes Simplex
Prophylactic acyclovir can reduce the recurrence of mucocutaneous herpes simplex virus (HSV) infection in both immunocompetent and immunocompromised patients. The efficacy of prophylactic acyclovir has primarily been restricted to reduction of recurrent mucocutaneous HSV infection and not does not extend to other clinical endpoints such as duration of fever, use of antibiotics or mortality. Prior to starting acyclovir it is recommended that patients with oral mucositis be tested for recurrence of HSV with positive findings on PCR analysis. Prophylactic acyclovir (80 mg/kg/day given orally in divided doses - 3-5 times daily [Maximum: 1000 mg/day]) can be used for recurrent HSV infection and may also be considered for those with positive anti-HSV titers or after a single episode of HSV infection. For those patients unable to take acyclovir by mouth give 250 mg/m^2/dose IV every 8 hours.

Prevention of Fungal Infections
Patients receiving steroids are at particularly high risk of invasive fungal infection and these organisms are a major cause of infection-related mortality. Antifungal prophylaxis can reduce morbidity and fungal infection-related mortality in severely neutropenic chemotherapy recipients. Patients that will have prolonged neutropenia are those receiving chemotherapy with a high risk of mucositis. Evidence for benefit is strongest for those conditions associated with > 15% rate of systemic fungal infection, prolonged neutropenia (such as acute myeloid leukemia (AML) patients) and stem cell transplant (SCT) recipients. The choice of the prophylaxis should be made in consultation with institutional infection profiles and infectious disease guidelines.

Management of Clinically or Microbiologically Documented Fungal Infection
Chest computerized tomography (CT) scans are usually more sensitive than chest X-ray scans (CXR) in demonstrating pulmonary fungal lesions. Chest CT scans should be considered in patients who are febrile and neutropenic since they may have a nonspecific CXR. Consider endoscopy for those patients with substernal pain or unexplained emesis. CT scans have a significant false negative rate in neutropenic patients, and hence, patients who have received empiric amphotericin or other antifungal therapy and have suspicious lesions should undergo surveillance CT scans of lungs, liver, spleen, kidneys, brain and sinuses at the time of recovery of counts in order to detect characteristic lesions. When neutrophils return, lesions visible at the time of neutropenia may appear larger, and negative scans may become positive. To assess success or failure of antifungal therapy and to distinguish inflammatory response from progressive fungus, it may be necessary to repeat scans of positive lesions after neutrophil recovery.

When possible, fungal lesions should be biopsied or surgically removed in order to identify the organism, to obtain cultures and sensitivities, and to rule out non-fungal causes of lesions such as bacterial infections or sterile inflammatory infiltrates. If antifungal therapy has been discontinued because of apparent cure, it should be empirically resumed at the time of the next neutropenia and continued until both neutrophil recovery has occurred and repeat surveillance scanning has been performed and found to be negative. This is at the discretion of the individual physician's best clinical judgement.

Drug interactions with Azole Antifungal agents:
Azole antifungal agents (i.e., itraconazole, voriconazole, posaconazole) given concurrently with vincristine may increase the risk of neurotoxicity. These agents may also interfere with the metabolism of other chemotherapy agents metabolized by the Cytochrome P450 enzymes.

Respiratory Syncytial Virus
Though there is no uniformly accepted treatment of respiratory syncytial virus (RSV) infections, many sources recommend a combination of ribavirin and IVIG. Dosages should conform to institutional pharmacy recommendations.

Palivizumab (Synagis®) 15 mg/kg IM monthly for up to 5 doses may be used to prevent RSV infection during RSV season (usually November to April) in susceptible high risk infants.

Varicella
Patients with primary varicella infection (chickenpox) should be treated promptly. They should be started on acyclovir 10mg/kg/dose q 8 hours (<1 year) or 500 mg/m^2/dose or 10mg/kg/dose q 8 hours (>1 year) IV, and monitored closely for the extent and development of invasive systemic disease. Chemotherapy should be held initially until assessment of disease and response to treatment, but can be resumed based on the clinical picture. Steroids should not be given during this time.

Susceptible patients exposed to Varicella Zoster should be given IVIG (400 mg/kg) or Varicella Zoster Immunoglobulin (VariZIG™ manufactured by Cangene of Canada) if available at the individual institution.

Empiric Management of Pulmonary Infiltrates
Pulmonary infiltrates should be evaluated in the context of the patient's clinical and laboratory profile. If the patient is not neutropenic, and the pulmonary lesions on CT scan are not particularly suggestive of a mold infection (e.g., aspergillus, mucor), consider using broad spectrum antibiotics. If the patient develops progressively worsening clinical or laboratory features, then more aggressive diagnostic measures should be undertaken. Pulmonary infiltrates should then be evaluated with bronchoscopy and biopsy, lavage, or open lung biopsy. If a procedure cannot be tolerated, begin empiric treatment with amphotericin B (or the lipid amphotericins). There is a high likelihood of fungal disease during Induction, Re-Induction and periods of intensive chemotherapy. Empiric coverage should include treatment for gram-negative and gram-positive bacteria, legionella (erythromycin), pneumocystis (TMP/SMX), and fungi (amphotericin) pending culture results. If fungal pulmonary disease is documented, surveillance radiographic imaging studies of the sinuses, abdomen/pelvis and brain are indicated. Surgical excision of pulmonary lesions should be considered at the discretion of the treating physician. Treatment of fungal infections with amphotericin B and/or other antifungal agents will be at the discretion of the treating physician. Combined therapy with ganciclovir and intravenous immune globin should be used in patients with suspected or documented cytomegalo-virus (CMV) pneumonitis.

Immunizations
For recommendations on immunization during chemotherapy see: Altman, AJ, ed. *Supportive Care of Children with Cancer*. 3rd ed. Baltimore, MD: The Johns Hopkins University Press; 2004. Chapter 2.
"Children immunized before or during therapy may lose or not attain protective antibody titers. Specific serum titers should be attained at diagnosis, post immunization and off–therapy to assess response and guide management of future exposures and further immunizations."

Recognition of when the spleen may be irradiated is of importance at the beginning of therapy as vaccination against encapsulated bacteria is advised (eg, Pneumovax). For recommendations see: Altman, AJ, ed. Supportive Care of Children with Cancer. 3rd ed. Baltimore, MD: The Johns Hopkins University Press; 2004. Chapter 2.

No live vaccines are recommended for patients receiving chemotherapy. This includes all live viral vaccines: MMR, OPV, LAIV, yellow fever, varicella (including MMRV and HZ vaccine), and vaccinia

(smallpox); and all live bacterial vaccines: BCG, and Ty21a Salmonella typhi vaccine. Varicella Vaccine may be given to the siblings of patients in remission and stable at the physician's discretion.

For recommendations on immunizations for HSCT recipients, see: Vaccination of Hematopoietic Stem Cell Transplant Recipients. Recommendations of Centers for Disease Control and Prevention, the Infectious Disease Society of America, and the American Society of Blood and Marrow Transplantation. Excerpt from "Guidelines for Preventing Opportunistic Infections Among Hematopoietic Stem Cell Transplant Recipients", MMWR 2000;49(RR-10):1-128, which can be found at: http://www.cdc.gov/vaccines/pubs/downloads/b_hsct-recs.pdf. Data are limited, but HSCT centers might consider the use of the 7-valent conjugate pneumococcal vaccine (Prevnar®).

Magnesium Supplementation

IV magnesium supplementation in the hydration fluids should be considered during administration of cisplatin or ifosfamide. Suggested hydration would be D_5W ½NS +10 mEq KCl/L + 1-2 grams (8-16 mEq) magnesium sulfate/L at 125 mL/m^2/hour.

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When chemotherapy regimens include cisplatin, routine supplementation with magnesium at a minimum of 6 mg (0.5mEq) elemental magnesium/kg/day PO in divided doses is recommended. Alternatively, a dosage regimen of 14 – 15 mEq elemental magnesium/m^2/day PO in divided dose can be utilized.

Magnesium Product Comparison Chart*

Product	Dosage Form (Mg=elemental magnesium)	Magnesium mEq/gm	Comment	Trade Name
Mg Carbonate	Cap 250 mg	23.7	Poorly Soluble and low absorption	
Mg Chloride	Injection 200 mg/mL (23.6 mg/mL Mg) SR tab 535 mg (64 mg Mg)	9.8	Used I.V./orally as 5% solution	Slo-Mag (various)
Mg Citrate	Sol'n: 60 mg/mL (3.2 mg/mL Mg)	4.4	Oral	Citrate of Magnesia
Mg Gluconate	Tab: 500 mg Sol'n 1000 mg/5 mL (54mg Mg/5mL)	4.8	Very soluble, well absorbed, less diarrhea	Magonate, Almora
Mg Hydroxide	Tab: 300 mg, 600 mg Sol'n 400 mg/5 mL, 800 mg/5 mL (34 mg/mL Mg, 67 mg/mL Mg)	34	Readily available, inexpensive	Milk of Magnesia
Mg Oxide	Tab: 400mg (241.3 mg Mg), 420 mg (253 mg Mg) 500 mg (302 mg Mg) Cap: 140mg (84.5 mg Mg)	49.6	Poorly Soluble, net absorption low; especially in malabsorptive states	Mag-200, Mag-Ox 400
Mg Sulfate	Injection: 10%, 12.5%, 50% (9.6, 12, 48 mg/mL Mg) Powder 1g (97.2 mg Mg)	8.1	Can be given I.V., I.M. or P.O.	Magnesium Sulfate injection, Epsom Salts

Magnesium products exhibit variable absorption; increase dosage incrementally until no further rise in serum magnesium occurs or until diarrhea ensues. Elemental Magnesium: 1 mEq = 12 mg = 0.5 mMol

* This list contains some of the more common Magnesium containing products

Mouth Care

Dental Consultation

Dental consultation and treatment is recommended prior to initiation of therapy for patients with poor oral hygiene and those with head/neck tumors, especially if radiation therapy will be given to the head and neck. Removal of braces prior to initiation of therapy should be evaluated. Routine dental examinations with radiographic examination and dental deplaquing/scaling may be performed during treatment only when the ANC > 1000/µL and platelets > 100,000/µL. Prophylactic antibiotics may be considered in patients with central venous access devices following the recommendations of the American Heart Association.[13]

Mucositis

Patients at risk for developing Grade 3 or 4 mucositis should be instructed on the importance of meticulous oral hygiene. Mucositis should be managed with IV hydration, hyperalimentation, effective analgesia, broad-spectrum gram-positive and gram-negative antibiotic therapy, and empiric antiviral and antifungal therapy as indicated. Stomatitis and esophagitis due to herpes virus may be confused with drug-induced mucositis, and viral cultures should be obtained frequently.

Neurotoxicity

Acute Neurotoxicity Following Ifosfamide

If Grade 4 neurotoxicity occurs during ifosfamide administration, investigators may consider administration of methylene blue pending recommendations from the institutional pharmacist and clinical pharmacologist. Cyclophosphamide and mesna should be considered for substitution of remaining ifosfamide doses.

Acute Neurotoxicity Following Intrathecal Methotrexate

Neurotoxicity has extreme protean manifestations, ranging from transient events, seizures or episodes of acute hemiparesis to severe necrotizing encephalopathies. These toxicities are poorly understood and currently it is impossible to predict who will suffer these complications. In addition, there are no data clearly linking the occurrence of an acute neurotoxic event to an increased risk of long-term neurocognitive dysfunction. Nor do changes present on magnetic resonance imaging (MRI) scan at the time of an acute event clearly correlate with or predict outcome. It is clear however, that central nervous system (CNS) prophylaxis is a mandatory component of curative therapy for children with acute lymphoblastic leukemia (ALL). Effective prophylaxis generally takes 2 forms: cranial, or less commonly, craniospinal radiation, with a limited number of doses of intrathecal (IT) therapy or prolonged IT therapy with either IT methotrexate (MTX) or triple IT therapy (MTX, cytarabine (Ara-C), and hydrocortisone). The exclusive use of IT Ara-C has not been studied or described in the context of ALL therapy nor can one demonstrate the safety of omitting multiple doses of IT therapy without concomitant use of cranial irradiation or high-dose MTX.

The following guidelines are offered for consideration following an acute event, but it must be recognized that there are little data to support these approaches, or any others. Thus, the treating physician must evaluate the patient and, with the family, make the best possible decision with respect to the relative risk and benefit of continued therapy.

Following an acute neurotoxic event, a history and physical exam should guide the differential diagnosis. A neurology consult may be of value and should be considered. In addition to the direct side effects of chemotherapy, seizures and other transient events may be linked to fever, infection, encephalitis, meningitis, hypertension, electrolyte disturbance, hypoglycemia, trauma, intracranial hemorrhage or thrombosis, narcotic withdrawal, illicit drug use, or other causes. Appropriate laboratory studies may include, but are not limited to, blood cultures, a complete blood count (CBC), electrolytes (including glucose, calcium, magnesium and phosphorus), renal and liver function studies, and/or an examination of

the cerebrospinal fluid (CSF). Imaging studies may include a CT and/or MRI scan. The CT is commonly normal in the absence of stroke, but if calcifications are present, this finding may be indicative of a more severe mineralizing leukoencephalopathy. MRI abnormalities may be pronounced, but transient. Posterior reversible encephalopathy may be present on magnetic resonance (MR) with extensive diffusion abnormalities, but these do not appear to correlate with subsequent demyelination or gliosis. Additional studies, including MR angiography and/or venogram should be considered, if clinically indicated (e.g., focal deficits). Many acute events are temporally related to the administration of IT therapy, commonly 9 to 11 days after the IT administration.

Following an acute event with recovery, there are few data to support or guide therapeutic interventions. These interventions must be managed by the treating physician in the best interest of the individual patient. These decisions are extremely difficult and may hinge on an individual's view of the importance of quality of life versus an increased risk of relapse. Since the greatest impact of CNS prophylaxis occurs early in therapy, the timing of these events may also influence clinical decisions.

The use of dextromethorphan as a neuroprotectant in the absence of a supportive clinical trial is not valid.

Hydrocephalus, microcephaly, or known abnormality of CSF flow preclude IT chemotherapy via LP. Intraventricular chemotherapy via Ommaya catheter may be used in place of IT therapy delivered by LP. Intraventricular chemotherapy should be given according to the same schedule, but at 50% of the corresponding age-based doses, that would be given by LP.

Acute Neurotoxicity following Vincristine

Severe neuropathic pain (Grade 3 or greater): Hold dose(s). When symptoms subside, resume at 50% previous dose, then escalate to full dose as tolerated. However, since vincristine is an important component of curative therapy, and the majority of neuropathies are ultimately reversible, treating physicians may choose to deliver full dose therapy. Severe peripheral neuropathies, with or without a positive family history might suggest the need for a molecular diagnostic evaluation to rule out Charcot Marie Tooth Disease (CMT), Type 1A or Hereditary neuropathy with liability to pressure palsies.

Vocal Cord paralysis: Hold dose(s). When symptoms subside, resume at a lower dose titrated to the severity of the original event, then escalate to full dose as tolerated. See above for comment on CMT.

Foot Drop, paresis: Should be Grade 4 to consider holding or decreasing dose. These toxicities are largely reversible, though possibly over months to years. Accordingly, holding doses of vincristine and/or lowering the dose may not result in rapid resolution of symptoms and may compromise cure. See above for comment on CMT. Physical therapy may be beneficial to maintain range of motion and provide AFO's and other forms of support. Drugs such as gabapentin may be of value.

Jaw pain: Treat with analgesics; do not modify vincristine dose unless determined to be in the best interest of the patient by the treating physician.

Nutrition

Aggressive measures, including enteral and parenteral feedings, should be used to prevent weight loss > 5% of pre-illness body weight or persistent hypoalbuminemia of < 3.2 mg/dL. Protein-calorie malnutrition due to chemotherapy-induced loss of appetite, nausea, vomiting, mucositis, and sepsis is a concern.

Caution is advised with the use of early feeding/ NG feeding in patients with difficult early courses or extensive mucositis/perineal breakdown. NEC and intestinal perforation have been observed in such infants. Total parenteral nutrition (TPN) should be strongly considered in such infants until it is certain there is no risk to the gut. Prophylactic use of enteral nutrition should be considered in patients at risk (AML, infants).

Patients with nasopharyngeal primary tumors often experience significant mucosal reactions during radiation. Early placement of gastrostomy tube for supplemental feeding, prior to beginning irradiation, may be indicated.

For further information, see the COG Cancer Control Nutrition Subcommittee Algorithm for Nutritional Intervention and Categories of Nutritional Status in the Pediatric Oncology Patient at: https://members.childrensoncologygroup.org/Disc/nursing/ClinicalPractice.asp.

Osteonecrosis

Osteonecrosis (ON) may develop during or following therapy and often involve multiple joints over time. ON is not limited to weight-bearing joints; common sites include hip, knee, ankle, heel, shoulder, and elbow. Symptoms and exam findings may include joint pain, joint stiffness, limited range of motion (e.g., pain with internal rotation of the hip), limited mobility or ambulation, and/or gait abnormalities. Diagnostic imaging is indicated for any patient with suggestive findings. MRI is superior in sensitivity and specificity to other modalities, especially for identifying early bone changes.

For patients with ALL: Consider omission of further corticosteroid therapy if ON develops during Maintenance. Further management should include input from orthopedic and oncologic perspectives.

Pancreatitis

Abdominal pain, vomiting, and previous treatment with asparaginase, are possible indicators of pancreatitis. An elevated amylase, lipase, and/or urinary amylase/creatinine ratio 1.5-2 times normal is associated with pancreatitis. Management of pancreatitis depending on the severity will include: bowel rest, nasogastric drainage, antibiotic coverage of bowel flora, fluid replacement and hyperalimentation.

Discontinue steroids, except for stress doses, in the presence of hemorrhagic pancreatitis or severe pancreatitis (abdominal pain > 72 hours and ≥ Grade 3 amylase elevation [≥ 2 x ULN]). Do not modify dose of steroids for asymptomatic elevations of amylase and/or lipase.

Severe pancreatitis is a <u>contraindication</u> to additional asparaginase administration. In the case of mild pancreatitis, asparaginase should be held. Further use of the drug should be evaluated by the treating physician.

Perineal/Perirectal Care

There is a high risk of Grade 3 or 4 perineal irritation with daunorubicin and high-dose methotrexate (MTX) therapy in infants. Placement of a Foley catheter for 48 to 72 hours during administration/urinary excretion of these drugs has dramatically reduced perineal breakdown. Use of a strong dermatologic barrier technique is also recommended. If severe breakdown occurs, manage skin care aggressively and strongly consider antibiotic coverage until skin heals. Do <u>not</u> proceed with further daunorubicin / high-dose MTX <u>until</u> skin begins to heal.

Management of perirectal cellulitis should include broad-spectrum antibiotic therapy with dual gram-negative coverage as well as anaerobic coverage (ie, ceftazidime + aminoglycoside + metronidazole; or piperacillin-tazobactam + aminoglycoside), sitz baths, a strong barrier technique, and effective analgesia. Consider further consultation with pediatric surgery and dermatology.

Renal Toxicity

Renal toxicity may occur secondary to many chemotherapeutic agents including: azacytidine, carmustine or lomustine, busulfan, melphalan, carboplatin, cisplatin, methotrexate, ifosfamide, interleukin 2 as well as drugs used with chemotherapy such as cyclosporine and aminoglycoside antibiotics.

Renal Toxicity Secondary to Ifosfamide

Renal toxicity is the primary, long-term dose-limiting side effect of ifosfamide. Available information indicates that the renal injury produced by ifosfamide is permanent, and in some cases, progressive. Renal irradiation, age < 3 years, and absence of 1 kidney are risk factors for severe renal toxicity,[14] as is a total cumulative dose of ifosfamide $\geq$ 60 g/m^2.[15]

All patients receiving ifosfamide should be carefully monitored for Fanconi Syndrome. Elements of Fanconi Syndrome include:

1. Renal phosphorus wasting with hypophosphatemia
2. Renal bicarbonate wasting with acidosis
3. Renal potassium wasting with hypokalemia (< 3 mEq/L)
4. 1+ glycosuria with serum glucose < 150 mg/dL
5. Proteinuria: a ratio of urine protein**:**urine creatinine > 0.2 occurring in the absence of significant malnutrition and acidosis due to sepsis/infection

Incomplete Fanconi Syndrome, with only 1 or a few of these elements, is common. Over time, these abnormalities may resolve, remain static, or progress.

Any patient who has any 2 of the metabolic abnormalities listed above, other than or in addition to glycosuria, should have the following studies done approximately 4 weeks after the onset of the abnormalities:

1. Nuclear glomerular filtration rate (GFR)
2. Measurement of non-fasting serum phosphorus (off supplementation and in the absence of malnutrition) on 2 consecutive days
3. Measurement of serum bicarbonate (off supplementation) on 2 consecutive days.

Significant Fanconi Syndrome will be defined as:

1. GFR < 50 mL/min/1.73m^2, not due to other causes (e.g., aminoglycoside toxicity, amphotericin B) in the presence of mineral/electrolyte wasting

   or
2. The GFR is any level, but there is significant evidence of persistent Renal Tubular Acidosis (RTA) and phosphorous wasting.

If significant Fanconi Syndrome occurs, report it immediately as adverse drug reaction. Renal toxicity should be reported on the end of phase report.

Significant phosphorus wasting will be defined as:

Pre-pubertal children: Phosphorus < 2.0 mg/dL
Post-pubertal children: Phosphorus < 1.5 mg/dL

Significant serum bicarbonate abnormality (without supplementation) will be defined as:

Children < 1 year of age: HCO_3 less than 12.0 mmol/L

Children ≥ 1 year of age: HCO_3 less than 14.0 mmol/L

Renal Toxicity Secondary to Cisplatin

Hydration with 0.9% NaCl has been proven safe and effective in decreasing cisplatin nephrotoxicity.[16,17] The use of mannitol with cisplatin is controversial.[16, 17] Also see section on magnesium supplementation for a recommendation on adding magnesium to the hydration fluid.

Reproduction

Menstrual Suppression

Menstruating females may receive suppression with daily administration of a low dose monophasic, combined, oral contraceptive pill. The patient should be instructed to remove the 7 placebo pills in each pack. Endometrial atrophy and amenorrhea can be induced with depo-medroxyprogesterone (Depo-Provera®) 150 mg every 12 weeks. If the patient is compliant and there is not a concern about estrogen, then birth-control pills would be the treatment of choice. There is a greater incidence of breakthrough bleeding with depo-medroxyprogesterone when used every 12 weeks. There is some concern about decreases seen in Z-scores of bone density (DEXA) scans when patients are treated over 2 years. Suppression of menses should be continued until the platelet count is ≥ 50,000/μL without transfusion support.

Tumor Lysis Syndrome

Patients at greatest risk are those with bulky disease or high tumor burdens with malignancies exquisitely sensitive to chemotherapy; WBC > 100,000/μL, lymphadenopathy, hepatosplenomegaly, elevated LDH, and large primary masses of the abdomen, thorax, or mediastinum. Diseases most commonly associated with TLS include ALL, T-cell Leukemia/Lymphoma and Non-Hodgkin's Lymphoma (e.g., Burkitt's lymphoma), although it can occur in tumors such as neuroblastoma where the bone marrow is completely replaced by tumor. The risk for serious acute TLS is usually restricted to the first 72 hours after initiation of therapy; however, it may spontaneously occur prior to treatment.

TLS is characterized by severe hyperuricemia, hyperphosphatemia, hyperkalemia, hypocalcemia, and acute renal failure. Suggested initial studies to be obtained prior to initiating therapy include CBC, prothrombin and activated partial thromboplastin times, fibrinogen, D-dimer, and serum electrolytes (including creatinine, blood urea nitrogen (BUN), uric acid, phosphorous, and calcium). Imaging pretreatment may include an abdominal ultrasound to assess renal parenchymal infiltration, as occasionally there may also be an obstructive element due to tumor pressure, and a chest x-ray including lateral to assess for mediastinal mass and tumor burden. Continued monitoring of these studies should be carried out at suitable intervals until abnormalities have resolved or the risk has abated.

Prevention and Monitoring

1. Maintain strict attention to patient's fluid balance (input and output)
2. Hydration with 2400-3000 mL/m^2/day of IV fluid (D_5 ¼ or D_5 ½) NS (no potassium) + $NaHCO_3$ 25-100 mEq/L. Adjust bicarbonate to maintain urine pH 6.5-7.5 and not in excess of 8.5 for patients taking allopurinol. No potassium should be administered until tumor lysis is controlled. Alkalinization is not recommended when treating with uricase or rasburicase.
3. Begin allopurinol prior to chemotherapy. Allopurinol should be infused in a separate IV line from the chemotherapy. Continue until peripheral blasts and extramedullary disease are

reduced.
Dose:
Daily doses >300mg should be administered in divided doses.

Children ≤10 years:
IV: 200mg/m^2/day in 1-3 divided doses; maximum dose: 600mg/day.
PO: 10mg/kg/day in 2-3 divided doses or 200-300 mg/m^2/day in 2-3 divided doses.
Maximum dose: 800mg/day.

Children >10 years and adults:
IV: 200-400 mg/m^2/day in 1-3 divided doses; maximum dose: 600mg/day
PO: 600-800mg/day in 2-3 divided doses.

4. In some situations it may be appropriate to use rasburicase (recombinant urate oxidase) as initial therapy, such as in patients who are at a significant risk of TLS due to disease or patient-related risk factors or those who are demonstrating signs of evolving TLS. Patients who present with renal insufficiency (serum creatinine (sCr) > 0.7 mg/dL in children or > 1.3 mg/dL in adults), either preexisting or due to new disease, and patients with hyperuricemia at presentation are also good candidates for upfront rasburicase. Dosing for rasburicase is 0.15-0.2 mg/kg/dose IV over 30 minutes daily until uric acid levels have normalized and patient is clinically stable; typically 1 to 3 days. Sodium bicarbonate is not required when using rasburicase. Rasburicase is contraindicated in patients with glucose-6-phosphate dehydrogenase (G-6PD) deficiency.
5. Check patient's urine for specific gravity and hematuria after every void.
6. Assess patient's weight twice daily.
7. Assess the patient's vital signs frequently, at a minimum of q 4 hours, and observe patient for irregular pulse and decrease in blood pressure.
8. Monitor the patient's laboratory values (i.e., electrolytes, calcium, uric acid, creatinine, and phosphate) at least q8 hours.
9. Hyperkalemia (> 6.0 mEq/L) leads to ventricular arrhythmias and possibly death.
    a. Assess for symptoms of cardiac arrhythmias by using a cardiac monitor if clinically indicated.
    b. Calcium administration is the fastest means of reversing the cardiac effects of hyperkalemia. Onset of action is within minutes but the duration is only one-half hour. Consider slow infusions and in a separate line from the sodium bicarbonate.
    c. Sodium bicarbonate as well as insulin and glucose administration will move excess potassium into the cell; administer sodium bicarbonate at 1-2 mEq/kg IV or administer continuous glucose infusion at 0.5 g/kg/hour with insulin 0.1 unit/kg/hour.
10. Maintain urine output >100 mL/m^2/hour administering mannitol 0.5 gram/kg or furosemide 1-2 mg/kg by IV as needed.
11. If urine output declines, an ultrasound study of the kidney may be useful to rule out tumor infiltration or obstructive uropathy.
12. Perform a minimum of 1 daily physical exam for signs of dyspnea, rales, wheezing, cardiac arrhythmias, edema, ascites, neuromuscular changes, and gastrointestinal complaints.
13. Minimize exogenous potassium and phosphorous intake.
14. Avoid IV contrast and nephrotoxic medications when possible.
15. Medical management of hypocalcemia, hyperphosphatemia, hypercalcemia, and/or renal failure should be undertaken aggressively and in consultation with nephrology and the intensive care unit (ICU).

16. Monitor calcium-phosphorus product; if > 60 discontinue alkalinization.

Additional Procedures:

1. More aggressive hydration, leukopheresis, or exchange transfusion may be considered for elevated WBC (> 100,000 to 200,000) and multiple metabolic abnormalities.
2. Dopamine 3 mcg/kg/minute may aid in increasing renal blood flow.
3. Hemofiltration or dialysis may be warranted.

   Dialysis indications when above fail:

   a. QRS interval widening with serum potassium > 6 mEq despite kayexalate and rising creatinine with urine output < 60 mL/m^2/hour.
   b. Serum uric acid > 10 mg/dL with rising creatinine and urine output < 60 mL/m^2/hour.
   c. Serum creatinine > 10 mg/dL.
   d. Serum phosphorus > 10 mg/dL or rapidly rising despite aluminum hydroxide with rising creatinine and urine output < 60 mL/m^2/hour.
   e. Volume overload.
   f. Symptomatic hypocalcemia with hyperphosphatemia.

Tumor lysis syndrome (TLS) guidelines are available on the COG website at:
https://members.childrensoncologygroup.org/_files/disc/nursing/TLSguidelines.pdf

Venous Access

Central venous access in the form of a Broviac or Hickman catheter, port-a-cath, or peripherally inserted central catheter (PICC) is recommended for patients receiving vesicants and is essential if vesicant medication is given as a continuous infusion. For patients requiring frequent blood draws, intensive chemotherapy, bone marrow transplant, and nutritional support, it is critical that a central, preferably double lumen, line be placed.

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